Review

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Review

First-Line Systemic Therapy Outcomes in Western Population with Locally Advanced and Metastatic Gastric Cancer - A Systematic Review

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Abstract: Globally, gastric cancer is a major cause of cancer mortality, with a 5-year survival rate of 32% for locally advanced and metastatic gastric cancer. This systematic literature review summarized the clinical, safety, and humanistic outcomes associated with systemic regimens given as first line therapy for locally advanced and metastatic gastric cancer. The search included articles published in English in PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials, and the American Society of Clinical Oncology meeting library, from inception to April 2022. Phase II and III randomized controlled trials conducted among western populations diagnosed with stage III and IV locally advanced and metastatic gastric cancer were included. Two investigators independently reviewed the studies, conducted data extraction, and assessed risk of bias in accordance with PRISMA guidelines. Twenty-four randomized controlled trials totaling 8,705 patients were included. Median overall survival ranged from 5.0-13.1 months, median progression-free survival ranged from 2.0-7.7 months, and objective response ranged from 13.0-64.1%. Two studies reported higher quality of life outcomes. Grade 3 and 4 adverse events were reported in most studies. Improvement in clinical outcomes can be seen in recently published randomized controlled trials for locally advanced and metastatic gastric cancer.

Keywords: advanced and metastatic gastric cancer; first-line systemic treatment; systematic review

1. Introduction

Gastric cancer is the fifth most diagnosed cancer and the fourth most common cause of cancer related mortality globally [1]. There are an estimated 26,560 cases of gastric cancer in the United States (US) alone and 11,180 deaths in 2021. In the US, 1.5% of new cancers diagnosed per year are attributed to gastric cancer [2]. Studies have shown that 65% of gastric cancer cases diagnosed in the US are at an advanced stage (tumor node metastasis stages T3 or T4) [3]. Locally advanced and metastatic gastric cancer has a poor prognosis with a survival rate of only 5-10% [4].

In cases of locally advanced and metastatic gastric cancer, systemic therapy is often the preferred treatment since it offers survival benefits [5]. Patients with advanced disease are usually treated with a combination chemotherapy that has become the accepted standard for first-line treatment [6]. According to recommendations from the National Comprehensive Cancer Network [5], a fluoropyrimidine (Fluorouracil), a platinum (oxaliplatin or cisplatin), and a taxane (docetaxel or

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paclitaxel) can be added to therapy. The National Comprehensive Cancer Network also recommends patients with metastatic gastric cancer consider undergoing testing for human epidermal growth factor receptor 2 (HER2) amplification and presence of programmed death-ligand 1 (PD-L1) [6]. In HER2-positive patients, trastuzumab is recommended as first-line therapy [7]. Immune checkpoint inhibitors are a recent class of drugs that act by inhibiting T-cell activation and effector functions leading to an anti-tumor response [8]. Specifically, immune checkpoint inhibitors in locally advanced and metastatic gastric cancer patients act by mediating the blockage of the programmed cell death protein 1 (PD-1)/PD-L1 axis. They are preferred in standard chemotherapy-refractory cases or those who have been previously treated with two or more chemotherapeutic regimens [9].

Immune activation by immune checkpoint inhibitors seems to have a more durable clinical benefit than traditional chemotherapy in locally advanced and metastatic gastric cancer and a lower incidence of adverse events [10]. The ATTRACTION-2 phase III clinical trials looked at Nivolumab or placebo in metastatic gastric cancer patients and showed significant overall survival that persisted over time [11]. Immune checkpoint inhibitor combinations can also lead to higher toxicities but no increase in activity as seen in MOONLIGHT trial with Nivolumab among locally advanced and metastatic gastric cancer patients [12]. Long-term side effects have also been challenging with immune checkpoint inhibitors. A real-world study looking at melanoma patients treated with immune checkpoint inhibitors found that 40% of patients had immune-related adverse events at follow-up [13].

The clinical efficacies of several targeted agents and immunotherapy treatment options have been tested in phase II and phase III randomized clinical trials. However, there is still ambiguity regarding the drug of choice for locally advanced and metastatic gastric cancer patients. Previously published systematic reviews evaluated first line systematic therapies in locally advanced and metastatic gastric cancer but each had some important limitations [14–18], are outdated do not include all systemic therapies, or included both gastric and esophageal cancer patients.

There is a lack of established screening programs in the western world, making early detection of gastric cancer difficult and survival rate in locally advanced and metastatic gastric cancer A/MGC is poor. Literature shows that treatment efficacy and survival outcomes vary between Asian and Western Patients. There remains is a lack of comprehensive, current evidence regarding therapies approved by the US Food and Drug Administration for locally advanced and metastatic gastric cancer. Hence, the purpose of this study was to perform a systematic review of randomized phase II and phase III treatment trials to compare the clinical efficacy, safety (adverse events), and humanistic outcomes of all first-line systemic therapeutic combinations among the western adult population with locally advanced and metastatic gastric cancer.

2. Results

2.1. Characteristics of Included Studies

A total of 8,689 unique references were identified from the database search and after reviewing titles and abstracts, 8,510 were excluded. In the remaining 179 full text articles, 24 studies met the inclusion criteria and were included in our systematic review. The selection process and reason for exclusion were reported in the PRISMA flow diagram (Figure 1). These 24 studies included eight phase II randomized controlled trials and 16 phase III randomized controlled trials.

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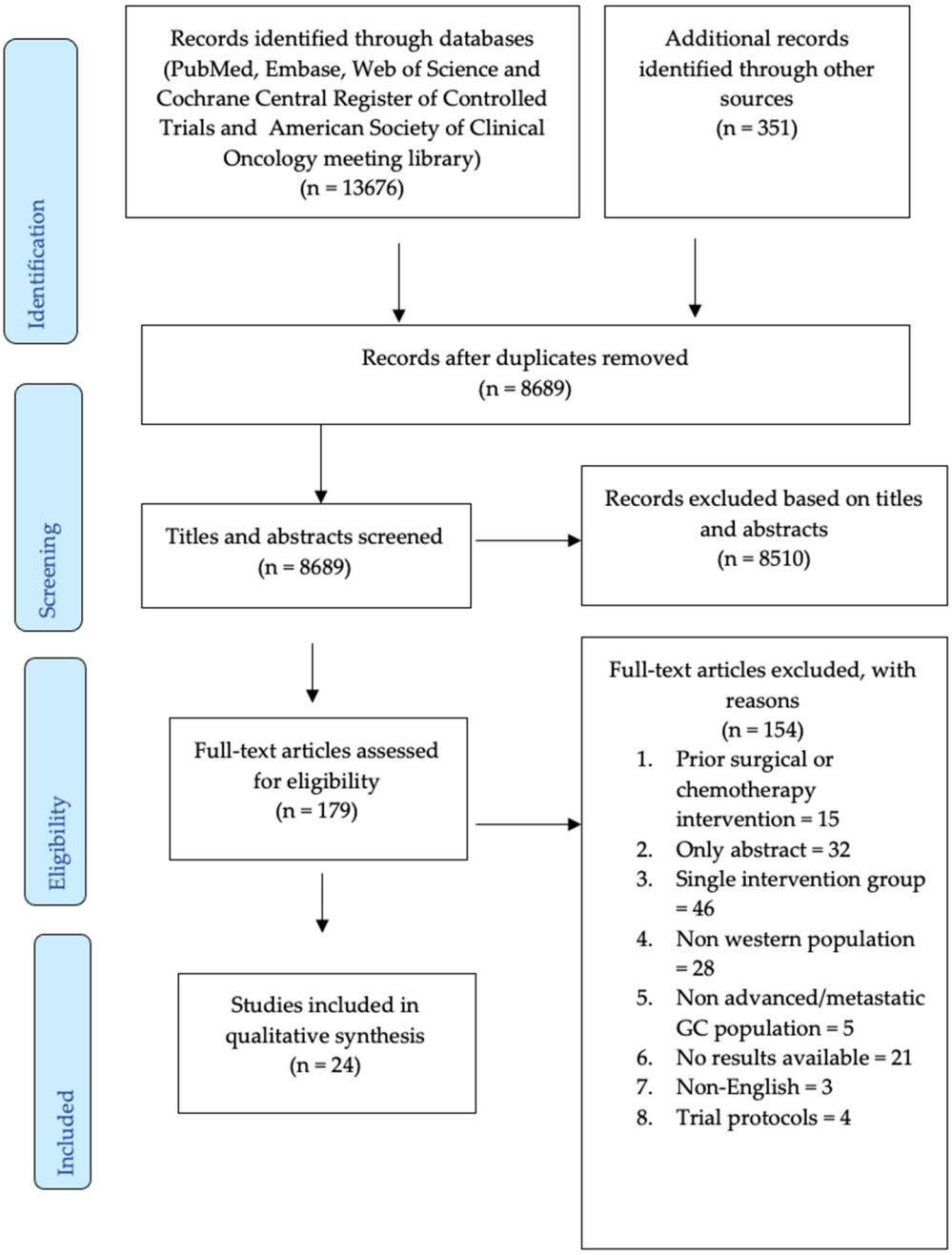

Figure 1. Systematic Review inclusion and exclusion flowchart.

