Critical Reviews in Oncology / Hematology 143 (2019) 27–45

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Systemic therapy for previously treated advanced gastric cancer: A systematic review and network meta-analysis

Ji Cheng[a,b,*], Ming Cai[a], Xiaoming Shuai[a], Jinbo Gao[a], Guobin Wang[a], Kaixiong Tao[a,*]

[a] Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, China
[b] Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, 02115, United States

ARTICLE INFO

Keywords:
Second-line systemic therapy
Refractory
Paclitaxel plus ramucirumab
Apatinib
Nivolumab

ABSTRACT

Although paclitaxel plus ramucirumab has been recommended as the preferred second-line strategy, other regimens also display potentially comparable efficacies. Record retrieval was conducted in PubMed, Web of Science, Cochrane Central Register of Controlled Trials, Embase, ASCO and ESMO meeting libraries. Randomized controlled trials featuring comparisons between different systemic treatments among previously treated patients with advanced gastric cancer were eligible for our systematic review. Network calculation were based on random-effects model and the relative ranking of each regimen was numerically indicated by P-score (CRD42018104672). Concerning second-line regimens, "paclitaxel plus olaparib" and "paclitaxel plus ramucirumab" dominated the overall survival ranking while "paclitaxel plus ramucirumab" additionally topped the hierarchy for progression-free survival. Among refractory or third-line only cases, apatinib reigned the hierarchy by significantly and insignificantly surpassing placebo and nivolumab respectively. In conclusion, paclitaxel plus ramucirumab is the optimal second-line regimen. Both apatinib and nivolumab could be potentially recommended as refractory regimens.

1. Introduction

Gastric cancer is the fifth most common malignancy and third leading cause of cancer relevant mortality worldwide, with more than half of its cases occurring in East Asia (Cancer, 2012; Siegel et al., 2018). Among those with metastatic or locally inoperable gastric cancer, fluoropyrimidine plus platinum is currently recommended as the preferred first-line regimen, which may be also in combination with trastuzumab for HER-2 positive patients (2018). Nonetheless, despite of the increasing survival benefits against advanced gastric cancer, there is still a considerable amount of patients failing those therapies and forced to receive further treatments.

Salvage second-line chemotherapy has been confirmed to significantly enhance the overall survival compared to best supportive care (Ford et al., 2014; Kang et al., 2012; Thuss-Patience et al., 2011). At present, cytotoxic chemotherapies including paclitaxel, docetaxel, irinotecan, as well as vascular endothelial growth factor 2 (VEGFR2) monoclonal antibody ramucirumab have all been recommended in the second-line setting (2018), especially for paclitaxel plus ramucirumab, which displayed significant survival superiority over paclitaxel monotherapy (Wilke et al., 2014) and thus has been regarded as the preferred second-line regimen (2018). Moreover, randomized controlled trials on the potential application of pembrolizumab and olaparib in the second-line setting were also reported recently (Bang et al., 2017; Shitara et al., 2018), making the medication pool of possible second-line options even larger. However, since most of the studies utilized paclitaxel monotherapy as the control arm, the relative efficacies between paclitaxel plus ramucirumab with other alternative regimens remain statistically ill-defined.

Even though with the treatment of second-line medications, a large proportion of patients continue to have disease progression, who are regarded as refractory cases and needed to receive third-line or further therapies (Hwang et al., 2017). Currently, there is no consensus on refractory medications, despite of several targeted drugs demonstrating significant survival benefits over placebo, such as nivolumab and apatinib (Hwang et al., 2017; Li et al., 2016). Therefore, a comprehensive evidence summary and proper literature interpretation on this frontier field are urgently needed.

Unfortunately, those already published systematic reviews (Badiani et al., 2015; Chan et al., 2017; Harvey, 2017; Iacovelli et al., 2014; Kim et al., 2013; Ter Veer et al., 2016; Zhang et al., 2016; Zheng et al., 2017; Zhu et al., 2017) either performed pairwise meta-analysis with significant clinical heterogeneity, or failed to conduct adequate and updated literature search and interpretation, especially not including

* Corresponding authors at: No. 1277 Jiefang Avenue, Wuhan, 430022, China.
E-mail addresses: jicheng1@hust.edu.cn (J. Cheng), kaixiongtao@hust.edu.cn (K. Tao).

https://doi.org/10.1016/j.critrevonc.2019.08.001
Received 29 October 2018; Received in revised form 9 February 2019; Accepted 2 August 2019

those trials published in the last two years (Table 4). Moreover, since network meta-analysis enables the ranking of all possible regimens even though without direct comparisons, we decided to perform a systematic review and network meta-analysis featuring systemic therapy for previously treated advanced gastric cancer.

2. Methods

2.1. Registration and guidelines

The protocol of this systematic review and network meta-analysis had been published in PROSPERO (CRD42018104672). The design, conduct and writing of this systematic review and network meta-analysis was strictly in accordance with the requirements from 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 judged and solved by the third investigator.

2.2. Search strategy

Electronic databases including PubMed, Web of Science, Cochrane Central Register of Controlled Trials and Embase were comprehensively examined. Additionally, we also thoroughly searched major databases for meeting abstracts, including ASCO and ESMO Meeting Library. The searching process started at June 1st until August 12th of 2018, covering the possible trials published from inception to August 2018. Both abstract and main text of the retrieved entries were rigorously assessed in order to guarantee the accuracy of selection. Furthermore, in case of omission, the reference lists of nine previously published systematic reviews had also been reviewed and compared with ours (Badiani et al., 2015; Chan et al., 2017; Harvey, 2017; Iacovelli et al., 2014; Kim et al., 2013; Ter Veer et al., 2016; Zhang et al., 2016; Zheng et al., 2017; Zhu et al., 2017) (Table 4). The full search strategies were presented in Supplementary materials.

2.3. Selection criteria

Studies that met the following criteria were eligibly included: 1. PICOS: Participant (patients with locally advanced inoperable, recurrent or metastatic gastric cancer, including gastro-esophageal junction cancer), Intervention (second or further line systemic therapies with cytotoxic chemotherapies or targeted medications after previous treatments), Comparator (paclitaxel plus ramucirumab in second-line setting and placebo in refractory setting), Outcome (survival or safety analysis) and Study design (phase 2 and phase 3 randomized controlled trials); 2. Trials reported from inception to August 2018 without language limitations.

Studies were excluded from systematic review due to the following reasons: 1. Interim or repetitive reports from the same registered study (we only included the one with the longest follow-up period); 2. Crossover design.

2.4. 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. According to the criteria on Cochrane Handbook 5.1, each domain could be judged as any of the three levels, including low risk, unclear risk or high risk of bias. Results of each study and their scoring evidences were described in eTable 2. 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.

2.5. Data extraction

Pre-designed forms were utilized to collect and organize the original data. General information, survival and safety data were extracted from main text, tables, survival curves or supplementary materials, which had been cross-checked by two different investigators in our team before quantitative incorporations. For different purposes, general data or subgroup data (such as the second-line only data from studies reporting both second-line and refractory treatments) were specifically extracted.

2.6. Baseline parameters and endpoints

All possible baseline parameters that could influence the clinical characteristics of each study were included and analyzed in our systematic review. 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 took charge of the project. Age referred to the median age of overall population. Here, population referred to the source region of patients that had been analyzed in the studies. Western population covered patients from West Europe, North America and Australia, while eastern population referred to those living in East Asia countries including Japan, South Korea and China. If the study contained both western and eastern population, or patients from other area in the world (such as South America), it was regarded as versatile population. Pathological specificity suggested whether there was a requirement of specific target positivity among recruited patients. Visceral involvement suggested the metastatic involvement of liver and lung. More details of baseline parameters were listed in Table 1.

The primary endpoint was overall survival, while secondary endpoints included progression-free survival, objective response rate, hematological adverse events and non-hematological adverse events. Generally, overall survival and progression-free survival 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 (eTable 1). Objective response rate equaled 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 defined as non-hematological adverse events. We only counted grade 3 or higher (National Cancer Institute Common Terminology Criteria for Adverse Events) adverse events due to their clinical significances.

2.7. Statistical analysis

Our systematic review contained both narrative and quantitative analysis. Those trials with high homogeneity as well as adequate original data were incorporated into network meta-analysis. Hazard ratio (HR) and its 95% confidential interval (95% CI) were used as the effect size for overall survival (OS) and progression-free survival (PFS). Risk ratio (RR) and its 95% CI were applied as the effect size for objective response rate (ORR), hematological and non-hematological adverse events. If survival data or its confidential interval was not directly provided, we estimated the values from Kaplan-Meier curves by methods described elsewhere (Tierney et al., 2007). 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. This key feature reflected on and highlighted the two fundamental assumptions of network meta-analysis, known as transitivity and consistency.

When the head-to-head results of A versus C and B versus C were respectively gained, then the hypothesis of transitivity also permitted a

Table 1
Baseline characteristics of eligible studies in systematic review.

Study	Leading country	Registration	Phase	Enrollment	Regimen	Administration	Sample size	Age	Gender (M/F)	Population	Pathological specificity
(Bang et al., 2018)	South Korea	NCT02625623	3	2015.12-2017.3	Avelumab	10 mg/kg IV on Day 1 every 2 weeks	185	59.0	140/45	Versatile	None
					Chemotherapy	Paclitaxel 80 mg/m2 IV on Days 1, 8 and 15 every 4 weeks or irinotecan 150 mg/m2 IV on Days 1 and 15 every 4 weeks	186	61.0	127/59		
(Shitara et al., 2018)	Japan	NCT02370498	3	2015.6-2016.7	Pembrolizumab	200 mg IV on Day 1 every 3 weeks	296	62.5	202/94	Versatile	None
					Paclitaxel	80 mg/m2 IV on Days 1, 8, and 15 every 4 weeks	296	60.0	208/88		
(Kang et al., 2018)	South Korea	NCT01839773	3	2013.4-2015.2	DHP107 (oral paclitaxel)	200 mg/m2 twice daily PO on Days 1, 8, and 15 every 4 weeks	118	59.0	91/27	Eastern	None
					Paclitaxel	175 mg/m2 IV on Day 1 every 3 weeks	118	59.0	94/24		
(Makiyama et al., 2018)	Japan	UMIN000009297	2	2012.12-2016.10	Paclitaxel	80 mg/m2 IV on Days 1, 8, and 15 every 4 weeks	45	> 20	NA	Eastern	HER2 positive
					Paclitaxel plus trastuzumab	Paclitaxel: 80 mg/m2 IV on Days 1, 8, and 15 every 4 weeks; Trastuzumab: Initial 8 mg/kg followed by 6 mg/kg IV on Day 1 every 3 weeks	44				
(Van Cutsem et al., 2017)	Belgium	NCT01457846	2	NA	AZD4547	80 mg twice daily PO on Day 1 to Day 14 every 3 weeks	41	60.6	29/12	Versatile	FGFR2 positive
					Paclitaxel	80 mg/m2 IV on Days 1, 8, and 15 every 4 weeks	30	61.9	22/8		
(Bang et al., 2017)	South Korea	NCT01924533	3	2013.9-2016.3	Paclitaxel plus olaparib	Paclitaxel: 80 mg/m2 IV on Days 1, 8, and 15 every 4 weeks; Olaparib: 100 mg twice daily PO on Day 1 to Day 28 every 4 weeks	263	58.0	174/89	Eastern	None
					Paclitaxel	Paclitaxel: 80 mg/m2 IV on Days 1, 8, and 15 every 4 weeks; Placebo: 100 mg twice daily PO on Day 1 to Day 28 every 4 weeks	262	59.0	185/77		
(Hwang et al., 2017)	Japan	NCT02267343	3	2014.11-2016.2	Nivolumab	3 mg/kg IV on Day 1 every 2 weeks	330	62	229/101	Eastern	None
					Placebo	3 mg/kg IV on Day 1 every 2 weeks	163	61	119/44		
(Shitara et al., 2017)	Japan	JapicCTI-132059	3	2013.3-2015.5	Nab-paclitaxel-q3w	260 mg/m2 IV on Day 1 every 3 weeks	243	66.0	178/65	Eastern	None
					Nab-paclitaxel-qw	100 mg/m2 IV on Days 1, 8, and 15 every 4 weeks	240	67.0	178/62		
					Paclitaxel	80 mg/m2 IV on Days 1, 8, and 15 every 4 weeks	243	65.0	176/67		
(Thuss-Patience et al., 2017)	South Korea	NCT01641939	3	2012.9-2013.10	Trastuzumab emtansine	2.4 mg/kg IV on Day 1 weekly	228	62.0	177/51	Versatile	HER2 positive
					Taxane	Docetaxel: 75 mg/m2 IV on Day 1 every 3 weeks; Paclitaxel: 80 mg/m2 IV on Days 1, 8, and 15 every 3 weeks	117	62.0	95/22		
(Lee et al., 2017)	South Korea	NCT00980603	2	2008.11-2012.9	Docetaxel plus S-1	Docetaxel: 60 mg/m2 IV on Day 1 every 3 weeks; S-1: 30 mg/m2 twice daily PO on Day 1 to Day 14 every 3 weeks	23	55.0	14/9	Eastern	None
					Docetaxel plus cisplatin	Each 60 mg/m2 IV on Day 1 every 3 weeks	23	55.0	20/3		
					Docetaxel	75 mg/m2 IV on Day 1 every 3 weeks	23	56.0	18/5		
(Al-Batran et al., 2017)	Germany	NCT01248403	3	NA	Paclitaxel plus everolimus	Paclitaxel: 80 mg/m2 IV on Days 1, 8 and 15 every 4 weeks; Everolimus: 10 mg PO on Day 1 to Day 28 every 4 weeks	150	62.0	NA	Western	None
					Paclitaxel	Paclitaxel: 80 mg/m2 IV on Days 1, 8 and 15 every 4 weeks; Placebo: 10 mg PO on Day 1 to Day 28 every 4 weeks	150				