Of the 24 included trials, 21 contained two treatment arms while the remaining three contained three treatment arms. Double chemotherapy combinations were used as first line therapy in five randomized controlled trials while the remaining 19 trials used triple or quadruple drug combination therapies. The total number of included patients per study ranged from 69 to 1,581. The median participant ages ranged from 52.7 to 70 years, and 48% to 84% of participants were male. The characteristics of the included randomized controlled trials and demographic characteristics of study participants are shown in Table 1.

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Table 1. Baseline characteristics of included randomized control trials of untreated locally advanced and metastatic gastric cancer.

Author, year	Country	Phase	Study design	Total N	Treatment arms	Age Median (range)	Males, n (%)
Ajani, 2005[19]	Multiple	II	Open label	155	Docetaxel-cisplatin	57 (21-83)	114 (74)
					Docetaxel-cisplatin-fluorouracil		
Ajani, 2007[20]	Multiple	III	Open label	445	Docetaxel-cisplatin-fluorouracil	55 (26-79)	(71.9)
					Cisplatin-fluorouracil	55 (25-76)	(70.5)
Ajani, 2010[21]	Multiple	III	Open label	1029	Cisplatin-S1	59.0 (18,85)+	729 (70.8)
					Cisplatin-fluorouracil		
Al-Batran, 2008[22]	Germany + Switzerland	III	NR	220	Fluorouracil-leucovorin-oxaliplatin	64 (33-86)	64 (57)
					Fluorouracil-leucovorin-cisplatin	64 (27-85)	81 (75)
Al-Batran, 2013[23]	Germany	III	Open label	143	Fluorouracil-leucovorin-oxaliplatin-docetaxel	69	51 (71)
					Fluorouracil-leucovorin-oxaliplatin	70	45 (63)
Bouche, 2004[24]	France	III	Open label	136	Leucovorin–5-flurouracil	64 (45-75)	(82)
					Leucovorin–5-flurouracil–cisplatin	64 (43-76)	(80)
					Leucovorin–5-flurouracil-irinotecan	65 (37-76)	(84)
Cascinu, 2010[25]	Italy	II	NR	78	5-flurouracil-cisplatin-doxorubicin	63 (33-75)	50 (64)
					5-flurouracil-cisplatin-mitomycin		
Catenacci, 2017[26]	Multiple	III	double-blind, placebo	609	Rilotumumab-epirubicin-cisplatin-capecitabine	61 (28-84)	(67)
					Placebo-epirubicin-cisplatin-capecitabine	59 (26-81)	(72)
Cocconi, 1994[27]	Italy	III	NR	130	Cisplatin-epirubicin-leucovorin-flurouracil	62 (28-74)	60 (71)
					Fluorouracil-doxorubicin-mitomycin	65 (40-75)	42 (81)
Coombes, 1994[28]	United Kingdom	NR	NR	69	Epirubicin	59.9 (9.3)*	27 (7.5)*
					Fluorouracil	55.6 (9.2)*	24 (7.3)*
Curran, 2009[29]	Multiple	III	NR	333	Irinotecan-fluorouracil	NR	NR
					Cisplatin-fluorouracil		
Fuchs, 2019[30]	Multiple	III	double-blind, placebo	645	Ramucirumab-flurouracil-cisplatin	60 (51-68)	214 (66)
					Placebo-flurouracil-cisplatin	62 (54-68)	215 (67)
Gubanski, 2010[31]	Sweden	II	Crossover	80	Irinotecan-5-fluorouracil-leucovorin	63 (39-79)	(67)
					Docetaxel-leucovorin	64 (42-75)	(87)
Högner, 2021[32]	Germany	II	Open label	87	Pazopanib-5-fluorouracil-oxaliplatin	65	37 (72)

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					Fluorouracil-leucovorin-oxaliplatin	60	17 (63)
Icli, 1998[33]	Turkey	III	NR	131	Etoposide-epirubicin-cisplatin	52.7 (9.2)*	(68.8)
					5-fluorouracil-epirubicin-cisplatin	52.7 (9.4)*	(59.7)
Janjigian, 2021[34]	Multiple	III	Open label	1581	Nivolumab-capecitabine-oxaliplatin or leucovorin-fluorouracil-oxaliplatin	62 (54-69)	540 (68)
					Capecitabine-oxaliplatin or leucovorin-fluorouracil-oxaliplatin	61 (53-68)	560 (71)
Kang, 2009[35]	Multiple	III	Open label	316	Cisplatin-capecitabine	56 (26-74)	103 (64)
					Cisplatin-fluorouracil	56 (22-73)	108 (69)
Ochend-uszko, 2015[36]	Poland	III	NR	56	Epirubicin-oxaliplatin-capecitabine	57.9 (10.8)	16 (55)
					Docetaxel-cisplatin-5-fluorouracil-leucovorin	60.3 (9.11)	13 (48)
Petersen, 2021[37]	Denmark	II	Open label	110	Docetaxel-carboplatin-capecitabine	64 (36-79)	79 (81)
					Epirubicin-oxaliplatin-capecitabine		
Roth, 2007[38]	Multiple	II	3-arm	119	Epirubicin-cisplatin-flurouracil	59 (32-71)	75
					Docetaxel-cisplatin	58 (40-70)	76
					Docetaxel-cisplatin-fluorouracil	61 (35-78)	61
Shitara, 2020[39]	Multiple	II	Open label	763	Pembrolizumab	61 (20-83)	180 (70.3)
					Pembrolizumab-cisplatin-capecitabine-fluorouracil	62 (22-83)	195 (75.9)
					Placebo-cisplatin-capecitabine-fluorouracil	62.5 (23-87)	179 (71.6)
Shitara, 2022[40]	Multiple	III	Open label	813	Nivolumab-ipilimumab	62 (22–84)	278 (68)
					Capecitabine-oxaliplatin or leucovorin-fluorouracil-oxaliplatin	61 (23–90)	280 (69)
Van Cutsem, 2006[41]	Multiple	III	Open label	457	Docetaxel-cisplatin-fluorouracil Cisplatin-fluorouracil	55 (25-79)	317 (71)
Webb, 1997[42]	United Kingdom	II	Open label	256	Epirubicin-cisplatin-flurouracil	59 (35-79)	99
					Fluorouracil-doxorubicin-methotrexate	60 (29-78)	110

NR = not reported in the study. S-1 is a novel oral fluoropyrimidine derivative. + = min-max. * = mean and standard deviation.

The characteristics of the cancer and outcomes reported are shown in Table 2. More than 50% of trial patients had a gastric tumor. The proportion of trial participants with metastatic disease was between 60% and 97.3%.

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Table 2. Characteristics of the cancer and reported outcomes.

Author, year	Tumor location - stomach gastric, n (%)	Disease stage, n (%)		No. of organs involved in metastases, n (%)		ECOG status n (%)		Outcomes
		Locally advanced	Metastatic	1-2	>2	0-1	≥2	
Ajani, 2005[19]	106 (68)	5 (3)	147 (95)	84 (61)	61 (39)	66 (43)	NR	Complete response, Objective response rate, Overall survival, partial response, Time to progression
Ajani, 2007[20]	NR	12 (3)	430 (97)	(53.8) (54.9)	(45.2) (44.6)	80 (36) 81 (36)	NR NR	Time to 5% deterioration of global health status from baseline
Ajani, 2010[21]	855 (83.1)	43 (4.2)	1085 (95.7)	NR	NR	1029 (58.6)	NR	Overall survival, Progression-free survival, Response rate
Al-Batran, 2008[22]	92 (82)	3 (2.7) 10 (9.3)	109 (97.3) 98 (90.7)	59 (52.7) 63 (58.3)	53 (47.4) 45 (41.7)	103 (92) 97 (90)	9 (8) 11 (10)	Overall survival, Progression-free survival, Response rate
Al-Batran, 2013[23]	45 (63)	22 (31) 22 (32)	50 (69) 49 (68)	Median = 2		67 (93) 65 (92)	5 (7) 6 (9)	Objective response rate
Bouche, 2004[24]	(71) (70) (67)	NR	NR	(80) (85) (83)	(20) (15) (17)	(73) (75) (78)	(27) (25) (22)	Overall survival, Progression-free survival, Response rate
Cascinu, 2011[25]	69 (89)	8 (10)	70 (89)	NR	NR	73 (93.7)	5 (6.3)	Objective response rate, Overall survival, Time to progression
Catenacci, 2017[26]	227 (75) 195 (64)	NR NR	284 (93) 283 (93)	NR	NR	304 (100) 304 (100)	0 (0) 1 (<1)	Duration of response, Overall survival, Progression-free survival, Time to progression
Cocconi, 1994[27]	NR	NR	NR	NR	NR	NR NR	5 (6) 5 (10)	Duration of response, Objective response rate, Overall survival, Time to progression
Coombes, 1994[28]	NR	NR	NR	NR	NR	NR	NR	Overall survival
Curran, 2009[29]	NR	NR	NR	NR	NR	NR	NR	Quality of life, Time to progression
Fuchs, 2019[30]	242 (74) 239 (75)	NR	NR	243 (75) 242 (76)	81 (25) 76 (24)	326 (100) 319 (100)	NR NR	Objective response rate, Overall survival, Progression-free survival, Time to progression
Gubanski, 2010[31]	NR NR	NR NR	NR NR	NR NR	NR NR	(88) (99)	(1) (18)	Overall survival, Progression-free survival

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Högner, 2021[32]	21 (41) 19 (70)	NR	NR	15 (27) 13 (48)	6 (71) 14 (51)	NR	NR	Objective response rate, Overall survival, Progression-free survival
Icli, 1998[33]	NR	17.2 20.9	82.8 79.1	NR	NR	(65.6) (68.6)	(34.4) (31.4)	Objective response rate, Overall survival
Janjigian, 2021[34]	544 (70) 556 (70)	27 (3) 34 (4)	757 (96) 756 (95)	164 (21) 183 (23)	602 (76) 583 (74)	NR	NR	Overall survival, Progression-free survival
Kang, 2009[35]	NR	NR	NR	127 (80) 126 (80)	32 (20) 27 (20)	Median=1 (0-1)	NR	Duration of response, Objective response rate, Overall survival, Progression-free survival
Ochend-uszko, 2015[36]	NR	1 (4) 3 (11)	28 (97) 24 (89)	27 (91) 23 (85)	2 (7) 4 (15)	26 (89) 25 (93)	3 (10) 2 (7)	Overall survival, Progression-free survival
Petersen, 2021[37]	25 (26)	10 (10)	88 (89)	54 (55)	44 (45)	98 (100)	NR	Overall survival, Progression-free survival
Roth, 2007[38]	NR	NR	(83) (82) (95)	(90) (79) (84)	(9) (21) (15)	NR	NR	Overall survival, Quality of life, Time to progression
Shitara, 2020[39]	176 (68.8) 170 (66.1) 181 (72.4)	NR	NR	NR	NR	NR	NR	NR
Shitara, 2022[40]	282 (69) 282 (70)	14 (3) 18 (4)	391 (96) 386 (96)	83 (20) 326 (80)	100 (25) 304 (75)	409 (100) 404 (100)	NR NR	Duration of response, Overall survival, Progression-free survival, Quality of life
Van Cutsem, 2006[41]	NR	12 (3)	43 (97)	242 (54)	200 (45)	161 (36)	NR	Objective response rate, Overall survival, Time to progression
Webb, 1997[42]	72 (57) 73 (56)	47 (37) 51 (40)	79 (63) 79 (60)	NR	NR	96 (76) 97 (75)	30 (24) 32 (25)	Objective response rate, Overall survival, Quality of life

NR = not reported in the study. ECOG = Eastern Cooperative Oncology Group.

2.2. Overall survival

Twenty one of the 24 included trials reported overall survival with 39 different treatment regimens. Only four of the 20 trials reporting overall survival identified a statistically significant difference between the intervention and comparison groups. One of the four studies with statistical significance was Cascinu, 2011 [25] that evaluated a three-drug combination of pegylated liposomal doxorubicin, 5-fluouracil and cisplatin with mitomycin-C, 5-fluouracil, and cisplatin as the comparative arm and found that the doxorubicin, 5-fluouracil, and cisplatin group had a higher overall survival (12.1 months vs 8.3 months). The second of the four studies was Catenacci, 2017 [26]. This was a phase III randomized controlled trial which compared a four-drug combination of rilotumumab plus standard of care (standard of care consisted of epirubicin, cisplatin, and capecitabine) compared to standard of care alone. The rilotumumab-standard of care group showed

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poorer outcomes in overall survival (8.8 months) compared to the standard of care group (10.7 months). The third of the four studies was Janjigian, 2021 [34]. This study was conducted among locally advanced and metastatic gastric cancer patients where nivolumab therapy with chemotherapy was compared to chemotherapy alone. The nivolumab group showed significantly higher overall survival (13.1 months vs 11.1 months) than the chemotherapy alone group.

The fourth study was Van Cutsem, 2006 [41]. This study compared docetaxel, cisplatin and fluorouracil with cisplatin-fluorouracil and found a longer overall survival (9.2 months) in the docetaxel, cisplatin and fluorouracil group compared to 8.6 months in the cisplatin-fluorouracil group among advanced gastric cancer patients. Among the remaining included studies that reported overall survival, 16 randomized controlled trials used various treatment regimens, 12 of which did not show statistical differences in overall survival between the treatment and comparator groups, while the remaining four randomized controlled trials did not report statistical results (Table 3).

Table 3. Efficacy of the first-line systemic treatments among trial patients with locally advanced and metastatic gastric cancer.

Author, year	Treatment arms	n for each arm	Overall survival, months		Progression free survival, months		Objective response rate, %		Other outcomes	
			Median	HR (95% CI); p	Median	HR (95% CI); p	Median	p value	Description	HR (95% CI); p
Ajani, 2005[19]	Docetaxel-cisplatin	76	9.6	1.19 (0.83-1.69)	NR	NR	26	NR	Time to progression: 5.9 months	0.80 (0.52-1.22)
	Docetaxel-cisplatin-fluorouracil	79	10.5		NR	NR	43		Time to progression: 5 months	
Ajani, 2007[20]	Docetaxel-cisplatin-fluorouracil	85	NR	NR	NR	NR	NR	NR	Time to 5% deterioration of global health status from baseline: 6.5 months	**1.45 (1.08-1.93) p=0.01**
	Cisplatin-fluorouracil	104	NR	NR	NR	NR	NR	NR	Time to 5% deterioration of global health status from baseline: 4.2 months	
Ajani, 2010[21]	Cisplatin-S1	521	8.6	0.92 (0.80-1.05) 0.20	4.8	0.99 (0.86-1.14)	29.0	NR	Median duration of response: 6.5 months	0.77 (0.57-1.03)
	Cisplatin-fluorouracil	508	7.9		5.5		32.0		Median duration of response: 5.8 months	
Al-Batran, 2008[22]	Fluorouracil-leucovorin-oxaliplatin	112	10.7 (8.5-13.9)	p=0.51	5.8 (4.5-6.6)	NR	34.8	NR	NR	NR
	Fluorouracil-leucovorin-cisplatin	102	8.8 (7.7-12.0)		3.9 (3.1-4.8)		24.50		NR	NR
Al-Batran, 2013[23]	Fluorouracil-leucovorin-oxaliplatin-docetaxel	72	NR	NR	NR	NR	48.6 (36.7-60.7)	**p=0.02**	Quality of life global health status scores at 0, 8, 16 and 24	No significant differenc