(*continued on next page*)

Table 1 (*continued*)

Study	Leading country	Registration	Phase	Enrollment	Regimen	Administration	Sample size	Age	Gender (M/F)	Population	Pathological specificity
(Moehler et al., 2016)	Germany	NCT01020630	2	NA	5-FU plus irinotecan plus leucovorin plus sunitinib	Irinotecan 180 mg/m2 IV on Day 1, followed by 5-FU 400 mg/m2 IV and 46 h leucovorin 400 mg/m2 plus 5-FU 2000 mg/m2 IV every two weeks; Sunitinib: 25 mg PO on Day 1 to Day 28 every 6 weeks	45	62.0	33/12	Western	None
					5-FU plus irinotecan plus leucovorin	Irinotecan 180 mg/m2 IV on Day 1, followed by 5-FU 400 mg/m2 IV and 46 h leucovorin 400 mg/m2 plus 5-FU 2000 mg/m2 IV every two weeks; Placebo: 25 mg PO on Day 1 to Day 28 every 6 weeks	45	57.0	30/15		
(Tebbutt et al., 2016)	Australia	ANZCT-R12612000239864	2	2012.11-2014.2	Regorafenib	160 mg PO on Day 1 to Day 21 every 4 weeks	97	63.0	78/19	Versatile	None
					Placebo plus BSC	160 mg PO on Day 1 to Day 21 every 4 weeks	50	62.0	40/10		
(Li et al., 2016)	China	NA	3	2011.1-2012.11	Apatinib-850	850 mg PO Day 1 to Day 28 every 4 weeks	176	58	132/44	Eastern	None
					Placebo	850 mg PO Day 1 to Day 28 every 4 weeks	91	58	69/22		
(Nakanishi et al., 2016)	Japan	NA	2	2007.10-2013.12	Paclitaxel plus S-1	Paclitaxel: 50 mg/m2 IV on Days 1 and 8 every 3 weeks; S-1: 80 mg/m2 PO on Day 1 to Day 14 every 3 weeks	38	64.0	29/9	Eastern	None
					Paclitaxel	80 mg/m2 IV on Days 1, 8, and 15 every 4 weeks	40	62.0	34/6		
(Bang et al., 2015)	South Korea	NCT01063517	2	2010.2-2012.5	Paclitaxel plus olaparib	Paclitaxel: 80 mg/m2 IV on Days 1, 8, and 15 every 4 weeks; Olaparib: 100 mg twice daily PO on Day 1 to Day 28 every 4 weeks	62	63.0	49/13	Eastern	None
					Paclitaxel	Paclitaxel: 80 mg/m2 IV on Days 1, 8, and 15 every 4 weeks; Placebo: 100 mg twice daily PO on Day 1 to Day 28 every 4 weeks	62	60.5	44/18		
(Tanabe et al., 2015)	Japan	NCT00639327	2-3	2008.2-2011.5	Irinotecan plus S-1	Irinotecan: 150 mg/m2 IV on Day 1 every 3 weeks; S-1: 40-60 mg/m2 twice daily PO on Day 1 to Day 14 every 3 weeks	145	67.0	99/46	Eastern	None
					Irinotecan	150 mg/m2 IV on Day 1 every 2 weeks	148	66.0	109/39		
(Kim et al., 2015)	South Korea	NA	2	2009.1-2012.1	Docetaxel	36 mg/m2 IV on Days 1 and 8 every 3 weeks	27	54.0	24/3	Eastern	None
					Docetaxel plus oxaliplatin	Docetaxel: 36 mg/m2 IV on Days 1 and 8 every 3 weeks; Oxaliplatin: 80 mg/m2 IV on Day 1 every 3 weeks	25	59.0	18/7		
(Nishikawa et al., 2015a)	Japan	UMIN000002571	3	2007.7-2011.12	Irinotecan plus cisplatin	Irinotecan: 60 mg/m2 IV on Day 1 every 2 weeks; Cisplatin: 30 mg/m2 IV on Day 1 every 2 weeks	84	67.0	68/16	Eastern	None
					Irinotecan	150 mg/m2 IV on Day 1 every 2 weeks	84	68.0	63/21		
(Nishikawa et al., 2015b)	Japan	UMIN000000677	2	2008.7-2012.3	Irinotecan	150 mg/m2 IV on Day 1 every 2 weeks	42	65.0	30/12	Eastern	None
					Paclitaxel	80 mg/m2 IV on Days 1, 8, and 15 every 4 weeks	43	65.0	35/8		
					Irinotecan plus S-1	Irinotecan: 80 mg/m2 IV on Days 1 and 15 every 5 weeks; S-1: 80 mg/m2 PO on Day 1 to Day 21 every 5 weeks	22	67.0	15/7		
					Paclitaxel plus S-1	Paclitaxel: 50 mg/m2 IV on Days 1 and 8 every 3 weeks; S-1: 80 mg/m2 PO on Day 1 to Day 14 every 3 weeks	20	63.0	12/8		

(*continued on next page*)

Table 1 (*continued*)

Study	Leading country	Registration	Phase	Enrollment	Regimen	Administration	Sample size	Age	Gender (M/F)	Population	Pathological specificity
(Lorenzen et al., 2015)	Germany	NCT01145404	2	2010.12-2013.2	Capecitabine plus lapatinib	Capecitabine: 1000 mg/m2 twice daily PO on Day 1 to Day 14 every 3 weeks; Lapatinib: 1250 mg PO on Day 1 to Day 21 every 3 weeks	18	56.0	17/1	Western	HER2 positive
					Lapatinib	1500 mg PO on Day 1 to Day 21 every3 weeks	19	62.0	14/5		
(Satoh et al., 2015)	South Korea	JapicCTI090849	2	2008.9-2009.12	Irinotecan plus nimotuzumab	Irinotecan: 150 mg/m2 IV on Day 1 every 2 weeks; Nimotuzumab: 400 mg IV on Day 1 weekly	40	60.0	33/7	Eastern	None
					Irinotecan	150 mg/m2 IV on Day 1 every 2 weeks	42	63.5	33/9		
(Wilke et al., 2014)	Germany	NCT01170663	3	2010.12-2012.9	Paclitaxel plus ramucirumab	Paclitaxel: 80 mg/m2 IV on Days 1, 8, and 15 every 4 weeks; Ramucirumab: 8 mg/kg IV on Days 1, 15 every 4 weeks	330	61.0	229/101	Versatile	None
					Paclitaxel	Paclitaxel: 80 mg/m2 IV on Days 1, 8, and 15 every 4 weeks; Placebo: 8 mg/kg IV on Days 1, 15 every 4 weeks	335	61.0	243/92		
(Satoh et al., 2014)	South Korea	NCT00486954	3	2008.3-2012.1	Paclitaxel plus lapatinib	Paclitaxel: 80 mg/m2 IV on Days 1, 8, and 15 every 4 weeks; Lapatinib: 1500 mg PO on Day 1 to Day 28 every 4 weeks	132	60.8	101/31	Eastern	HER2 positive
					Paclitaxel	80 mg/m2 IV on Days 1, 8, and 15 every 4 weeks	129	60.4	106/23		
(Higuchi et al., 2014)	Japan	UMIN000001028	3	2008.4-2011.7	Irinotecan plus cisplatin	Irinotecan: 60 mg/m2 IV on Day 1 every 2 weeks; Cisplatin: 30 mg/m2 IV on Day 1 every 2 weeks	64	66.0	49/15	Eastern	None
					Irinotecan	150 mg/m2 IV on Day 1 every 2 weeks	63	67.0	55/8		
(Ford et al., 2014)	UK	ISRCTN13366390	3	2008.4-2012.4	Docetaxel	75 mg/m2 IV on Day 1 every 3 weeks	84	65.0	69/15	Western	None
					BSC	NA	84	66.0	67/17		
(Fuchs et al., 2014)	USA	NCT00917384	3	2009.10-2012.1	Ramucirumab	8 mg/kg IV on Day 1 every 2 weeks	238	60.0	169/69	Versatile	None
					Placebo plus BSC	8 mg/kg IV on Day 1 every 2 weeks	117	60.0	79/38		
(Hironaka et al., 2013)	Japan	UMIN000001252	3	2007.8-2010.8	Irinotecan	150 mg/m2 IV on Days 1 and 15 every 4 weeks	111	65.0	87/24	Eastern	None
					Paclitaxel	80 mg/m2 IV on Days 1, 8, and 15 every 4 weeks	108	64.5	84/24		
(Ohtsu et al., 2013)	Japan	NCT00879333	3	2009.7-2010.11	Everolimus	10 mg PO every day	439	62.0	322/117	Versatile	None
					Placebo plus BSC	10 mg PO every day	217	62.0	161/56		
(Li et al., 2013)	China	NCT00970138	2	2009.6-2010.10	Apatinib-425	425 mg twice daily PO Day 1 to Day 28 every 4 weeks	46	53	34/12	Eastern	None
					Apatinib-850	850 mg PO Day 1 to Day 28 every 4 weeks	47	55	39/8		
					Placebo	850 mg PO Day 1 to Day 28 every 4 weeks	48	54	36/12		
(Roy et al., 2013)	UK	NCT00813072	2	2008.1-2010.6	PEP02 (liposomal irinotecan)	120 mg/m2 IV on Day 1 each cycle	44	56.0	35/9	Versatile	None
					Irinotecan	300 mg/m2 IV on Day 1 each cycle	44	62.0	34/10		
					Docetaxel	75 mg/m2 IV on Day 1 each cycle	44	58.0	34/10		
(Sym et al., 2013)	South Korea	NA	2	2007.3-2009.12	Irinotecan	150 mg/m2 IV on Day 1 every 2 weeks	29	60.0	20/9	Eastern	None
					5-FU plus irinotecan plus leucovorin	Irinotecan 150 mg/m2 IV plus leucovorin 20 mg/m2 IV followed by 5-FU 2000 mg/m2 IV every 2 weeks	30	61.0	14/16		
(Yi et al., 2012)	South Korea	NCT01238055	2	2008.12-2011.2	Docetaxel plus sunitinib	Docetaxel: 60 mg/m2 IV on Day 1 every 3 weeks; Sunitinib: 37.5 mg PO every day	56	54.0	40/16	Eastern	None
					Docetaxel	60 mg/m2 IV on Day 1 every 3 weeks	49	52.0	33/16		

(*continued on next page*)

Table 1 (*continued*)

Study	Leading country	Registration	Phase	Enrollment	Regimen	Administration	Sample size	Age	Gender (M/F)	Population	Pathological specificity
(Kang et al., 2012)	South Korea	NCT00821990	3	2008.9-2010.9	Chemotherapy	Docetaxel 60 mg/m2 IV on Day 1 every 3 weeks or irinotecan 150 mg/m2 IV on Day 1 every 2 weeks	133	56.0	93/40	Eastern	None
					BSC	NA	69	56.0	44/25		
(Thuss-Patience et al., 2011)	Germany	NCT00144378	3	2002.10-2006.12	Irinotecan	250 mg/m2 IV on Day 1 every 3 weeks	21	58.0	18/3	Western	None
					BSC	NA	19	55.0	11/8		
(Maruta et al., 2007)	Japan	NA	2	2004.1-2005.12	Docetaxel	60 mg/m2 IV on Day 1 every 3 weeks	12	64.8	9/3	Eastern	None
					Docetaxel plus doxifluridine	Docetaxel: 60 mg/m2 IV on Day 1 every 3 weeks; Doxifluridine: 600 mg PO every day	12	61.3	9/3		

Study	Level of treatment	First-line regimen	Metastasis (Y/N)	Visceral involvement (Y/N)	Peritoneal involvement (Y/N)	Measurability (Y/N)	PS (0/1/2)	Location (G/J)	Histological type (I/D)	Ratio of subsequent therapy	Journal
(Bang et al., 2018)	Third line	NA	Advanced	NA	NA	135/50	66/119/0	122/63	Comparable	58/185	Ann Oncol
						141/45	62/124/0	138/48		70/186	
(Shitara et al., 2018)	Second line	Fluoropyrimidine plus platinum	292/4	NA	82/214	NA	127/169/0	207/89	44/85	136/296	Lancet
			294/2		84/212		137/158/1	200/96	74/65	171/296	
(Kang et al., 2018)	Second line	Fluoropyrimidine monotherapy or fluoropyrimidine plus platinum	96/22	57/61	42/76	Measurable	**116/2**	Gastric	NA	NA	Ann Oncol
			94/24	63/55	46/72		**117/1**				
(Makiyama et al., 2018)	Second line	Fluoropyrimidine plus platinum plus trastuzumab	Advanced	NA	NA	Measurable or evaluable	0-2	Gastric and junction	NA	NA	J Clin Oncol
(Van Cutsem et al., 2017)	Second line	Fluoropyrimidine plus platinum	40/1	35/6	8/33	38/3	NA	Gastric and junction	NA	NA	Ann Oncol
			30/0	20/10	10/20	30/0					
(Bang et al., 2017)	Second line	Fluoropyrimidine plus platinum doublet	260/3	NA	NA	183/78	117/145/0	250/12	111/107	NA	Lancet Oncol
			254/8			177/83	107/154/0	259/2	106/123		
(Hwang et al., 2017)	Third or further line	Versatile	Advanced	96/234	63/267	268/62	95/235/0	272/30	120/106	155/330	Lancet
				34/129	42/121	131/32	48/115/0	135/12	55/63	72/163	
(Shitara et al., 2017)	Second line	Fluoropyrimidine monotherapy or fluoropyrimidine plus platinum	Advanced	NA	131/112	150/93	167/72/4	Gastric	103/140	Roughly 70% in each arm	Lancet Gastroenterol Hepatol
					131/109	150/90	168/70/2		103/137		
					130/113	169/74	168/71/4		110/132		
(Thuss-Patience et al., 2017)	Second line	Fluoropyrimidine plus platinum plus trastuzumab	218/10	142/86	NA	204/24	99/128/0	151/77	88/43	117/228	Lancet Oncol
			113/4	77/40		102/15	43/73/1	84/33	49/12	65/117	
(Lee et al., 2017)	Second line	Fluoropyrimidine plus cisplatin doublet	18/5	8/15	8/15	Measurable	1/20/2	Gastric	Comparable	13/23	Cancer Res Treat
			18/5	9/14	11/12		1/20/2			12/23	
			22/1	9/14	9/14		2/21/0			19/23	
(Al-Batran et al., 2017)	Second or further line	Fluoropyrimidine plus platinum	Advanced	NA	NA	Measurable or evaluable	0-2	Gastric and junction	NA	NA	J Clin Oncol
(Moehler et al., 2016)	Second or further line	Docetaxel based or platinum based	Metastatic	NA	NA	Measurable	0-2	22/23	NA	NA	BMC Cancer
								23/20			
(Tebbutt et al., 2016)	Second or further line	Fluoropyrimidine plus platinum	96/1	68/29	28/69	Measurable	41/56/0	60/37	NA	33/93	J Clin Oncol
			48/2	41/9	19/31		21/29/0	31/19		36/54	
(Li et al., 2016)	Third or further line	NA	Advanced	NA	43/133	Measurable	48/128/0	69/22	NA	NA	J Clin Oncol
					25/66		15/76/0	43/14			
(Nakanishi et al., 2016)	Second line	S-1 monotherapy and S-1 plus cisplatin	71/7	7/31	21/17	18/20	30/7/1	Gastric	18/20	17/38	Int J Clin Oncol
				10/30	19/21	15/25	31/6/3		20/20	17/40	
(Bang et al., 2015)	Second line	Fluoropyrimidine plus platinum	Advanced	19/43	26/36	53/9	32/30/0	Gastric	Comparable	30/62	J Clin Oncol
				24/38	27/35	47/15	28/32/2			27/62	
(Tanabe et al., 2015)	Second line	S-1 monotherapy and doublet	Advanced	64/81	36/109	118/27	117/28/0	Gastric and junction	Comparable	81/145	Ann Oncol
				62/86	43/105	122/26	116/32/0			91/148	

(*continued on next page*)

Table 1 (*continued*)

Study	Level of treatment	First-line regimen	Metastasis (Y/N)	Visceral involvement (Y/N)	Peritoneal involvement (Y/N)	Measurability (Y/N)	PS (0/1/2)	Location (G/J)	Histological type (I/D)	Ratio of subsequent therapy	Journal
(Kim et al., 2015)	Second line	Fluoropyrimidine plus cisplatin	Advanced 17/8	19/8 9/16	11/16 9/16	Measurable	5/21/1 3/21/1	Gastric	NA	11/27 10/25	Anticancer Res
(Nishikawa et al., 2015a)	Second line	S-1 monotherapy	66/18 71/13	115/53	163/5	66/18 70/14	68/16/0 68/16/0	Gastric	46/38 38/46	58/84 55/84	Eur J Cancer
(Nishikawa et al., 2015b)	Second line	S-1 monotherapy and S-1 plus platinum	Advanced	NA	NA	NA	**42/0** **41/2** **21/1** **20/0**	Gastric	NA	NA	J Clin Oncol
(Lorenzen et al., 2015)	Second line	Fluoropyrimidine plus platinum	Metastatic	NA	NA	Measurable	8/8/2 10/8/1	5/9 10/6	9/3 10/2	NA	Eur J Cancer
(Satoh et al., 2015)	Second line	5-FU based	Metastatic	16/24 25/17	NA	38/2 39/3	19/21/0 17/25/0	36/4 41/1	Comparable	NA	Gastric Cancer
(Wilke et al., 2014)	Second line	Fluoropyrimidine plus platinum	Advanced	NA	163/167 152/183	267/63 273/62	117/213/0 144/191/0	264/66 264/71	145/115 135/133	158/330 154/335	Lancet Oncol
(Satoh et al., 2014)	Second line	5-FU plus cisplatin	87/45 80/49	3/258	NA	Measurable	60/72/0 48/81/0	Gastric	56/44 54/44	NA	J Clin Oncol
(Higuchi et al., 2014)	Second line	S-1 monotherapy and doublet	44/20 40/23	NA	13/51 20/43	Measurable or evaluable	44/20/0 43/20/0	Gastric	32/32 32/31	48/64 47/63	Eur J Cancer
(Ford et al., 2014)	Second line	Fluoropyrimidine plus platinum	73/11 74/10	63/21 54/30	NA	66/17 64/19	24/46/14 22/50/12	39/27 37/32	NA	NA	Lancet Oncol
(Fuchs et al., 2014)	Second line	Fluoropyrimidine based or fluoropyrimidine plus platinum	Advanced	NA	64/174 45/72	218/20 106/11	67/171/0 31/85/1	178/60 87/30	52/96 35/44	75/238 46/117	Lancet
(Hironaka et al., 2013)	Second line	Fluoropyrimidine plus platinum doublet	Metastatic	NA	28/83 28/80	88/23 91/17	**107/4** **104/4**	Gastric	54/57 54/54	80/111 97/108	J Clin Oncol
(Ohtsu et al., 2013)	Second or further line	Fluoropyrimidine based or fluoropyrimidine plus platinum	Advanced	282/157 146/71	NA	379/60 192/25	144/269/25 70/120/27	321/118 148/69	Comparable	172/439 98/217	J Clin Oncol
(Li et al., 2013)	Third or further line	Fluoropyrimidine plus platinum	45/1 43/4 48/0	31/15 33/14 32/16	4/42 4/43 6/42	Measurable	2/44/0 3/44/0 1/47/0	Gastric and junction	NA	NA	J Clin Oncol
(Roy et al., 2013)	Second line	NA	43/1 40/4 43/1	NA	NA	Measurable	**41/3** **41/3** **40/4**	37/7 35/9 30/14	NA	NA	Ann Oncol
(Sym et al., 2013)	Second line	Platinum based	19/10 17/13	10/19 13/17	16/13 17/13	NA	**27/2** **27/3**	27/2 27/3	NA	NA	Cancer Chemother Pharmacol
(Yi et al., 2012)	Second line	Fluoropyrimidine plus platinum	47/9 47/2	29/27 21/28	17/39 22/27	Measurable or evaluable	2/28/6 3/43/3	Gastric and junction	NA	NA	Br J Cancer

(*continued on next page*)

Table 1 (*continued*)

Study	Level of treatment	First-line regimen	Metastasis (Y/N)	Visceral involvement (Y/N)	Peritoneal involvement (Y/N)	Measurability (Y/N)	PS (0/1/2)	Location (G/J)	Histological type (I/D)	Ratio of subsequent therapy	Journal
(Kang et al., 2012)	Second or further line	Fluoropyrimidine plus platinum	Metastatic	42/91 33/36	56/77 35/34	92/41 47/22	72/61/0 36/33/0	Gastric	NA	53/133 15/69	J Clin Oncol
(Thuss-Patience et al., 2011)	Second line	Fluoropyrimidine plus platinum	Metastatic	12/9 10/9	9/12 9/10	Measurable or evaluable	**17/4** **14/5**	12/9 11/8	5/14 3/13	NA	Eur J Cancer
(Maruta et al., 2007)	Second line	S-1 monotherapy and S-1 plus cisplatin	8/4 6/6	6/6 3/9	3/9 2/10	Measurable or evaluable	6/5/1 5/6/1	Gastric	Comparable	1/12 3/12	Med Oncol

Notes: Underlined data in PS (0/1/2) indicated that the numbers should be interpreted as PS (0 and 1) vs PS (2). The word "comparable" 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.
Abbreviations: BSC: best supportive care; NA: not available; IV: intravenous administration; PO: oral administration; M/F: male/female; Y/N: yes/no; G/J: gastric/junction; I/D: intestinal/diffused.

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. Both methodological designs (such as randomized controlled trials) and clinical features (such as pathological positivity, previous regimen and performance status) were crucial for assessment of transitivity. 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. I^2 static was the chief indicator of statistical heterogeneity, with its value < 25%, 25%–50% and > 50% indicating low, moderate and high heterogeneity respectively. Besides, Q static of heterogeneity and its P value also facilitated the assessment of statistical heterogeneity. If the P value of Q static was less than 0.05, it suggested that there was a significant heterogeneity within.

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 network calculations might indicate inconsistency within the network meta-analysis while also suggest the unsuitability for transitivity. Among closed loops of each network, we utilized a loop-specific method which assessed the mutual variance between direct and indirect results. Inconsistency factor (IF) was applied as the quantitative indicator which suggested the existence of inconsistency once its 95% confidence interval excluded zero. Meanwhile, Q static 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 basis 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.

A network plot and comparison-adjusted funnel plot were applied to display the network structure and examine the publication bias across the included trials respectively, where the more symmetrical it was, the less probability of publication bias the merged results would have. 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 for demonstrating the entire regimens with their relative confidential intervals. In addition, we also utilized P-score to rank all regimens based on their network estimates. The closer P-score approached 1, the best regimen it could be. Sensitivity analysis was performed to detect the stability of pooled outcomes, which included deleting studies with estimated hazard ratio from Kaplan-Meier curves and phase 2 randomized trials. Both pairwise and network meta-analysis were conducted on R software 3.4.3, assisted by STATA 14.0 in terms of graphical functions.

2.8. 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.

3. Results

3.1. Baseline characteristics

After screening through 2454 preliminary records, a total of 36 randomized controlled trials were eligibly included into our systematic review (eFig. 1), corresponding to 8436 participants. Overall, the median age was around 60 and the sex ratio was male dominant. Japan (n = 12), South Korea (n = 12) and Germany (n = 5) were the top

three leading countries. 22 studies were characterized by eastern population, while 5 and 9 trials featured western and versatile population respectively. Among 36 eligible trials, 27, 5, 1 and 3 studies reported second-line only, second and further line, third-line only as well as third and further line treatment respectively. The majority of trials recruited unselected patients in terms of pathological specificity (n = 31), while only a few investigations focused on HER2 (n = 4) and FGFR2 (n = 1) positive patients respectively. Moreover, patients from 30 studies received fluoropyrimidine-based first-line regimens and 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 (Table 1). Meanwhile, additional information including key definitions and evaluation criteria of eligible studies in our systematic review were listed in eTable 1.