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									weeks: 56.5 ± 24.4, 53.6 ± 19.9, 56.8 ± 19.5 and 53.7 ± 22.8 Quality of life global health status scores at 0, 8, 16 and 24 weeks: 49.4 ± 24.7, 58.2 ± 19.8, 53.3 ± 21.0 and 55.5 ± 16.9	es between arms
	Fluorouracil-leucovorin-oxaliplatin	71	NR	NR	NR	NR	28.2 (18.1-40.1)			
Bouche, 2004[24]	Leucovorin–5-flurouracil	45	6.8 (2.6-11.1)	NR	3.2 (1.8-4.6)	NR	13 (3.4-23.3)	NR	Mean difference in global quality of life scores between Leucovorin–5-flurouracil vs Leucovorin–5-flurouracil-irinotecan = 2.2. Mean difference in global quality of life scores between Leucovorin–5-flurouracil–cisplatin vs Leucovorin–5-flurouracil-irinotecan = 0.8	**Treatment effect: 0.89; p<0.01**
	Leucovorin–5-flurouracil–cisplatin	44	9.5 (6.9-12.2)	NR	4.9 (3.5-6.3)		27 (14.1-40.4)			
	Leucovorin–5-flurouracil-irinotecan	45	11.3 (9.3-13.3)	NR	6.9 (5.5-8.3)		40 (25.7-54.3)			
Cascinu, 2011[25]	5-flurouracil-cisplatin-doxorubicin	39	12.1	**0.63 (0.34-0.91) p=0.02**	NR	NR	64.1 (48-77)	**p=0.04**	Time to progression: 7.9 month	**0.62, (0.37-0.97) p=0.04**
	5-flurouracil-cisplatin-mitomycin	39	8.3		NR	NR	39 (24-54)		Time to progression: 5.1 months	
Catenacci, 2017[26]	Rilotumumab-epirubicin-cisplatin-capecitabine	298	8·8 (7·7–10·2)	**1·34 (1·10–1·63) p<0·01)**	5·6 (5·3–5·9)	**1·26 (1·04–1·51)**	29·8 (24·3–35·7)	NR	Time to progression: 6·1 month (95% CI=5·7–7·9) Duration of response: 2·8 months (IQR=2·7–2·9)	1·24 (0·96–1·59) p=0·10
	Placebo-epirubicin-cisplatin-capecitabine	299	10·7 (9·6–12·4)		6·0 (5·7–7·2)		44·6 (38·5–50·8)		Time to progression: 7·1 month (5·9–7·9) Duration of response: 2·8 months (2·6–2·9)	
Cocconi, 1994[27]	Cisplatin-epirubicin-	85	8.1 (0.2-33.5)	p=0.24	NR	NR	43	**P<0.01**	Time to progression: 4.7	p=0.58

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	leucovorin-flurouracil								month (0.2-26.5)	
	Fluorouracil-doxorubicin-mitomycin	52	5.6 (0.5-49.1)		NR	NR	15		2.6 month (0.5-33.2)	
Coombes, 1994[28]	Epirubicin	36	88.2% died	p=0.65	NR	NR	NR	NR	NR	NR
	Fluorouracil	33	3.9% died		NR	NR	NR	NR	NR	NR
Curran, 2009[29]	Irinotecan-fluorouracil	172	NR	NR	NR	NR	NR	NR	Time to progression: 5 month; Global health status mean 62.4 (20.1)	p=0.088; p=0.061
	Cisplatin-fluorouracil	165	NR	NR	NR	NR	NR	NR	Time to progression: 4.2 months; Global health status mean- 56.9 (21.1)	
Fuchs, 2019[30]	Ramucirumab-flurouracil-cisplatin	326	11·2 (9·9–11·9)	0·96 (0·80–1·16) p=0·67	5·7 (5·5–6·5)	**0.75, (0.61–0.94) p=0.01**	41.1 (35.8-46.4)	p=0.17	Time to progression: 6.8 month (5.9-7.7)	p=0.70 (0.57-0.86)
	Placebo-flurouracil-cisplatin	319	10·7 (9·5–11·9)		5·4 (4·5–5·7)		36.4 (31.1-41.6)		Time to progression: 5.8 months (5.6-6.4)	
Gubanski, 2010[31]	Irinotecan-5-fluorouracil-leucovorin	39	11.5	p=0.3	4.9	NR	NR	NR	NR	NR
	Docetaxel-leucovorin	39	10.6		5.0		NR	NR	NR	NR
Högner, 2022[32]	Pazopanib-5-fluorouracil-oxaliplatin	51	10.2 (5.5-14.9)	1.01 (0.62-1.65) p=0.95	4.7 (2.9-6.5)	0.96 (0.60-1.55) p=0.88	25	NR	NR	NR
	Fluorouracil-leucovorin-oxaliplatin	27	7.3 (4.9-9.7)		4.5 (1.8-7.1)		26		NR	NR
Icli, 1998[33]	Etoposide-epirubicin-cisplatin	64	6.0	p>0.05	NR	NR	20.30	p=0.63	NR	NR
	5-fluorouracil-epirubicin-cisplatin	67	5.0		NR	NR	15.30		NR	NR
Janjigian, 2021[34]	Nivolumab-capecitabine-oxaliplatin or leucovorin-fluorouracil-oxaliplatin	789	13·1 (6·7–19·1)	**0·71 (0·59–0·86) p<0·01**	7·7 (7·0–9·2)	**0·68 (0·56–0·81) p<0·01**	NR	NR	NR	NR
	Capecitabine-oxaliplatin or leucovorin-fluorouracil-oxaliplatin	792	11·1 (5·8–16·1)		6·1 (5·6–6·9)		NR	NR	NR	NR
Kang, 2009[35]	Cisplatin-capecitabine	160	10.4 (9.1–11.0)	0.85, (0.65–1.11)	5.6 (4.9–7.3)	**0.81, (0.63–**	46 (38-55)	**1.80 (1.11–**	Mean duration of response:7.6 months	0.88 (0.56–1.36)

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	Cisplatin-fluorouracil	156	8.9 (7.3–10.2)		5.0 (4.2–6.3)	**1.04) p< 0.01**	32 (24-41)	**2.94) p=0.02**	Mean duration of response: 6.2 months	p=0.55
Ochendszko, 2015[36]	Epirubicin-oxaliplatin-capecitabine	29	9.5	p=0.14	6.4	p=0.44	NR	NR	NR	NR
	Docetaxel-cisplatin-5-fluorouracil-leucovorin	27	11.9		6.8		NR	NR	NR	NR
Petersen, 2021[37]	Docetaxel-carboplatin-capecitabine	49	9.8 (8.2-11.0)	NR	6.1 (5.5-7.1)	NR	NR	NR	NR	NR
	Epirubicin-oxaliplatin-capecitabine	49	10.2 (8.0-11.9)	NR	5.1 (4.3-7.0)		NR	NR	NR	NR
Roth, 2007[38]	Epirubicin-cisplatin-flurouracil	40	8.3 (7.2-13.0)	NR	NR	NR	NR	NR	Time to progression: 4.9 (3.2-6.1) months	NR
	Docetaxel-cisplatin	38	11 (7.8-12.5)	NR	NR	NR	NR	NR	Time to progression: 3.6 (2.8-4.5) months	
	Docetaxel-cisplatin-fluorouracil	41	10.4 (8.3-12.0)	NR	NR	NR	NR	NR	Time to progression: 4.6 (3.5-5.6) months	
Shitara, 2020[39]	Pembrolizumab	256	10.6 (7.7-13.8)		2.0 (1.5-2.8)	**1.66 (1.37-2.01)**	NR	NR	NR	NR
	Pembrolizumab-cisplatin-capecitabine-fluorouracil	257	12.5 (10.8-13.9)	0.91 (0.69-1.18)	6.9 (5.7-7.3)		NR	NR	NR	NR
	Placebo-cisplatin-capecitabine-fluorouracil	250	11.1 (9.2-12.8)	0.85 (0.70-1.03)	6.4 (5.7-7.0)	0.84 (0.70-1.02) p=0.04	NR	NR	NR	NR
Shitara, 2022[40]	Nivolumab-ipilimumab	409	11.2 (9.2-13.4)	0.89 (0.71-1.10) p=0.23	2.8 (2.6-3.6)	**1.66 (1.40-1.95)**	NR	NR	Duration of response: 13.8 months (9.4-17.7)	NR
	Capecitabine-oxaliplatin or leucovorin-fluorouracil-oxaliplatin	404	11.6 (10.1-12.7)		7.1 (6.9-8.2)		NR	NR	Duration of response: 6.8 months (5.6-7.2)	NR
Van Cutsem, 2006[41]	Docetaxel-cisplatin-fluorouracil	221	9.2 (8.4-10.6)	**1.29 (1.0-1.6) p=0.02**	NR	NR	81 (37)	p=0.01	Time to progression: 5.6 (4.9-5.9) months	**1.47 (1.19-1.82)**
	Cisplatin-fluorouracil	224	8.6 (7.2-9.5)		NR	NR	57 (25)		Time to progression: 3.7 (3.4-4.5) months	

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Webb, 1997[42]	Epirubicin-cisplatin-flurouracil	111	8.9	NR	NR	NR	45 (36-54)	p<0.01	NR	NR
	Fluorouracil-doxorubicin-methotrexate	108	5.7	NR	NR	NR	21 (13-29)		NR	NR

S1 is a novel oral fluoropyrimidine derivative. NR = not reported in the study. CI = confidence interval. HR = hazards ratio. Hazards ratio and p values in **bold** indicates statistically significant values of p<0.05.