3.2. Risk of bias

Overall, the included studies had low risk of bias since more than half of the assessment parameters were scored as low risk of bias (60%), while unclear risk (24%) or high risk of bias (16%) took up relatively small proportions (eFig. 2). None of the eligible studies were in high risk of bias concerning methodological design (eTable 2).

Specifically, since the majority of trials were centrally allocated and adequately randomized, 56% and 67% 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 open-label design, 69% of the include trials were scored as high risk of bias in terms of blinding or participants and personnel. Due to independent response reviewing, nearly half of the studies were assessed as low risk of bias in terms of blinding of outcome assessment (47%). In addition, because most of the studies were analyzed based on the intention-to-treat population as well as had reported enough endpoints, 89% and 83% 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, half of the studies were appraised as low risk of bias with respect to other source of bias (50%) (eFig. 2).

3.3. Second-line unselected patients with fluoropyrimidine-based first-line regimens

3.3.1. Primary endpoint (overall survival)

(Network geometry) There were totally 21 randomized controlled trials merged into the quantitative analysis, corresponding to 22 network nodes (eFig. 3 and Table 2).

(Network and pairwise calculation) Since paclitaxel plus ramucirumab was the standard second-line regimen, “PRa” was therefore selected as the common comparator. Based on P-score ranking of the network meta-analysis, “PO” (network HR 95%CI: 1.00 (0.70–1.28), P-score = 0.909) was the best ranking node, however which was nearly identical to common comparator “PRa” (network HR 1.00, P-score = 0.907). The network forest plot and league table were demonstrated in Figs. 1 and e5 respectively. Since no direct evidences between “PO” and “PRa” had been reported, this ranking was statistically generated by network estimation via the pairwise comparisons between “P” versus “PO” (random HR 95%CI: 1.34 (1.12–1.61)) and “P” versus “PRa” (random HR 95%CI: 1.34 (1.12–1.59)).

(Consistency and statistical heterogeneity) In addition to the insignificant value of Q static (Q-inconsistency: P = 0.970), the 95% confidence interval of IF by loop-specific method also indicated that the network was in high consistency (IF 95% CI 0.03 (0.00–1.57)), where the direct and indirect effect sizes in the loop were highly overlapped (eTable 3). In terms of statistical heterogeneity, both I^2 static (I^2 = 0%) and Q static (Q-heterogeneity: P = 0.302) implied that there was no significant heterogeneity across the network.

(Publication bias) There was no publication bias among the included studies due to symmetrical distribution of effect sizes inside the funnel plot (eFig. 4).

(Sensitivity analysis) Irrespective of removing studies with estimated hazard ratios from Kaplan-Meier curves (Kim et al., 2015; Lee et al., 2017; Maruta et al., 2007) or phase 2 trials (Bang et al., 2015; Kim et al., 2015; Lee et al., 2017; Maruta et al., 2007; Nakanishi et al., 2016; Satoh et al., 2015; Yi et al., 2012), both “PO” and “PRa” closely ranked as the top two nodes. Particularly, after excluding phase 2 trials, “PRa” was slightly better than “PO”, becoming the highest-ranking node in the entire hierarchy (eFigs. 6 and 7).

(Subgroup analysis) Although the entire network was in low heterogeneity, we still performed subgroup analyses to enhance the homogeneity in each subgroup network, which helped to examine the outcome stability as well as offer more specific clinical information (eTable 4). There were totally 6 subgroups, including fluoropyrimidine monotherapy, fluoropyrimidine plus platinum, eastern population, western population, performance status (0) and performance status (1). Due to insufficient studies to construct networks, we could not analyze the subgroup results of fluoropyrimidine monotherapy and western population in a quantitative way. As a result, “PO” was the top-ranking node with insignificant slight margin over “PRa” in subgroups of fluoropyrimidine plus platinum first-line regimen (eFig. 8), eastern population (eFig. 9) as well as performance status (0) (eFig. 10), while “PRa” reigned the hierarchy among patients with performance status (1) (eFig. 11).

3.3.2. Secondary endpoint

(Progression-free survival) Data from 12 studies were included into the pooled analysis (Table 2). “PRa” became the optimal node in the entire hierarchy (network HR 1.00, P-score = 0.983) and showed significant superiority against “PO” which ranked in the second place (network HR 95%CI: 1.39 (1.10–1.76), P-score = 0.701) (eFig. 12). Similarly, the network was in low heterogeneity (I^2 = 0%, Q-heterogeneity: P = 0.626; Unavailable for inconsistency assessment).

(Objective response rate) 13 studies were merged into the hierarchical comparison (Table 2). “PRa” again ranked in the first place for achieving objective response rate (network RR 1.00, P-score = 0.925), displaying insignificant superiority over “PO” (network RR 95%CI: 0.88 (0.54–1.42), P-score = 0.840) (eFig. 13). No significant heterogeneity and inconsistency were detected (I^2 = 0%, Q-heterogeneity: P = 0.873: Q-inconsistency: P = 0.494).

(Hematological adverse events) 13 studies were included into the network meta-analysis (Table 2). “Pe” was the most tolerable node in the ranking (network RR 95%CI: 0.09 (0.03-0.26), P-score = 1.000). Meanwhile, “PO” ranked in the middle of the hierarchy (network RR 95%CI: 0.80 (0.42–1.54), P-score = 0.434) and was slightly better than “PRa” (network RR 1.00, P-score = 0.267) (eFig. 14). “IC” versus “I” was the major cause of significant heterogeneity inside the network (I^2 = 65.64%, P = 0.027). After removing either study responsible for “IC” versus “I”, including Nishikawa 2015-1 (Nishikawa et al., 2015a) and (Higuchi et al., 2014), the overall heterogeneity reduced to low level (I^2 = 21.42%) and the relative ranking of nodes remained unchanged (data not shown).

(Non-hematological adverse events) A total of 13 studies were included into the network meta-analysis (Table 2). Again, “Pe” was the most tolerable node concerning non-hematological adverse events (network RR 95%CI: 0.42 (0.16–1.08), P-score = 0.942). Moreover, “PO” ranked in the third place (network RR 95%CI: 0.68 (0.32–1.45), P-score = 0.755) and was also slightly superior than “PRa” (network RR 1.00, P-score = 0.505) (eFig. 15). No significant heterogeneity or inconsistency were confirmed (I^2 = 37.39%, Q-heterogeneity: P = 0.290: Q-inconsistency: P = 0.082).

Table 2
Survival and safety data of studies featuring second-line systemic treatment among unselected patients with fluoropyrimidine-based first-line therapy.

Study	Regimen	Node	Sample size	Overall survival		Progression-free survival
				Hazard ratio	Network meta-analysis	Hazard ratio
Shitara et al. (2017)	Pembrolizumab	Pe	296	0.94 (95% CI, 0.79-1.12)	Included	1.49 (95% CI, 1.25-1.77)
	Paclitaxel	P	296			
Kang et al. (2018)	DHP107 (oral paclitaxel)	Dh	118	1.04 (95% CI, 0.76-1.41)	Included	0.85 (95% CI, 0.64-1.13)
	Paclitaxel	P	118			
Bang et al. (2017)	Paclitaxel plus olaparib	PO	263	0.79 (95% CI, 0.65-0.97)*	Included	0.84 (95% CI, 0.69-1.02)*
	Paclitaxel	P	262			
Shitara et al. (2017)	Nab-paclitaxel-q3w	N3	243	N3 vs P: 1.06 (95% CI, 0.87-1.31)	Included	N3 vs P: 1.03 (95% CI, 0.85-1.24)
	Nab-paclitaxel-qw	N1	240	N1 vs P: 0.97 (95% CI, 0.79-1.19)		N1 vs P: 0.88 (95% CI, 0.73-1.06)
	Paclitaxel	P	243			
Lee et al. (2017)	Docetaxel plus S-1	DS	23	**DS vs DC: 0.66 (95% CI, 0.29-1.50)**	Included	**DS vs DC: 0.85 (95% CI, 0.35-2.09)**
	Docetaxel plus cisplatin	DC	23	**DS vs D: 1.23 (95% CI, 0.48-3.19)**		**DS vs D: 0.88 (95% CI, 0.39-1.96)**
	Docetaxel	D	23	**DC vs D: 1.83 (95% CI, 0.76-4.43)**		**DC vs D: 0.69 (95% CI, 0.33-1.44)**
Tebbutt et al. (2016)	Regorafenib	R	41	NA	NA	0.49 (95% CI, 0.28-0.86)
	Placebo plus BSC	B	21			
Nakanishi et al. (2016)	Paclitaxel plus S-1	PS	38	0.83 (95% CI, 0.51-1.36)	Included	0.86 (95% CI, 0.54-1.37)
	Paclitaxel	P	40			
Bang et al. (2015)	Paclitaxel plus olaparib	PO	62	0.56 (95% CI, 0.35-0.87)	Included	0.80 (95% CI, 0.54-1.18)*
	Paclitaxel	P	62			
Tanabe et al. (2015)	Irinotecan plus S-1	IS	145	0.99 (95% CI, 0.78-1.25)	Included	0.85 (95% CI, 0.67-1.07)
	Irinotecan	I	148			
Kim et al. (2015)	Docetaxel	D	27	**0.88 (95% CI, 0.44-1.76)**	Included	**1.61 (95% CI, 0.75-3.47)**
	Docetaxel plus oxaliplatin	DOx	25			
Nishikawa et al. (2015a)	Irinotecan plus cisplatin	IC	84	0.83 (95% CI, 0.60-1.17)	Included	0.86 (95% CI, 0.62-1.20)
	Irinotecan	I	84			
Nishikawa et al. (2015b)	Irinotecan	I	42	NA	NA	NA
	Paclitaxel	P	43			
	Irinotecan plus S-1	IS	22			
	Paclitaxel plus S-1	PS	20			
Satoh et al. (2015)	Irinotecan plus nimotuzumab	IN	40	0.99 (95% CI, 0.62-1.60)	Included	0.86 (95% CI, 0.52-1.44)
	Irinotecan	I	42			
Wilke et al. (2014)	Paclitaxel plus ramucirumab	PRa	330	0.75 (95% CI, 0.63-0.89)	Included	0.60 (95% CI, 0.51-0.71)
	Paclitaxel	P	335			
Higuchi et al. (2014)	Irinotecan plus cisplatin	IC	64	1.00 (95% CI, 0.69-1.44)	Included	0.68 (95% CI, 0.47-0.98)
	Irinotecan	I	63			
Ford et al. (2014)	Docetaxel	D	84	0.71 (95% CI, 0.52-0.98)	Included	NA
	BSC	B	84			
Fuchs et al. (2014)	Ramucirumab	Ra	238	0.77 (95% CI, 0.61-0.99)	Included	0.50 (95% CI, 0.39-0.64)
	Placebo plus BSC	B	117			
Hironaka et al. (2013)	Irinotecan	I	111	1.13 (95% CI, 0.86-1.49)	Included	1.14 (95% CI, 0.88-1.49)
	Paclitaxel	P	108			
Ohtsu et al. (2013)	Everolimus	E	313	0.94 (95% CI, 0.73-1.23)	Included	NA
	Placebo plus BSC	B				
Yi et al. (2012)	Docetaxel plus sunitinib	DSu	56	0.94 (95% CI, 0.60-1.49)	Included	NA
	Docetaxel	D	49			

(*continued on next page*)

Table 2 (*continued*)

Study	Regimen	Node	Sample size	Overall survival		Progression-free survival
				Hazard ratio	Network meta-analysis	Hazard ratio
Kang et al. (2012)	Chemotherapy	Ch	100	0.62 (95% CI, 0.43-0.89)	Included	NA
	BSC	B	48			
Thuss-Patience et al. (2011)	Irinotecan	I	21	0.48 (95% CI, 0.25-0.92)	Included	NA
	BSC	B	19			
Maruta et al. (2007)	Docetaxel	D	12	**2.63 (95% CI, 0.27-25.27)**	Included	NA
	Docetaxel plus doxifluridine	DDo	12			