2.3. Progression-Free Survival

Thirteen of the 24 included randomized controlled trials using 39 regimens reported progression free survival outcomes. Only six of the 13 randomized controlled trials showed statistically significant improvement in progression-free survival. The first study reporting progression-free survival by Catenacci, 2017 [26] was a phase III trial among advanced gastric cancer patients with rilotumumab plus standard of care (standard of care consisted of epirubicin, cisplatin, and capecitabine) compared to standard of care alone. This study showed that rilotumumab plus standard of care had a shorter progression-free survival (5.6 months) compared to standard of care alone (6.07 months). The second study reporting progression-free survival by Fuchs, 2019 [30] was a phase III trial comparing ramucirumab and standard first-line therapy (fluorouracil and capecitabine) with placebo plus standard first-line therapy. Ramucirumab plus first line therapy showed significantly longer progression-free survival (5.7 months) compared to placebo and first line therapy (5.4 months). The third study reporting progression-free survival by Janjigian, 2021 [34] was a phase III randomized controlled trial which compared the role of the newer agent nivolumab and standard chemotherapy with standard chemotherapy alone. Nivolumab and standard chemotherapy showed longer progression-free survival (7.7 months) compared to the chemotherapy alone group (6.1 months). The fourth study reporting progression-free survival by Kang, 2009 [35] was a randomized phase III noninferiority trial which compared capecitabine/cisplatin to 5-fluorouracil/cisplatin. The capecitabine/cisplatin group showed significant noninferiority for progression-free survival for patients with advanced gastric cancer (5.6 months) versus 5.0 months for the 5-fluorouracil/cisplatin group. The fifth study reporting progression-free survival by Shitara, 2020 [39] was a phase III trial comparing three groups (group 1: pembrolizumab alone, group 2: standard chemotherapy, group 3: pembrolizumab and standard chemotherapy). Progression-free survival was higher in group 2 (standard chemotherapy) when compared to group 1 (pembrolizumab alone) with 6.4 months and 2.0 months progression-free survival respectively. The sixth study reporting progression-free survival by Shitara, 2022 [40] compared nivolumab plus ipilimumab to chemotherapy alone (i.e., the CheckMate 649 trial). Chemotherapy alone showed a longer progression-free survival (7.1 months) than nivolumab plus ipilimumab (2.8 months) (Table 3).

2.4. Objective response rate

Of the 14 randomized controlled trials that reported objective response rate, five showed statistically significant overall response rates. The first trial reporting a statistically significant response rate, Al-Batran, 2013 [22], compared fluorouracil-leucovorin-oxaliplatin-docetaxel to fluorouracil-leucovorin-oxaliplatin in a sample of older adult advanced gastric cancer patients. The fluorouracil-leucovorin-oxaliplatin-docetaxel group showed a higher overall response rate of 48.6% compared to 28.2% in the fluorouracil-leucovorin-oxaliplatin group. The second trial reporting a statistically significant response rate, Cascinu, 2011 [25], compared 5-fluorouracil, cisplatin and pegylated liposomal doxorubicin to 5-fluorouracil, cisplatin and mitomycin-C. The 5-fluorouracil, cisplatin and pegylated liposomal doxorubicin group showed a higher overall response rate (64.1%) compared to the 5-fluorouracil, cisplatin, and mitomycin-C group (38.5%). The third trial reporting a statistically significant response rate, Cocconi, 1994,[27] compared cisplatin, epirubicin, leucovorin, and fluorouracil with the standard combination of fluorouracil, doxorubicin, and mitomycin. This trial found a higher overall response rate with cisplatin-epirubicin-leucovorin-flurouracil (43%) than

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fluorouracil-doxorubicin-mitomycin (15%). The fourth trial reporting a statistically significant response rate, Kang, 2009 [37], was a multinational phase III trial among advanced gastric cancer patients that compared capecitabine and cisplatin to 5-fluorouracil and cisplatin. This trial found a higher response rate (46%) with capecitabine and cisplatin than 5-fluorouracil and cisplatin (32%). The fifth trial reporting a statistically significant response rate, Webb, 1997 [42], compared epirubicin-cisplatin-5-fluorouracil with 5-fluorouracil-doxorubicin-methotrexate. A higher response rate of 45% was seen with epirubicin-cisplatin-5-fluorouracil than with 5-fluorouracil-doxorubicin-methotrexate (21%) (Table 3).

2.5. Other Outcomes Reported

Some of the other statistically significant clinical efficacy outcomes reported in included clinical trials were: time to 5% deterioration of global health status from baseline (a quality-of-life assessment), mean difference in global health scores (also a quality-of-life measure), and time to progression. Anjani, 2007 [20] prospectively assessed quality of life as one of the secondary end points of the phase III trial that compared docetaxel-cisplatin-fluorouracil with cisplatin-fluorouracil. Time to 5% deterioration of global health status from baseline was longer in the docetaxel-cisplatin-fluorouracil group (6.5 months) compared to 4.2 months in the cisplatin-fluorouracil group showing the better preservation of quality of life with the addition of docetaxel. All three treatments arms in the Bouche, 2004 [24] trial had improved global quality of life health scores when compared to baseline. Time to progression was statistically significantly improved in two studies: Cascinu, 2011 [25] and Van Cutsem, 2006 [41] (Table 3).

2.6. Adverse events and safety

Twenty-two of the 24 randomized controlled trials included reported some grade of adverse events in study patients. Only grade three and higher treatment-related adverse events were summarized in Table 4. The most common grade 3–4 hematological toxicities were neutropenia, anemia, thrombocytopenia, and leucopenia. While the most common nonhematological toxicities were nausea, vomiting, diarrhea, and fatigue (Table 4).

Table 4. Grade three or four adverse events and outcomes reported in included studies.

Author, year	Sample size	Treatment arms	Neutropenia, n (%)	Anemia, n (%)	Thrombocytopenia, n (%)	Leukopenia, n (%)	Nausea, n (%)	Vomiting, n (%)	Diarrhea, n (%)	Fatigue, n (%)
Ajani, 2005[19]	76	Docetaxel-cisplatin-fluorouracil	65 (87)	24 (32)	1 (1)	49 (65)	8 (11)	NR	4 (5)	NR
	79	Docetaxel-cisplatin	66 (86)	22 (29)	9 (12)	53 (69)	16 (20)	NR	16 (20)	NR
Ajani, 2010[21]	521	Cisplatin-S1	167 (32)	107 (21)	43 (8)	71 (14)	39 (8)	41 (8)	NR	64 (12)
	508	Cisplatin-fluorouracil	320 (64)	105 (21)	68 (14)	167 (3)	49 (10)	49 (10)	NR	67 (13)
Al-Batran, 2008[22]	112	Fluorouracil-leucovorin-oxaliplatin	13 (12)	3 (3)	4.5 (4)	7 (6)	5 (5)	3 (3)	7 (6)	4 (4)
	102	Fluorouracil-leucovorin-cisplatin	15 (15)	7 (7)	4 (4)	12 (12)	9 (9)	6 (6)	5 (5)	7 (7)
Al-Batran, 2013[23]	72	Fluorouracil-leucovorin-oxaliplatin-docetaxel	38 (53)	8 (11)	2 (3)	21 (29)	15 (21)	3 (4)	6 (8)	8 (11)
	71	Fluorouracil-leucovorin-oxaliplatin	9 (13)	3 (4)	2 (3)	4 (6)	5 (7)	1 (2)	1 (2)	5 (7)
Bouche, 2004[24]	45	Leucovorin–5-flurouracil	(11)	(16)	(2)	NR	(18)	NR	(2)	NR
	44	Leucovorin–5-flurouracil-cisplatin	(61)	(30)	(2)	NR	(23)	NR	(2)	NR
	45	Leucovorin–5-flurouracil-irinotecan	(40)	(16)	(0)	NR	(9)	NR	(22)	NR