Study	Progression-free survival	Objective response rate		Hematological adverse events		Non-hematological adverse events	
	Network meta-analysis	Response/total	Network meta-analysis	Event/total	Network meta-analysis	Event/total	Network meta-analysis
Shitara et al. (2017)	Included	33/296 37/296	Included	7/294 40/276	Included	21/294 33/276	Included
Kang et al. (2018)	Included	22/118 20/118	Included	96/118 104/118	Included	33/118 30/118	Included
Bang et al. (2017)	Included	44/263 28/262	Included	232/262-5 146/259-5	Included	124/262 101/259	Included
Shitara et al. (2017)	Included	38/150 49/150 41/169	Included	235/244-2 152/241-2 109/243-2	Included	107/244 31/241 23/243	Included
Lee et al. (2017)	**Not included**	2/23 1/23 1/23	**Not included**	6/23 12/24 12/23	**Not included**	12/23 14/24 10/23	**Not included**
Tebbutt et al. (2016)	**Not included**	NA	NA	NA	NA	NA	NA
Nakanishi et al. (2016)	Included	4/18 4/15	Included	15/38 15/40	Included	12/38 12/40	Included
Bang et al. (2015)	Included	14/53 9/47	Included	41/61 31/62	Included	10/61 17/62	Included
Tanabe et al. (2015)	Included	9/118 9/122	Included	120/145 59/149	Included	52/145 56/149	Included
Kim et al. (2015)	**Not included**	4/27 6/25	**Not included**	0/27 13/25	**Not included**	2/27 4/25	**Not included**
Nishikawa et al. (2015a)	Included	11/65 10/65	Included	52/82 28/81	Included	20/82 29/81	Included
Nishikawa et al. (2015b)	NA	3/42 7/43 1/22 1/20	Included	17/42-2 10/43-2 6/22-2 5/20-2	Included	7/42-3 2/43-3 7/22-3 2/20-3	Included
Satoh et al. (2015)	Included	7/38 4/39	Included	32/40 26/42	Included	31/40 27/42	Included
Wilke et al. (2014)	Included	92/330 54/335	Included	225/327 124/329	Included	265/327 186/329	Included
Higuchi et al. (2014)	Included	14/64 10/63	Included	35/64 40/66	Included	12/64 19/66	Included
Ford et al. (2014)	NA	NA	NA	25/81 6/74	**Not included**	77/81 65/74	**Not included**
Fuchs et al. (2014)	**Not included**	8/238 3/117	**Not included**	15/236 9/115	**Not included**	89/236 51/115	**Not included**
Hironaka et al. (2013)	Included	12/88 19/91	Included	109/110 80/108	Included	65/110 36/108	Included

(*continued on next page*)

Table 2 (*continued*)

Study	Progression-free survival	Objective response rate		Hematological adverse events		Non-hematological adverse events	
	Network meta-analysis	Response/total	Network meta-analysis	Event/total	Network meta-analysis	Event/total	Network meta-analysis
Ohtsu et al. (2013)	NA	NA	NA	NA	NA	NA	NA
Yi et al. (2012)	NA	23/56	**Not included**	53/56	**Not included**	9/56	**Not included**
		7/49		32/49		2/49	
Kang et al. (2012)	NA	NA	NA	NA	NA	NA	NA
Thuss-Patience et al. (2011)	NA	NA	NA	NA	NA	NA	NA
Maruta et al. (2007)	NA	2/12	**Not included**	10/12	**Not included**	4/12	**Not included**
		5/12		8/12		1/12	

Abbreviations: CI: confidence interval; NA: not available.

Naming rules for nodes: Pembrolizumab: Pe; Paclitaxel: P; DHP107: Dh; Olaparib: O; Nab-paclitaxel-q3w: N3; Nab-paclitaxel-qw: N1; Docetaxel: D; S-1: S; Cisplatin: C; Regorafenib: R; Placebo plus BSC or BSC: B; Irinotecan: I; Oxaliplatin: Ox; Nimotuzumab: N; Ramucirumab: Ra; Everolimus: E; Sunitinib: Su; Chemotherapy: Ch; Doxifluridine: Do.

Notes: The asterisked hazard ratio with 95% CI of Bang 2017 and Bang 2015 were transformed from 97.5% CI and 80% CI respectively. The bold-type and underlined hazard ratios were estimated from Kaplan-Meier curves. "Not included" suggested that these data were not included into the specific network calculations due to failure of forming a single network (Since a complete network could not be formed in terms of progression-free survival, objective response rate, hematological and non-hematological adverse events, the network calculations were based on their largest sub-networks accordingly, which were constructed by paclitaxel and irinotecan related trials). 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. Specifically, anemia, neutropenia, leucopenia, neutrophil count decreased and white blood cell count decreased were selected for Bang 2017, neutropenia and leucopenia were selected for Shitara 2017 as well as leukopenia, neutropenia, nausea, diarrhea and fatigue for Nishikawa 2015-2.

3.4. Second-line HER2 positive patients

A total of 4 trials were eligible, consisting of 732 patients. Each study only recruited patients with histologial positivity of HER2 based on pathological reports. In terms of survival efficacies, among patients with trastuzumab-free first-line regimens, neither capecitabine plus lapatinib (HR 95%CI: 1.06 (0.34–3.29)) nor paclitaxel plus lapatinib (HR 95%CI: 0.84 (0.64–1.11)) surpassed their corresponding monotherapies lapatinib and paclitaxel respectively (eTable 5). Similarly, despite of adding trastuzumab into first-line regimens, trastuzumab-based second-line regimens failed to gain significant survival superiority over taxane monotherapy (HR 95%CI: 1.23 (0.75–1.99) and 1.15 (0.87–1.51) respectively) (eTable 5). However, it was noteworthy that paclitaxel plus lapatinib was significantly better than paclitaxel among patients with greater HER2 positivity (IHC3+, n = 101, HR 95%CI: 0.59 (0.37-0.93)) (Satoh et al., 2014). In addition, all doublets were comparable to monotherapies regarding adverse events (eTable 5).

3.5. Refractory unselected patients (previously treated by at least two-lines of systemic regimens)

(Overall survival) 6 studies were included into the network calculation (Table 3). The pooled results were in low inconsistency however significant heterogeneity (I^2 = 73.02%, Q-heterogeneity: P = 0.028, Q-inconsistency: P = 0.109). "A8" was the best ranking node (network HR 95%CI: 0.49 (0.29-0.84), P-score = 0.795) and the only one that was significantly better than common comparator "B" (Fig. 2). After removing the source of heterogeneity (Li 2016 (Li et al., 2016)) from the calculation, the systemic heterogeneity level significantly reduced (I^2 = 0%) and "A8" remained as the top node with even more advantage (network HR 95%CI: 0.35 (0.23-0.54), P-score = 0.965).

(Overall survival for third-line only) 5 randomized controlled trials were merged into the pooled analysis (Table 3). Again, "A8" topped the ranking as the best node (network HR 95%CI: 0.70 (0.49-0.99), P-score = 0.793) without detecting any systemic heterogeneity (I^2 = 0%), which was significantly better than common comparator "B" (eFig. 16).

(Secondary endpoints) In terms of progression-free survival, "A4" and "A8" closely ranked as the top two nodes in the hierarchy, both of which were significantly superior to "B" (eFig. 17). However, regarding objective response rate, "N" reigned the entire hierarchy by surpassing both "A4" as well as "A8", all of which were significantly better than common comparator "B" (eFig. 18). Moreover, "A8" was the most tolerable node and slightly better than "B" concerning hematological adverse events (eFig. 19) however significantly worse than common comparator in terms of non-hematological adverse events (eFig. 20).

4. Discussion

Due to high failure rate among advanced gastric cancer patients who receive systemic treatments, salvage second-line or refractory systemic regimens have become more and more inevitable and thus drawn significant academic attentions currently. However, all of the previously published systematic reviews are insufficient to cover this field properly or convincingly, either due to inadequate literature retrieval or heterogeneous and incorrect quantitative approaches (Table 4). Our systematic review was by far the most comprehensive summary of systemic therapies for previously treated advanced gastric cancer, especially by utilizing quantitative network meta-analysis, which was based on high clinical homogeneity and reliable statistical methods.

For second-line unselected patients with fluoropyrimidine-based first-line regimens, "PO" (paclitaxel plus olaparib) and "PRa" (paclitaxel plus ramucirumab) dominated the overall survival ranking. Meanwhile, the sensitivity analyses also verified the general results,

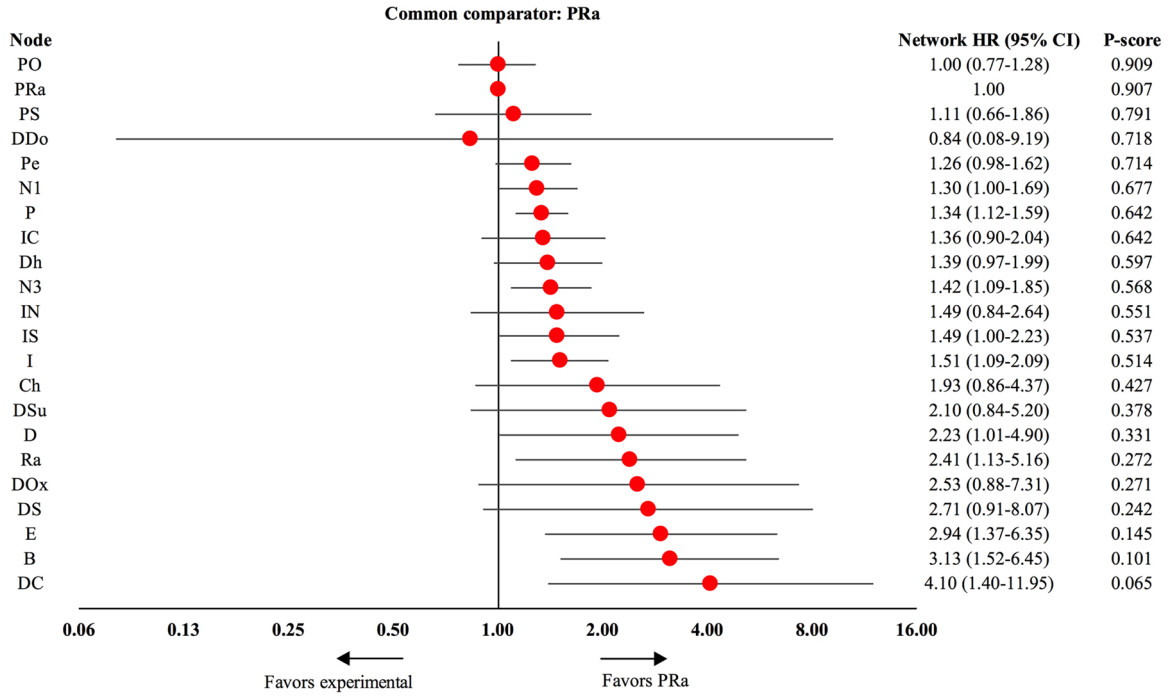

Fig. 1. Network forest plot of overall survival for second-line unselected patients with fluoropyrimidine-based first-line regimens.

despite that after removing phase 2 trials, "PRa" topped the hierarchy with a tiny superiority against "PO". Among subgroup analyses, "PO" and "PRa" also closely ranked in the top two spots in subgroups of fluoropyrimidine plus platinum and performance status (0) while "PO" slightly enlarged its advantage against "PRa" in eastern population and "PRa" topped the hierarchy with a slight advantage in performance status (1) subgroup. As for secondary endpoints, "PRa" led the ranking by significantly as well as insignificantly surpassing the second-place "PO" in progression-free survival and objective response rate respectively. Moreover, both "PRa" and "PO" had acceptable and comparable adverse events with each other. Although there were no direct pairwise evidences between "PO" and "PRa", our quantitative analysis was consistent with current recommendations that "PRa" seemed to be the best regimen in second-line setting. As for "PO", although its phase 2 trial displayed significant survival benefits against paclitaxel monotherapy (Bang et al., 2015), the phase 3 trial subsequently failed to provide statistical significance (Bang et al., 2017), which deprived olaparib of FDA approval for clinical application against advanced gastric cancer. The slight network superiority of "PO" over "PRa" might be actually due to the credit of its phase 2 trial results since after the removal of phase 2 trials, "PRa" reigned the entire hierarchy. Meanwhile, "PRa" was significantly better than "PO" in progression-free survival, depicting the less competitive role of "PO" in inhibiting disease progression. Besides, both "PO"-containing studies were based only on eastern population while the "PRa"-containing trial was conducted within global population that offered more extensive evidences. Therefore, taken together, paclitaxel plus ramucirumab is still the most valuable regimen for second-line setting while olaparib-based medications also have the potential to become vital alternatives against advanced gastric cancer, especially among eastern population where paclitaxel plus ramucirumab seems less effective (Wilke et al., 2014). Further studies such as the non-inferiority assessment between "PO" and "PRa" could be implemented in the future.