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Cascinu, 2011[25]	39	5-flurouracil-cisplatin-doxorubicin	6 (15)	0 (0)	2 (5)	NR	1 (3)	NR	0 (0)	NR
	39	5-flurouracil-cisplatin-mitomycin-C	10 (26)	0 (0)	8 (21)	NR	1 (3)	NR	1 (3)	NR
Catenacci, 2017[26]	298	Rilotumumab-epirubicin-cisplatin-capecitabine	111 (37)	97 (33)	NR	NR	128 (43)	100 (34)	61 (20)	103 (35)
	299	Placebo-epirubicin-cisplatin-capecitabine	126 (42)	125 (42)	NR	NR	153 (51)	98 (33)	81 (27)	100 (33)
Cocconi, 1994[27]	85	Cisplatin-epirubicin-leucovorin-flurouracil	8 (9)	1 (1)	4	NR	17	10 (37)	3 (11)	NR
	52	Fluorouracil-doxorubicin-mitomycin	0 (0)	1 (2)	0	NR	4	2 (8)	2 (8)	NR
Curran, 2009[29]	172	Irinotecan-fluorouracil	(24.8)	NR	(2)	NR	NR	NR	(22)	NR
	165	Cisplatin-fluorouracil	(51.6)	NR	(12)	NR	NR	NR	(7)	NR
Fuchs, 2019[30]	326	Ramucirumab-fluorouracil-cisplatin	85 (26)	39 (12)	25 (8)	NR	22 (7)	21 (7)	15 (5)	27 (8)
	319	Placebo-fluorouracil-cisplatin	85 (27)	44 (14)	11 (4)	NR	26 (8)	31 (10)	23 (7)	25 (9)
Gubanski,2010[31]	39	Irinotecan-5-fluorouracil-leucovorin	NR	NR	NR	NR	(4)	NR	(5)	(9)
	39	Docetaxel-leucovorin	NR	NR	NR	NR	(12)	NR	(2)	(3)
Högner, 2022[32]	51	Pazopanib-5-fluorouracil-oxaliplatin	12 (24)	1 (2)	1 (2)	3 (6)	8 (16)	3 (6)	1 (2)	4 (8)
	27	Fluorouracil-leucovorin-oxaliplatin	1 (4)	3 (11)	3 (11)	NR	NR	2 (7)	2 (7)	1 (4)
Icli, 1998[33]	64	Etoposide-epirubicin-cisplatin	NR	NR	NR	NR	(6.3)	NR	(1.6)	NR
	67	5-fluorouracil-epirubicin-cisplatin	NR	NR	NR	NR	(9)	NR	(1.5)	NR
Janjigian, 2021[34]	789	Nivolumab-capecitabine-oxaliplatin or leucovorin-fluorouracil-oxaliplatin	31 (4)	3 (<1)	4 (1)	NR	0 (0)	2 (<1)	2 (<1)	0 (0)
	792	Capecitabine-oxaliplatin or leucovorin-fluorouracil-oxaliplatin	23 (3)	1 (<1)	1 (1)	NR	0 (0)	0 (0)	0 (0)	19 (1)
Kang, 2009[35]	160	Cisplatin-capecitabine	25 (16)	NR	NR	4 (3)	3 (2)	11 (7)	8 (5)	1 (<1)
	156	Cisplatin- fluorouracil	29 (19)	NR	NR	6 (4)	4 (3)	13 (8)	7 (5)	4 (<3)
Ochenduszko, 2015[36]	29	Epirubicin-oxaliplatin-capecitabine	21 (72)	2 (7)	0 (0)	2 (7)	1 (4)	0 (0)	1 (4)	2 (7)
	26	Docetaxel-cisplatin-5-fluorouracil-leucovorin	13 (50)	2 (7)	0 (0)	3 (12)	10 (29)	0 (0)	1 (4)	1 (4)
Petersen, 2021[37]	49	Docetaxel-carboplatin-capecitabine	42 (82)	3 (6)	NR	NR	0 (0)	NR	4 (8)	3 (6)
	49	Epirubicin-oxaliplatin-capecitabine	42 (82)	3 (6)	NR	NR	0 (0)	NR	4 (8)	3 (6)
Roth, 2007[38]	40	Epirubicin-cisplatin-flurouracil	(59)	NR	(3)	NR	NR	NR	(6)	NR
	38	Docetaxel-cisplatin	(76)	NR	(0)	NR	NR	NR	(3)	NR
	41	Docetaxel-cisplatin-flurouracil	(80)	NR	(3)	NR	NR	NR	(15)	NR
Shitara, 2020[39]	254	Pembrolizumab	0 (0)	NR	0 (0)	0 (0)	1 (0.4)	0(0)	1 (1)	1 (0)
	250	Pembrolizumab-cisplatin-capecitabine-fluorouracil	63 (25)	NR	7 (3)	7 (3)	19 (8)	12(5)	12 (5)	19 (8)
	244	Placebo-cisplatin-capecitabine-fluorouracil	68 (28)	NR	6 (3)	10 (4)	18 (7)	14(6)	14 (6)	14 (6)
Shitara, 2022[40]	403	Nivolumab-ipilimumab	1 (<1)	5 (1)	1 (<1)	0 (0)	6 (1)	4(1)	11 (3)	11 (3)
	389	Capecitabine-oxaliplatin or Leucovorin-fluorouracil-oxaliplatin	44 (11)	9 (2)	7 (2)	9 (2)	16 (4)	11(3)	15 (4)	8 (2)

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Van Cutsem, 2006[41]	221	Docetaxel-cisplatin-fluorouracil	181 (82)	40 (18)	17 (8)	144 (65)	32 (14)	NR	43 (19)	NR
	224	Cisplatin- fluorouracil	126 (57)	57 (26)	30 (13)	70 (31)	38 (17)	NR	18 (8)	NR
Webb, 1997[42]	126	Epirubicin-cisplatin-flurouracil	NR	(8)	(4)	(36)	(17)	NR	(6)	NR
	130	Fluorouracil-doxorubicin-methotrexate	NR	(10)	(8)	(39)	(5)	NR	(7)	NR

NR = not reported in the study. Row % might not add up to 100% as every patient would not experience an adverse event and some can have multiple adverse events.

2.7. Risk of bias assessment

Of the 24 included studies, 11 studies had a low overall risk of bias and 13 studies had some concerns overall. None of the eligible studies were at high risk of bias as rated by the five domains of the risk-of-bias tool [43]. Specifically, 20 out of the 24 randomized controlled trials were evaluated as low risk of bias concerning randomization as all the trials included specific information about randomization techniques. Since some of the trials were open-label, five studies were identified as having some risk of bias concerns in the deviations from intended interventions domain. Due to the nature of locally advanced and metastatic gastric cancer there was some missing outcomes data due to attrition, death, or loss of follow-up. Nine studies showed some risk of bias concerns in the missing outcome data domain. All clinical trials used appropriate methods to measure clinical outcomes, quality of life and adverse events reporting, thus all 24 studies had low risk of bias in the measurement of outcomes domain. Lastly, because most of the studies were analyzed based on the intention-to-treat population and had well reported clinical and safety endpoints, the selection of reported results domain was appraised as having a low risk of bias in 23 of the 24 studies (Table 5).

Table 5. Risk of bias summary of all included randomized control trials using the Cochrane Risk of Bias tool.

Author, Year	Randomization	Deviations from intended intervention	Missing outcome data	Measurement of outcome	Selection of reported results	Overall
Ajani, 2005[19]	Low	Some	Some	Low	Low	Some
Ajani, 2007[20]	Low	Low	Some	Low	Low	Some
Ajani, 2010[21]	Low	Low	Some	Low	Low	Some
Al-Batran, 2008[22]	Some	Some	Low	Low	Low	Some
Al-Batran, 2013[23]	Low	Low	Low	Low	Low	Low
Bouche, 2004[24]	Low	Low	Low	Low	Low	Low
Cascinu, 2011[25]	Low	Low	Low	Low	Low	Low
Catenacci, 2017[26]	Low	Low	Low	Low	Low	Low
Cocconi, 1994[27]	Low	Low	Some	Low	Low	Some
Coombes, 1994[28]	Some	Low	Low	Low	Low	Some
Deng, 2013[29]	Low	Low	Low	Low	Low	Low
Fuchs, 2019[30]	Low	Low	Some	Low	Low	Some
Gubanski, 2010[31]	Low	Low	Low	Low	Low	Low
Högner, 2022[32]	Low	Low	Low	Low	Low	Low
Icli, 1998[33]	Low	Low	Some	Low	Low	Some
Janjigian, 2021[34]	Low	Low	Low	Low	Low	Low
Kang, 2009[35]	Low	Some	Some	Low	Low	Some
Ochenduszko, 2015[36]	Low	Low	Low	Low	Low	Low
Petersen, 2021[37]	Low	Some	Some	Low	Low	Some

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Roth, 2007[38]	Some	Some	Low	Low	Low	Some
Shitara, 2020[39]	Low	Low	Low	Low	Low	Low
Shitara, 2022[40]	Low	Low	Low	Low	Low	Low
Van Cutsem, 2006[41]	Low	Low	Some	Low	Low	Some
Webb, 1997[42]	Some	Low	Low	Low	Some	Some

Low = low risk of bias, Some = some concerns in risk of bias.

3. Discussion

First-line treatment recommendations for patients with locally advanced and metastatic gastric cancer have been constantly updated in the United States. The National Comprehensive Cancer Network Gastric Cancer Guidelines (Version 2.2022) recommends fluoropyrimidine (fluorouracil or capecitabine) and platinum-based antineoplastic (oxaliplatin or cisplatin) and trastuzumab (for HER2 overexpression positive adenocarcinoma) or nivolumab (for HER2 overexpression negative adenocarcinoma) as preferred first-line systemic therapy for unresectable, recurrent, or metastatic gastric cancer [5]. This systematic review identified numerous first-line therapeutic options investigated in 24 randomized controlled trials among patients with locally advanced and metastatic gastric cancer before April 2022. Across treatment arms in the included randomized controlled trials, median overall survival was between 5.0 months and 13.1 months, median progression free survival was between 2.0 months and 7.7 months, and the objective response rate was between 13.0% and 64.1%. The wide range of values across these outcomes highlighted some inconsistencies across the included studies. Multiple factors likely contributed to this cross-study variability such as differences in trial phases, treatment arms, sample sizes, disease stages included, and the Eastern Cooperative Oncology Group (ECOG) status of the included patients. Specific examples of the outcomes studied are reported and discussed in the context of what is already known in the following sections.

3.1. Overall survival

The combination of nivolumab plus chemotherapy seems to produce the longest overall survival (hazard ratio=0·71, 95% confidence interval [CI]=0·59–0·86), while the shortest overall survival length was seen with the 5-fluorouracil-epirubicin-cisplatin combination. Reasons to explain this are not well documented, but it is never-the-less an encouraging finding. Immune checkpoint inhibitors have durable and significantly higher clinical efficacy than chemotherapy alone in locally advanced and metastatic gastric cancer patients. In accordance with the above outcomes, the combination of nivolumab and fluoropyrimidine with platinum-based antineoplastics is the recommended treatment for locally advanced and metastatic gastric cancer [5] due to its better overall survival outcomes. Compared with the prior systematic review conducted by Cheng and colleagues in 2018 [44] which included studies that contained both gastric and esophageal cancer cases and included world-wide trial populations, our systematic review focused on studies that included only western populations with gastric cancer [44]. The Cheng et al. study found that fluoropyrimidine plus platinum-based triple therapies (hazard ratio=0.91, 95% CI=0.83–0.99) showed the biggest improvement in overall survival in patients with advanced gastric cancer. An older systematic review by Wagner, 2006 [45] looked at first-line chemotherapy in patients with advanced gastric cancer and included overall survival as the primary outcome. This study also showed a three-drug regimen of fluorouracil, cisplatin, and an anthracycline (doxorubicin or epirubicin) achieved better survival results (hazard ratio=0.77, 95% CI=0.62-0.91) than a two drug (fluorouracil-cisplatin) combination. With the recent advancements in immunotherapies, nivolumab (a PD-L1 inhibitor) has demonstrated a significant survival benefit in the locally advanced and metastatic gastric cancer population and our review supports these results [46].

3.2. Progression-free survival

Similar to the overall survival results, a combination of nivolumab and chemotherapy showed the longest progression-free survival duration of 7.7 months (hazard ratio=0·68, 95% CI=0·56–0·81)

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among our included randomized controlled trials. In support of our findings, the CheckMate-649 trial results indicated that nivolumab was the first PD-L1 inhibitor to demonstrate superior progression-free survival duration of 7.7 months (hazard ratio=0·68, 95% CI=0·56–0·81) among our included benefits among advanced gastric cancer patients [46]. CheckMate-649 is the largest randomized, global phase III study of an immune checkpoint inhibitor-based therapy as first-line therapy for patients with gastric and esophageal cancers conducted to date. While our systemic review found that nivolumab plus chemotherapy showed the longest progression-free survival, in contrast to our findings, an older systematic review and network meta-analysis by Cheng and colleagues in 2018[44] found that fluoropyrimidine-platinum-based triple-medication therapy (hazard ratio=0.75, 95% CI=0.54–1.04) was the best regimen for progression-free survival. However, at the time Cheng et al. was conducted, nivolumab was still under development and therefore was not included. Another review article by Takashima, 2017 investigated survival outcomes in advanced gastric cancer in phase III trials. Median progression-free survival was calculated from 11 trials from all over the world and found to be in the range of 3.1 to 7.4 months [47]. The phase III trials included in this review did not include newer studies utilizing immunotherapies like nivolumab because the search was conducted from 2007-2015.

3.3. Objective response rate

In this review objective response rate was highest in the Cascinu, 2011[25] study with 64.1% in the doxorubicin-5-fluorouracil-cisplatin group. An American Society of Clinical Oncology post on the long-term support data of the CheckMate-649 trial of nivolumab plus chemotherapy group reported that with longer follow-up, the nivolumab-chemotherapy group had a higher objective response rate (58%) than chemotherapy alone [46]. As per the older systematic review by Cheng and colleagues, 5-fluorouracil plus platinum doublet (oxaliplatin or cisplatin) have demonstrated statistically significant results among the 89 global studies investigated. Another older review by Koizumi, 2007 [48] looking at global status of chemotherapies in advanced gastric cancer concluded that a promising objective response rate did not always translate into a survival benefit.

3.4. Other outcomes

Our review showed that mean global health status significantly improved from baseline in two different studies. Interim results of nivolumab-chemotherapy versus chemotherapy from the CheckMate-649 trial showed that change from baseline in health-related quality of life as assessed by EuroQol-5-dimension (EQ-5D) scores favored nivolumab-chemotherapy [49]. A systematic review by van Amelsfoort in 2021 evaluated health-related quality of life among patients with non-metastatic locally advanced gastric cancer. This review found that health-related quality of life deteriorated during the first three months after surgery and chemoradiotherapy [50].

3.5. Limitations

This review had some limitations. Oncology is a very complex and rapidly evolving area, thus there was significant heterogeneity in treatment arms and outcomes seen. Next, only systemic therapies were summarized in this review, thus surgical interventions and radiation therapy which are cardinal in the treatment of gastric cancer were not captured. Also, our study included only randomized controlled trials conducted in western populations and thus results cannot be extrapolated to make global conclusions. Clinical efficacy and safety outcomes seen in observational studies and real-world studies were also beyond the scope of this systematic review and thus our results do not necessarily reflect subsequent changes in clinical practice. In addition, publication bias can be a concern for any systematic review as studies which did not identify the treatment to be effective may not have been published. To minimize publication bias, our literature search also included any unpublished or ongoing trials. With a variety of novel immune check point inhibitors and targeted therapies that are being explored in the oncology space, some of the ongoing trials do not have comprehensive information captured yet published.

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3.6. Future research

With emerging clinical data for checkpoint inhibitors in locally advanced and metastatic gastric cancer, immunotherapies such as nivolumab have the potential to improve outcomes in patients who have unresectable, locally advanced and metastatic gastric cancer and may provide new treatment options for this patient population in the future. Identification of predictive biomarkers for gastric cancer are being increasingly developed [51]. Examples include tumor agnostic biomarker mismatch repair or microsatellite instability which is a robust biomarker of immune responses. Evaluation of PD-L1 expression in tumors is critical as higher levels of PD-L1 are associated with poor prognosis. Future research should aim to supplement the published data by conducting larger real world observational studies, consider the widespread testing for biomarkers for locally advanced and metastatic gastric cancer, and also seek to evaluate the economic and quality of life burden of locally advanced and metastatic gastric cancer.

4. Materials and Methods

4.1. Types of studies

Phase II and phase III randomized controlled trials were included in the systematic review if they compared a systemic first line single agent or combination therapy, as per the National Comprehensive Cancer Network guidelines (version 2.2022),[5] with another type of systemic first line therapy, placebo, best supportive care, or no treatment as comparison groups. We included the full text or the abstract of studies if data for outcomes were reported. We included trials with mixed disease stages if they reported outcomes separately for metastatic disease.