For second-line HER2 positive patients, there is currently lacking of consensus on therapeutic options. Among patients characterized by standard fluoropyrimidine plus platinum plus trastuzumab as first-line regimen, taxane plus trastuzumab failed to show survival superiority over taxane monotherapy in second-line setting. Although Satoh et al (Satoh et al., 2014) reported that among patients with greater HER2 positivity (IHC3 +), paclitaxel plus lapatinib displayed significant survival superiority against paclitaxel alone, however, since patients from this study were based on non-trastuzumab first-line regimen (5-FU plus cisplatin), whether it could meet current needs remained unclear. Therefore, paclitaxel monotherapy should be recommended as the preferred second-line regimen among HER2 positive patients who receive standard first-line treatment until further evidences come out.

Since it is a relatively new field in gastric cancer therapeutics, there is no specific recommendations on therapeutic options for refractory patients who fail at least two lines of previous treatments. In our quantitative analysis, apatinib, especially apatinib 850 mg once, dominated the hierarchy in overall survival and progression-free survival, among both general refractory and third-line only population, demonstrating significant survival superiority as well as comparable tolerability against placebo. Nivolumab only reigned the ranking of objective response rate, along with apatinib showing significant advantage over placebo. However, it was still unable to determine which one should be recommended as the preferred refractory regimen, since if we only compared overall survival results in phase 3 trials, the effect size of nivolumab was more favorable than apatinib in refractory setting while apatinib was the only one that significantly surpassed placebo in third-line only setting (Table 3). Besides, both nivolumab and apatinib were investigated only among eastern population and apatinib had not yet been officially approved by FDA for clinical usage in advanced gastric cancer. Recently, after we closed the literature retrieval in August 12th, CheckMate-032 study (Janjigian et al., 2018) reported the latest results that nivolumab with or without ipilimumab displayed clinically meaningful antitumor activity, durable responses, encouraging long-term OS, and a manageable safety profile in patients with chemotherapy-refractory esophagogastric cancer, which was the first evidence confirming that nivolumab could also be effective in western population. Therefore, as a result, both apatinib and nivolumab could be potentially recommended as refractory regimens due to their significant superiority against placebo, however their mutual efficacies still need to be verified in further global investigations.

Although our systematic review was rigorously designed and conducted, there were still some limitations within. Firstly, this network

Table 3
Survival and safety data of studies among refractory patients (third-line or more).

Study	Regimen	Node	Sample size	Overall survival: all refractory cases		Overall survival: third-line only	
				Hazard ratio	Network meta-analysis	Hazard ratio	Network meta-analysis
Bang et al. (2018)	Avelumab	A	185	1.10 (95% CI, 0.90-1.40)	Included	1.10 (95% CI, 0.90-1.40)	Included
	Chemotherapy	C	186				
Kang et al. (2012)	Nivolumab	N	330	0.63 (95% CI, 0.51-0.78)	Included	0.82 (95% CI, 0.50-1.35)	Included
	Placebo	B	163				
Tebbutt et al. (2016)	Regorafenib	R	97	NA	NA	NA	NA
	Placebo plus BSC	B	50				
Li (2016)	Apatinib-850	A8	176	0.71 (95% CI, 0.54-0.94)	Included	0.70 (95% CI, 0.49-0.99)	Included
	Placebo	B	91				
Ohtsu et al. (2013)	Everolimus	E	439	0.90 (95% CI, 0.70-1.15)	Included	0.90 (95% CI, 0.70-1.15)	Included
	Placebo plus BSC	B	217				
Li et al. (2013)	Apatinib-425	A4	46	A4 vs A8: 1.28 (95% CI, 0.75-2.17)	Included	NA	NA
	Apatinib-850	A8	47	A4 vs B: 0.41 (95% CI, 0.24-0.72)			
	Placebo	B	48	A8 vs B: 0.37 (95% CI, 0.22-0.62)			
Kang et al. (2012)	Chemotherapy	C	133	0.81 (95% CI, 0.45-1.46)	Included	0.81 (95% CI, 0.45-1.46)	Included
	BSC	B	69				

Study	Progression-free survival: all refractory cases		Objective response rate: all refractory cases		Hematological adverse events: all refractory cases		Non-hematological adverse events: all refractory cases	
	Hazard ratio	Network meta-analysis	Response/total	Network meta-analysis	Event/total	Network meta-analysis	Event/total	Network meta-analysis
Bang et al. (2018)	1.73 (95% CI, 1.40-2.20)	**Not included**	4/185	**Not included**	0/184	**Not included**	19/184	**Not included**
			8/186		28/177		70/177	
Kang et al. (2012)	0.60 (95% CI, 0.49-0.75)	Included	30/268	Included	38/330	Included	153/330	Included
			0/131		19/161		65/161	
Tebbutt et al. (2016)	0.32 (95% CI, 0.19-0.55)	Included	NA	NA	NA	NA	NA	NA
Li (2016)	0.44 (95% CI, 0.33-0.60)	Included	5/176	Included	29/176	Included	93/176	Included
			0/91		6/91		33/91	
Ohtsu et al. (2013)	NA	NA	NA	NA	NA	NA	NA	NA
Li et al. (2013)	A4 vs A8: 1.22 (95% CI, 0.68-2.20)	Included	6/46	Included	11/46	Included	22/46	Included
	A4 vs B: 0.21 (95% CI, 0.11-0.38)		3/47		4/47		11/47	
	A8 vs 8: 0.18 (95% CI, 0.10-0.34)		0/48		9/48		6/48	
Kang et al. (2012)	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: CI: confidence interval; NA: not available.
Naming rules for nodes: Avelumab: A; Chemotherapy: C; Nivolumab: N; Placebo, Placebo plus BSC and BSC: B; Regorafenib: R; Apatinib-850: A8; Everolimus: E; Apatinib-425: A4;
Notes: "Not included" suggested that these data were not included into the specific network calculations due to failure of forming a single network (Since a complete network could not be formed in terms of progression-free survival, objective response rate, hematological and non-hematological adverse events, the network calculations were based on their largest sub-networks accordingly).

Table 4
Characteristics of previous related systematic reviews.

Previous related systematic reviews	(Zhu et al., 2017)	(Zheng et al., 2017)	(Harvey, 2017)	(Chan et al., 2017)	(Ter Veer et al., 2016Ter Veer et al., 2016)	(Zhang et al., 2016)	(Badiani et al., 2015)	(Iacovelli et al., 2014)	(Kim et al., 2013)
Therapeutic line	Second	Third	Second	Third	Second/Third	Second	Second	Second	Second
Meta-analysis	Network	Pairwise	Network	Pairwise	Pairwise	Pairwise	Network	Pairwise	Pairwise
Limitations on first-line regimen	No	No	FP	No	No	No	FP	FP	No
Other key limitations	HER-2 excluded	No	No	Must have one placebo or BSC arm	No	Doublet versus single cytotoxic agent	No	Must have one placebo or BSC arm	Chemotherapy versus BSC
Deadline of included studies	June 2014	August 2016	2015	July 2016	January 2016	August 2015	February 2015	February 2014	March 2013
Type of included studies	Phase 3 RCT	RCT and non-RCT	RCT	Phase 2/3 RCT	Phase 2/3 RCT	RCT	RCT	RCT	Phase 3 RCT
Major conclusions	Paclitaxel plus ramucirumab combination is the most effective second-line therapy.	The third-line chemotherapy is superior to the best supportive care in advanced gastric cancer patients who had been pretreated with first-line and second-line chemotherapy.	Ramucirumab plus paclitaxel is the best treatment.	Third-line treatment improves survival benefits compared to best supportive care.	Ramucirumab plus taxane is the preferred second-line treatment. Taxane or irinotecan monotherapy are alternatives, although the absolute survival benefit was limited. In third-line setting, apatinib monotherapy is preferred.	In comparison with single cytotoxic agent alone, the addition of targeted agent to mono-chemotherapy as salvage treatment for pretreated AGC patients provide substantial survival benefits, while no significant survival benefits were observed in doublet cytotoxic chemotherapy regimens.	Both paclitaxel monotherapy and ramucirumab plus paclitaxel determine a significant prolongation in survival as compared with BSC.	Active and available therapies are able to prolong survival in patients with advanced gastric cancer with a different outcome based on initial patient's performance status, irrespective of chemotherapy or ramucirumab.	This meta-analysis demonstrated evidence to support second-line chemotherapy in advanced gastric cancer.
Major drawbacks	Some of the original survival data were actually the combined results of both second-line and third-line treatments. They did not use the subgroup data which might cause unexpected heterogeneity, including those from Ohtsu 2013 and Kang 2012. Meanwhile, it only discovered the survival comparisons without any analysis on safety profiles.	The quantitative analysis incorporated both randomized and non-randomized trials. Meanwhile, due to significant differences among chemotherapeutic types, it was also not proper to perform a quantitative synthesis especially a pairwise meta-analysis.	Serious methodological defects were detected in this meta-analysis, including lacking of proper assessment of risk of bias and network inconsistency. Meanwhile, it only discovered the survival comparisons without any analysis on safety profiles.	Due to significant differences among chemotherapeutic types, it was not proper to perform a quantitative synthesis especially a pairwise meta-analysis.	This study only conducted separate pairwise meta-analyses, which was unable to rank all regimens simultaneously, especially when there were multiple options in the second-line setting. Besides, one trial with cross-over design had also been included, which might induce bias into the results.	This study only conducted separate pairwise meta-analyses, which was unable to rank all regimens simultaneously and contained significant heterogeneity. Meanwhile, Jadad's Scale was not a proper tool for the assessment of risk of bias. Besides, one non-randomized trial was also included.	Serious methodological defects were detected in this meta-analysis, including lacking of analysis on network inconsistency. Meanwhile, it only discovered the survival comparisons without any analysis on safety profiles.	This study only conducted separate pairwise meta-analyses, which was unable to rank all regimens simultaneously. Meanwhile, Jadad's Scale was not a proper tool for the assessment of risk of bias.	No detailed method was described in terms of risk of bias assessment. Moreover, this meta-analysis only conducted comparisons between chemotherapy and BSC in three trials, which was far short of current demand.

(*continued on next page*)

Table 4 (*continued*)

Previous related systematic reviews		(Zhu et al., 2017)	(Zheng et al., 2017)	(Harvey, 2017)	(Chan et al., 2017)	(Ter Veer et al., 2016Ter Veer et al., 2016)	(Zhang et al., 2016)	(Badiani et al., 2015)	(Iacovelli et al., 2014)	(Kim et al., 2013)
Number of all included studies (RCT only)		8 (8)	20 (6)	7 (7)	5 (5)	**28 (28)**	**10 (10)**	7 (7)	5 (5)	3 (3)
Included RCT (in comparison to our systematic review)	Bang 2018									
	Shitara 2018									
	Kang 2018									
	Makiyama 2018									
	Van Cutsem 2017					**Included***				
	Bang 2017									
	Kang 2017									
	Shitara 2017									
	Thuss-Patience 2017									
	Lee 2017					**Included***				
	Al-Batran 2017									
	Moehler 2016		Included			**Included***				
	Pavlakis 2016				Included	Included				
	Li 2016		Included		Included	Included				
	Nakanishi 2016					Included				
	Bang 2015					Included				
	Tanabe 2015					Included	Included			
	Kim 2015					Included	Included			
	Nishikawa 2015-1					Included	Included			
	Nishikawa 2015-2					Included				
	Lorenzen 2015					Included	Included			
	Satoh 2015					Included	Included			
	Wilke 2014	Included		Included		Included	Included	Included		
	Satoh 2014					Included	Included			
	Higuchi 2014	Included				Included				
	Ford 2014	Included		Included		Included		Included	Included	**Included***
	Fuchs 2014	Included		Included		Included		Included	Included	
	Hironaka 2013	Included	Included	Included		Included		Included		
	Ohtsu 2013	Included		Included	Included	Included		Included	Included	
	Li 2013		Included		Included	Included				
	Roy 2013					Included				
	Sym 2013					Included	Included			
	Yi 2012		Included			Included				
	Kang 2012	Included	Included	Included	Included	Included		Included	Included	Included
	Thuss-Patience 2011	Included		Included		Included		Included	Included	Included
	Maruta 2007					Included	Included			

Abbreviations: FP: fluoropyrimidine plus platinum; BSC: best supportive care; RCT: randomized controlled trials.

Notes: The underlined and bold-type number of studies: 27 of 28 randomized trials in Ter Veer's systematic review overlapped with ours. One trial, Nishina 2016 (PMID: 26,386,560) was excluded from our study due to its crossover design. Moreover, 9 of 10 randomized trials in Zhang's systematic review overlapped with ours. One trial, Ueda 2013 (PMID: 24,222,156) that was included in Zhang's systematic review, was actually a non-randomized trial. Therefore, we did not include it into our systematic review. The asterisk and bold-type "Included" meant that those trials were cited as meeting abstracts in previous systematic reviews however formally published when we conducted our study.

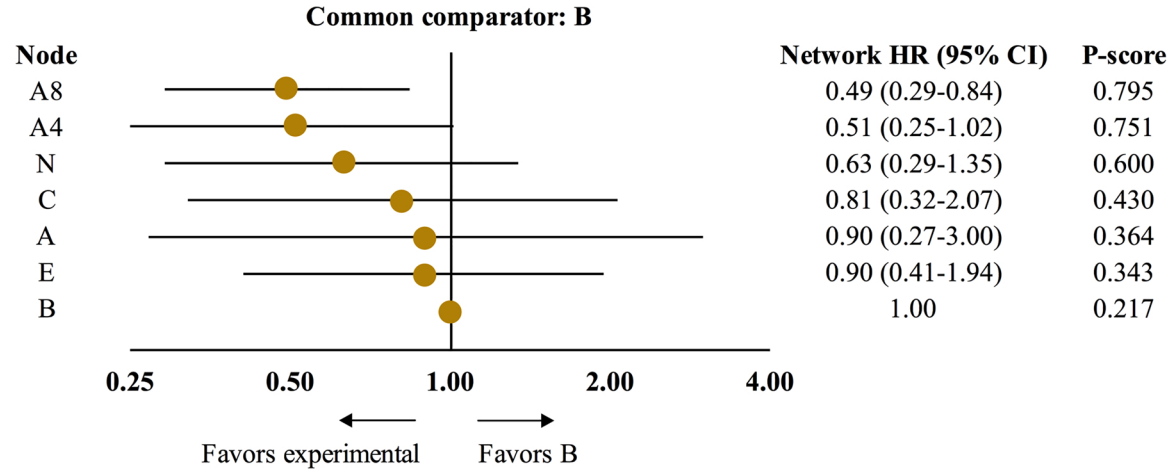

Fig. 2. Network forest plot of overall survival for refractory unselected patients.

meta-analysis was not based on individual-patient data (IPD), which could minimize the heterogeneity inside the quantitative network compared to study-level synthesis. However, since the network was verified to be highly consistent, stable and homogenous, conclusions of our pooled analysis were still credible and applicable. Secondly, although our systematic review included as much eligible literatures as we could, the amount of included trials still needs to be increased by future updates, especially for refractory setting, which could enhance the statistical power and thus the credibility of the final results.

In conclusion, paclitaxel plus ramucirumab is the optimal regimen for second-line unselected patients with fluoropyrimidine-based first-line regimens while olaparib-based medications also have the potential to become vital alternatives against advanced gastric cancer, especially among eastern population where paclitaxel plus ramucirumab seems less effective. Paclitaxel monotherapy should be recommended as the preferred second-line regimen among HER2 positive patients who receive standard first-line treatment. Both apatinib and nivolumab could be potentially recommended as refractory regimens due to their significant superiority against placebo, however their mutual efficacies still need to be verified in further global investigations.

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.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

Acknowledgements

We thank all staff in our department for providing clinical and methodological advices during the entire performance of our meta-analysis. This study is funded by National Natural Science Foundation of China(81902487) to Scientific Research Training Program for Young Talents (Union Hospital, Tongji Medical College, Huazhong University of Science and Technology) to Ji Cheng; National Natural Science Foundation of China (81874184) to Kaixiong Tao;

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2019.08.001.

References

Al-Batran, S.-E., Riera-Knorrenschild, J., Pauligk, C., Goetze, T.O., Hegewisch-Becker, S., Seraphin, J., Thuss-Patience, P.C., Kopp, H.-G., Dechow, T.N., Vogel, A., Luley, K.B., Pink, D., Stahl, M., Kullmann, F., Hebart, H.F., Siveke, J.T., Egger, M., Homann, N., Probst, S., Lorenzen, S., 2017. A randomized, double-blind, multicenter phase III study evaluating paclitaxel with and without RAD001 in patients with gastric cancer who have progressed after therapy with a fluoropyrimidine/platinum-containing regimen (RADPAC). J. Clin. Oncol. 35 (4_suppl) 4-4.

Badiani, B., Maratea, D., Messori, A., 2015. Second-line treatments for advanced gastric cancer: interpreting outcomes by network meta-analysis. World J. Clin. Oncol. 6 (4), 73–79.

Bang, Y.J., Im, S.A., Lee, K.W., Cho, J.Y., Song, E.K., Lee, K.H., Kim, Y.H., Park, J.O., Chun, H.G., Zang, D.Y., Fielding, A., Rowbottom, J., Hodgson, D., O'Connor, M.J., Yin, X., Kim, W.H., 2015. Randomized, double-blind phase II trial with prospective classification by ATM protein level to evaluate the efficacy and tolerability of olaparib plus paclitaxel in patients with recurrent or metastatic gastric Cancer. J. Clin. Oncol. 33 (33), 3858–3865.

Bang, Y.J., Ruiz, E.Y., Van Cutsem, E., Lee, K.W., Wyrwicz, L., Schenker, M., Alsina, M., Ryu, M.H., Chung, H.C., Evesque, L., Al-Batran, S.E., Park, S.H., Lichinitser, M., Boku, N., Moehler, M.H., Hong, J., Xiong, H., Hallwachs, R., Conti, I., Taieb, J., 2018. Phase 3, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment for patients with advanced gastric or gastro-oesophageal junction cancer: primary analysis of JAVELIN Gastric 300. Ann. Oncol. 29 (10), 2052–2060. https://doi.org/10.1093/annonc/mdy264.

Bang, Y.J., Xu, R.H., Chin, K., Lee, K.W., Park, S.H., Rha, S.Y., Shen, L., Qin, S., Xu, N., Im, S.A., Locker, G., Rowe, P., Shi, X., Hodgson, D., Liu, Y.Z., Boku, N., 2017. Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 18 (12), 1637–1651.

Cancer I.A.f.R.o, 2012. Globocan 2012: Stomach Cancer. http://gco.iarc.fr/today/fact-sheets-cancers?cancer=5&type=0&sex=0.

Chan, W.L., Yuen, K.K., Siu, S.W., Lam, K.O., Kwong, D.L., 2017. Third-line systemic treatment versus best supportive care for advanced/metastatic gastric cancer: a systematic review and meta-analysis. Crit. Rev. Oncol. Hematol. 116, 68–81.

Ford, H.E., Marshall, A., Bridgewater, J.A., Janowitz, T., Coxon, F.Y., Wadsley, J., Mansoor, W., Fyfe, D., Madhusudan, S., Middleton, G.W., Swinson, D., Falk, S., Chau, I., Cunningham, D., Kareclas, P., Cook, N., Blazeby, J.M., Dunn, J.A., Investigators, C.-, 2014. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol. 15 (1), 78–86.

Fuchs, C.S., Tomasek, J., Yong, C.J., Dumitru, F., Passalacqua, R., Goswami, C., Safran, H., Dos Santos, L.V., Aprile, G., Ferry, D.R., Melichar, B., Tehfe, M., Topuzov, E., Zalcberg, J.R., Chau, I., Campbell, W., Sivanandan, C., Pikiel, J., Koshiji, M., Hsu, Y., Liepa, A.M., Gao, L., Schwartz, J.D., Tabernero, J., Investigators, R.T., 2014. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 383 (9911), 31–39.

Harvey, R.C., 2017. Second-line treatments for advanced gastric Cancer: a network meta-analysis of overall survival using parametric modelling methods. Oncol. Ther. 5 (1), 53–67.

Higuchi, K., Tanabe, S., Shimada, K., Hosaka, H., Sasaki, E., Nakayama, N., Takeda, Y., Moriwaki, T., Amagai, K., Sekikawa, T., Sakuyama, T., Kanda, T., Sasaki, T., Azuma, M., Takahashi, F., Takeuchi, M., Koizumi, W., Tokyo Cooperative Oncology Group,

T.J, 2014. Biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for advanced gastric cancer: a randomised phase III trial (TCOG GI-0801/BIRIP trial). Eur. J. Cancer 50 (8), 1437–1445.

Hironaka, S., Ueda, S., Yasui, H., Nishina, T., Tsuda, M., Tsumura, T., Sugimoto, N., Shimodaira, H., Tokunaga, S., Moriwaki, T., Esaki, T., Nagase, M., Fujitani, K., Yamaguchi, K., Ura, T., Hamamoto, Y., Morita, S., Okamoto, I., Boku, N., Hyodo, I., 2013. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J. Clin. Oncol. 31 (35), 4438–4444.

Hwang, I.G., Ji, J.H., Kang, J.H., Lee, H.R., Lee, H.Y., Chi, K.C., Park, S.W., Lee, S.J., Kim, S.T., Lee, J., Park, S.H., Park, J.O., Park, Y.S., Lim, H.Y., Kang, W.K., 2017. A multicenter, open-label, randomized phase III trial of first-line chemotherapy with capecitabine monotherapy versus capecitabine plus oxaliplatin in elderly patients with advanced gastric cancer. J. Geriatr. Oncol. 8 (3), 170–175.

Iacovelli, R., Pietrantonio, F., Farcomeni, A., Maggi, C., Palazzo, A., Ricchini, F., de Braud, F., Di Bartolomeo, M., 2014. Chemotherapy or targeted therapy as second-line treatment of advanced gastric cancer. A systematic review and meta-analysis of published studies. PLoS One 9 (9), e108940.

Janjigian, Y.Y., Bendell, J., Calvo, E., Kim, J.W., Ascierto, P.A., Sharma, P., Ott, P.A., Peltola, K., Jaeger, D., Evans, J., de Braud, F., Chau, I., Harbison, C.T., Dorange, C., Tschaika, M., Le, D.T., 2018. CheckMate-032 study: efficacy and safety of nivolumab and nivolumab plus ipilimumab in patients with metastatic esophagogastric cancer. J. Clin. Oncol. 36 (28), 2836–2844. https://doi.org/10.1200/JCO.2017.76.621. Epub 2018 Aug 15.

Kang, J.H., Lee, S.I., Lim, D.H., Park, K.W., Oh, S.Y., Kwon, H.C., Hwang, I.G., Lee, S.C., Nam, E., Shin, D.B., Lee, J., Park, J.O., Park, Y.S., Lim, H.Y., Kang, W.K., Park, S.H., 2012. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J. Clin. Oncol. 30 (13), 1513–1518.

Kang, Y.K., Ryu, M.H., Park, S.H., Kim, J.G., Kim, J.W., Cho, S.H., Park, Y.I., Park, S.R., Rha, S.Y., Kang, M.J., Cho, J.Y., Kang, S.Y., Roh, S.Y., Ryoo, B.Y., Nam, B.H., Jo, Y.W., Yoon, K.E., Oh, S.C., 2018. Efficacy and safety findings from DREAM: a phase III study of DHP107 (oral paclitaxel) versus i.v. Paclitaxel in patients with advanced gastric cancer after failure of first-line chemotherapy. Ann. Oncol. 29 (5), 1220–1226.

Kim, H.S., Kim, H.J., Kim, S.Y., Kim, T.Y., Lee, K.W., Baek, S.K., Kim, T.Y., Ryu, M.H., Nam, B.H., Zang, D.Y., 2013. Second-line chemotherapy versus supportive cancer treatment in advanced gastric cancer: a meta-analysis. Ann. Oncol. 24 (11), 2850–2854.

Kim, J.Y., Ryoo, H.M., Bae, S.H., Kang, B.W., Chae, Y.S., Yoon, S., Baek, J.H., Kim, M.K., Lee, K.H., Lee, S.A., Song, H.S., Kim, J.G., 2015. Multi-center randomized phase II study of weekly docetaxel versus weekly docetaxel-plus-Oxaliplatin as a second-line chemotherapy for patients with advanced gastric Cancer. Anticancer Res. 35 (6), 3531–3536.

Lee, K.W., Kim, B.J., Kim, M.J., Han, H.S., Kim, J.W., Park, Y.I., Park, S.R., 2017. A multicenter randomized phase II study of docetaxel vs. docetaxel plus cisplatin vs. docetaxel plus S-1 as second-line chemotherapy in metastatic gastric cancer patients who had progressed after cisplatin plus either S-1 or capecitabine. Cancer Res. Treat. 49 (3), 706–716.

Li, J., Qin, S., Xu, J., Guo, W., Xiong, J., Bai, Y., Sun, G., Yang, Y., Wang, L., Xu, N., Cheng, Y., Wang, Z., Zheng, L., Tao, M., Zhu, X., Ji, D., Liu, X., Yu, H., 2013. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. J. Clin. Oncol. 31 (26), 3219–3225.

Li, J., Qin, S., Xu, J., Xiong, J., Wu, C., Bai, Y., Liu, W., Tong, J., Liu, Y., Xu, R., Wang, Z., Wang, Q., Ouyang, X., Yang, Y., Ba, Y., Liang, J., Lin, X., Luo, D., Zheng, R., Wang, X., Sun, G., Wang, L., Zheng, L., Guo, H., Wu, J., Xu, N., Yang, J., Zhang, H., Cheng, Y., Wang, N., Chen, L., Fan, Z., Sun, P., Yu, H., 2016. Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. J. Clin. Oncol. 34 (13), 1448–1454.

Lorenzen, S., Riera Knorrenschild, J., Haag, G.M., Pohl, M., Thuss-Patience, P., Bassermann, F., Helbig, U., Weissinger, F., Schnoy, E., Becker, K., Stocker, G., Ruschoff, J., Eisenmenger, A., Karapanagiotou-Schenkel, I., Lordick, F., 2015. Lapatinib versus lapatinib plus capecitabine as second-line treatment in human epidermal growth factor receptor 2-amplified metastatic gastro-oesophageal cancer: a randomised phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Eur. J. Cancer 51 (5), 569–576.

Makiyama, A., Sagara, K., Kawada, J., Kashiwada, T., Hosokawa, A., Horie, Y., Satake, H., Yamamoto, Y., Tanioka, H., Shinozaki, K., Nishikawa, K., Uchino, K., Sukawa, Y., Yamanaka, T., Yamazaki, K., Hironaka, S., Boku, N., Hyodo, I., Esaki, T., Muro, K., 2018. A randomized phase II study of weekly paclitaxel ± trastuzumab in patients with HER2-positive advanced gastric or gastro-esophageal junction cancer refractory to trastuzumab combined with fluoropyrimidine and platinum: WJOG7112G (T-ACT). J. Clin. Oncol. 36 (15_suppl) 4011-4011.

Maruta, F., Ishizone, S., Hiraguri, M., Fujimori, Y., Shimizu, F., Kumeda, S., Miyagawa, S., 2007. A clinical study of docetaxel with or without 5′DFUR as a second-line chemotherapy for advanced gastric cancer. Med. Oncol. 24 (1), 71–75.

Moehler, M., Gepfner-Tuma, I., Maderer, A., Thuss-Patience, P.C., Ruessel, J., Hegewisch-Becker, S., Wilke, H., Al-Batran, S.E., Rafiyan, M.R., Weissinger, F., Schmoll, H.J., Kullmann, F., von Weikersthal, L.F., Siveke, J.T., Weusmann, J., Kanzler, S., Schimanski, C.C., Otte, M., Schollenberger, L., Koenig, J., Galle, P.R., 2016. Sunitinib added to FOLFIRI versus FOLFIRI in patients with chemorefractory advanced adenocarcinoma of the stomach or lower esophagus: a randomized, placebo-controlled phase II AIO trial with serum biomarker program. BMC Cancer 16, 699.

Nakanishi, K., Kobayashi, D., Mochizuki, Y., Ishigure, K., Ito, S., Kojima, H., Ishiyama, A., Fujitake, S., Shikano, T., Morita, S., Kodera, Y., 2016. Phase II multi-institutional prospective randomized trial comparing S-1 plus paclitaxel with paclitaxel alone as second-line chemotherapy in S-1 pretreated gastric cancer (CCOG0701). Int. J. Clin. Oncol. 21 (3), 557–565.

Nishikawa, K., Fujitani, K., Inagaki, H., Akamaru, Y., Tokunaga, S., Takagi, M., Tamura, S., Sugimoto, N., Shigematsu, T., Yoshikawa, T., Ishiguro, T., Nakamura, M., Morita, S., Miyashita, Y., Tsuburaya, A., Sakamoto, J., Tsujinaka, T., 2015a. Randomised phase III trial of second-line irinotecan plus cisplatin versus irinotecan alone in patients with advanced gastric cancer refractory to S-1 monotherapy: TRICS trial. Eur. J. Cancer 51 (7), 808–816.

Nishikawa, K., Imamura, H., Kawase, T., Gotoh, M., Kimura, Y., Ueda, S., Matsuyama, J., Kawada, J., Sugimoto, N., Fujita, J., Tamura, T., Fukushima, N., Sakai, D., Shimokawa, T., Kurokawa, Y., Satoh, T., Tsujinaka, T., Furukawa, H., 2015b. A randomized phase II factorial design trial of CPT-11 versus PTX versus each combination with S-1 in patients with advanced gastric cancer refractory to S-1: final results of OGSG0701. J. Clin. Oncol. 33 (3_suppl) 117-117.

Ohtsu, A., Ajani, J.A., Bai, Y.X., Bang, Y.J., Chung, H.C., Pan, H.M., Sahmoud, T., Shen, L., Yeh, K.H., Chin, K., Muro, K., Kim, Y.H., Ferry, D., Tebbutt, N.C., Al-Batran, S.E., Smith, H., Costantini, C., Rizvi, S., Lebwohl, D., Van Cutsem, E., 2013. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. J. Clin. Oncol. 31 (31), 3935–3943.

Roy, A.C., Park, S.R., Cunningham, D., Kang, Y.K., Chao, Y., Chen, L.T., Rees, C., Lim, H.Y., Tabernero, J., Ramos, F.J., Kujundzic, M., Cardic, M.B., Yeh, C.G., de Gramont, A., 2013. A randomized phase II study of PEP02 (MM-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma. Ann. Oncol. 24 (6), 1567–1573.

Satoh, T., Lee, K.H., Rha, S.Y., Sasaki, Y., Park, S.H., Komatsu, Y., Yasui, H., Kim, T.Y., Yamaguchi, K., Fuse, N., Yamada, Y., Ura, T., Kim, S.Y., Munakata, M., Saitoh, S., Nishio, K., Morita, S., Yamamoto, E., Zhang, Q., Kim, J.M., Kim, Y.H., Sakata, Y., 2015. Randomized phase II trial of nimotuzumab plus irinotecan versus irinotecan alone as second-line therapy for patients with advanced gastric cancer. Gastric Cancer 18 (4), 824–832.

Satoh, T., Xu, R.H., Chung, H.C., Sun, G.P., Doi, T., Xu, J.M., Tsuji, A., Omuro, Y., Li, J., Wang, J.W., Miwa, H., Qin, S.K., Chung, I.J., Yeh, K.H., Feng, J.F., Mukaiyama, A., Kobayashi, M., Ohtsu, A., Bang, Y.J., 2014. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN–a randomized, phase III study. J. Clin. Oncol. 32 (19), 2039–2049.

Shitara, K., Ozguroglu, M., Bang, Y.J., Di Bartolomeo, M., Mandala, M., Ryu, M.H., Fornaro, L., Olesinski, T., Caglevic, C., Chung, H.C., Muro, K., Goekkurt, E., Mansoor, W., McDermott, R.S., Shacham-Shmueli, E., Chen, X., Mayo, C., Kang, S.P., Ohtsu, A., Fuchs, C.S., investigators, K, 2018. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet 392 (10142), 123–133.

Shitara, K., Takashima, A., Fujitani, K., Koeda, K., Hara, H., Nakayama, N., Hironaka, S., Nishikawa, K., Makari, Y., Amagai, K., Ueda, S., Yoshida, K., Shimodaira, H., Nishina, T., Tsuda, M., Kurokawa, Y., Tamura, T., Sasaki, Y., Morita, S., Koizumi, W., 2017. Nab-paclitaxel versus solvent-based paclitaxel in patients with previously treated advanced gastric cancer (ABSOLUTE): an open-label, randomised, non-inferiority, phase 3 trial. Lancet Gastroenterol. Hepatol. 2 (4), 277–287.

Siegel, R.L., Miller, K.D., Jemal, A., 2018. Cancer statistics, 2018. CA Cancer J. Clin. 68 (1), 7–30.

Sym, S.J., Hong, J., Park, J., Cho, E.K., Lee, J.H., Park, Y.H., Lee, W.K., Chung, M., Kim, H.S., Park, S.H., Shin, D.B., 2013. A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. Cancer Chemother. Pharmacol. 71 (2), 481–488.

Tanabe, K., Fujii, M., Nishikawa, K., Kunisaki, C., Tsuji, A., Matsuhashi, N., Takagane, A., Ohno, T., Kawase, T., Kochi, M., Yoshida, K., Kakeji, Y., Ichikawa, W., Chin, K., Terashima, M., Takeuchi, M., Nakajima, T., group, J.G.-s, 2015. Phase II/III study of second-line chemotherapy comparing irinotecan-alone with S-1 plus irinotecan in advanced gastric cancer refractory to first-line treatment with S-1 (JACCRO GC-05). Ann. Oncol. 26 (9), 1916–1922.

Tebbutt, N.C., Price, T.J., Ferraro, D.A., Wong, N., Veillard, A.S., Hall, M., Sjoquist, K.M., Pavlakis, N., Strickland, A., Varma, S.C., Cooray, P., Young, R., Underhill, C., Shannon, J.A., Ganju, V., Gebski, V., 2016. Panitumumab added to docetaxel, cisplatin and fluoropyrimidine in oesophagogastric cancer: ATTAX3 phase II trial. Br. J. Cancer 114 (5), 505–509.

Ter Veer, E., Haj Mohammad, N., van Valkenhoef, G., Ngai, L.L., Mali, R.M., van Oijen, M.G., van Laarhoven, H.W., 2016. Second- and third-line systemic therapy in patients with advanced esophagogastric cancer: a systematic review of the literature. Cancer Metastasis Rev. 35 (3), 439–456.

Thuss-Patience, P.C., Kretzschmar, A., Bichev, D., Deist, T., Hinke, A., Breithaupt, K., Dogan, Y., Gebauer, B., Schumacher, G., Reichardt, P., 2011. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer—a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur. J. Cancer 47 (15), 2306–2314.

Thuss-Patience, P.C., Shah, M.A., Ohtsu, A., Van Cutsem, E., Ajani, J.A., Castro, H., Mansoor, W., Chung, H.C., Bodoky, G., Shitara, K., Phillips, G.D.L., van der Horst, T., Harle-Yge, M.L., Althaus, B.L., Kang, Y.K., 2017. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. Lancet Oncol. 18 (5), 640–653.

Tierney, J.F., Stewart, L.A., Ghersi, D., Burdett, S., Sydes, M.R., 2007. Practical methods

for incorporating summary time-to-event data into meta-analysis. Trials 8, 16.
Van Cutsem, E., Bang, Y.J., Mansoor, W., Petty, R.D., Chao, Y., Cunningham, D., Ferry, D.R., Smith, N.R., Frewer, P., Ratnayake, J., Stockman, P.K., Kilgour, E., Landers, D., 2017. A randomized, open-label study of the efficacy and safety of AZD4547 monotherapy versus paclitaxel for the treatment of advanced gastric adenocarcinoma with FGFR2 polysomy or gene amplification. Ann. Oncol. 28 (6), 1316–1324.
Wilke, H., Muro, K., Van Cutsem, E., Oh, S.C., Bodoky, G., Shimada, Y., Hironaka, S., Sugimoto, N., Lipatov, O., Kim, T.Y., Cunningham, D., Rougier, P., Komatsu, Y., Ajani, J., Emig, M., Carlesi, R., Ferry, D., Chandrawansa, K., Schwartz, J.D., Ohtsu, A., Group, R.S., 2014. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 15 (11), 1224–1235.
Yi, J.H., Lee, J., Lee, J., Park, S.H., Park, J.O., Yim, D.S., Park, Y.S., Lim, H.Y., Kang, W.K., 2012. Randomised phase II trial of docetaxel and sunitinib in patients with metastatic gastric cancer who were previously treated with fluoropyrimidine and platinum. Br. J. Cancer 106 (9), 1469–1474.
Zhang, Y., Ma, B., Huang, X.T., Li, Y.S., Wang, Y., Liu, Z.L., 2016. Doublet versus single agent as second-line treatment for advanced gastric cancer: a meta-analysis of 10 randomized controlled trials. Medicine (Baltimore) 95 (8), e2792.
Zheng, Y., Zhu, X.Q., Ren, X.G., 2017. Third-line chemotherapy in advanced gastric cancer: a systematic review and meta-analysis. Medicine (Baltimore) 96 (24), e6884.
Zhu, X., Ko, Y.J., Berry, S., Shah, K., Lee, E., Chan, K., 2017. A Bayesian network meta-analysis on second-line systemic therapy in advanced gastric cancer. Gastric Cancer 20 (4), 646–654.