4.2. Types of participants

Adults aged 18 years and older with histologically confirmed adenocarcinoma of the stomach and locally advanced unresectable or metastatic disease were included. Trials and studies of patients with adjacent organs and lymph node metastasis (defined as American Joint Committee on Cancer tumor node metastasis stage III) and distant metastatic (defined as American Joint Committee on Cancer tumor node metastasis stage IV) gastric cancer were included. No restrictions in terms of sex, drug dosage, radiologic examination, or treatment duration were applied.

4.3. Types of interventions

All comparisons of systemic therapies for the treatment of locally advanced and metastatic gastric cancer as per National Comprehensive Cancer Network guidelines 2022 [5] were included, such as: immune checkpoint inhibitors; single-agent chemotherapy; double/triple agent chemotherapy; and targeted drug therapy.

4.4. Types of outcome measures

All relevant outcomes available in the reports were included, such as: overall survival (defined as survival time from the start of the intervention until death from any cause); progression-free survival (defined as survival time without disease progression or death from the start of the intervention, i.e., randomization); time to progression (defined as time from randomization in the study to tumor progression); objective response rate (defined as the proportion of patients with a complete response or partial response to treatment according to Response Evaluation Criteria in Solid Tumors); quality of life (measured using a validated scale/questionnaire); and grade three or higher serious adverse events (measured using National Cancer Institute-Common Terminology Criteria for Adverse Events) [52].

4.5. Search strategy

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Literature searches were conducted to identify all published and unpublished phase II and phase III randomized controlled trials. Four electronic databases (PubMed, Embase, Web of Science, and Cochrane Central Register of Controlled Trials) were thoroughly searched as were abstracts from the American Society of Clinical Oncology (ASCO) meeting library. Reference lists of primary studies were reviewed and included articles were checked for any further references. Google and Google Scholar were also searched to identify any missing trials.

The search strategy was built with the help of a health sciences librarian, and it consisted of a combination of Medical Subject Heading (MeSH) terms and text words related to gastric cancer, metastases, and first line systemic therapies. The MEDLINE search strategy (Table 6) was developed first, and then adapted for use in the other databases (Appendix 1). The search was confined to English language publications and trials conducted among western populations, and was conducted from database inception until April 2022. Trials with the longest follow up periods were selected if multiple reports existed for the same trial.

Table 6. PubMed Search Strategy.

("Stomach"[Mesh] OR "stomach"[ALL] OR "Gastric"[ALL] OR "Esophagogastric"[ALL] OR "oesophagogastric"[ALL] OR "Gastroesophageal"[ALL] OR "gastrooesophageal"[ALL]) AND ("Neoplasms"[Mesh] OR "Carcinoma"[Mesh] OR "Stomach Neoplasms"[Mesh] OR "Adenocarcinoma"[Mesh] OR "Cancer*"[ALL] OR "Neoplasm*"[ALL] OR "Adenocarcinoma*"[ALL] OR "Carcinoma*"[ALL] OR "Tumor*"[ALL] OR "Neoplasm, Stomach"[ALL] OR "Stomach Neoplasm"[ALL] OR "Neoplasms, Stomach"[ALL] OR "Gastric Neoplasms"[ALL] OR "Gastric Neoplasm"[ALL] OR "Neoplasm, Gastric"[ALL] OR "Neoplasms, Gastric"[ALL] OR "Cancer of Stomach"[ALL] OR "Stomach Cancers"[ALL] OR "Gastric Cancer"[ALL] OR "Cancer, Gastric"[ALL] OR "Cancers, Gastric"[ALL] OR "Gastric Cancers"[ALL] OR "Stomach Cancer"[ALL] OR "Cancer, Stomach"[ALL] OR "Cancers, Stomach"[ALL]) AND ("Neoplasm Metastasis"[Mesh] OR "secondary" [Subheading] OR "Advanced"[ALL] OR "Metastatic"[ALL] OR "Metastasis"[ALL] OR "Recurrent"[ALL] OR "Unresectable"[ALL] OR "Inoperable"[ALL] OR "Incurable"[ALL] OR "Neoplasm metastasis"[ALL] OR "Secondary neoplasm*"[ALL] OR "Secondary cancer*"[ALL] OR "Secondary tumor*"[ALL] OR "Stage III"[ALL] OR "Stage IV"[ALL]) AND (("Controlled Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR "Clinical Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Randomised"[ALL] OR "Randomized"[ALL] OR "Randomly"[ALL] OR "Random"[ALL] OR "Randomized controlled trial*"[ALL] OR "Controlled clinical trial*"[ALL] OR "Trial*"[ALL] OR "Clinical trial*"[ALL] OR "placebo"[ALL])) AND ("Drug Therapy"[Mesh] OR "Antineoplastic Agents"[Mesh] OR "Chemotherapy, Adjuvant"[Mesh] OR "Combined Modality Therapy"[Mesh] OR "Antineoplastic Combined Chemotherapy Protocols"[Mesh] OR "Palliative Care"[Mesh] OR "Antineoplastic Agents"[ALL] OR "Drug therapy"[ALL] OR "Chemotherapy"[ALL] OR "Adjuvant chemotherapy"[ALL] OR "Antineoplastic combined chemotherapy"[ALL] OR "Palliative care"[ALL] OR "First-line therapy"[ALL] OR "first line"[ALL] OR "Supportive care"[ALL] OR "Antineoplastic Combined Chemotherapy Protocols"[ALL] OR "Systemic therapy"[ALL])

4.6. Selection Criteria

Studies were included if they described phase II or phase III randomized controlled trials, included metastatic gastric cancer patients with tumor node metastasis phase III or phase IV, included patients who received at least one anti-tumor systemic therapy as recommended by National Comprehensive Cancer Network guidelines 2022, or described both gastric and esophageal cancer cases where subgroup data on gastric cancer were available.

Studies were excluded if they were non-randomized controlled trials designs or preclinical experiments, observational studies, case reports, duplicate publications, commentaries or editorials, pooled analyses, clinical trials without comparisons, published in languages other than English,

included trial participants from outside western populations, described therapies other than first-line systemic therapy, or described only palliative care trials.

Two reviewers (S.M and D.A)independently screened all titles and abstracts identified using the search methods described. The full texts of all possibly relevant studies were retrieved and assessed for eligibility. Any discordance was resolved by consensus and with the help of a third reviewer (T.W) where necessary. A data screening tool that was specifically designed for this purpose was used. Ineligible studies with reasons for exclusion were identified and recorded. The selection process was recorded in sufficient detail to complete a PRISMA flow diagram (Figure 1).

4.7. Data extraction and management

A standard data collection form was designed for this study and included details on the study characteristics and outcomes. Two independent reviewers (S.M and D.A) extracted study characteristics and outcome data from included studies and met to agree consensus.

4.8. Risk of bias assessment

Two independent authors (SM and DA) assessed the included studies in accordance with version two of the Cochrane risk-of-bias tool for randomized trials [43]. The two reviewers compared their evaluations and resolved any possible discrepancies with a third reviewer who is a content expert (T.W). Overall risk of bias for each study included was reported in accordance with the risk-of-bias tool as low risk of bias, some concerns, or high risk of bias.

4.9. Data synthesis

Endnote was used to organize studies from different databases and to remove duplicate studies. A table summarizing the studies included was created using the captured study characteristics and outcomes. The design, conduct and writing of this systematic review was in accordance with the PRISMA Checklist.

5. Conclusions

With the evolving treatment landscape, improvement in clinical and safety outcomes can be seen in recent published randomized controlled trials. The potential of new targeted treatments and immunotherapies may present more favorable forthcoming options for locally advanced and metastatic gastric cancer.

Author Contributions: Conceptualization, S.M., D.A, D.R.A, M.Y., M.S., and T.W.; methodology, S.M. and D.A.; software, S.M. and D.A; validation, S.M., D.A., D.R.A., M.Y., M.S. and T.W.; formal analysis, S.M. and D.A.; investigation, S.M., D.A., and M.Y.; resources, T.W., M.Y., and D.R.A.; data curation, S.M. and D.A.; writing—original draft preparation, S.M. and D.A.; writing—review and editing, S.M., D.A., D.R.A., M.Y., M.S., and T.W.; visualization, S.M. and D.A.; supervision, D.R.A., M.Y., M.S., and T.W.; project administration, S.M., D.A., D.R.A., M.Y., M.S., and T.W.; funding acquisition, T.W. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix 1: Search Strategy for Systematic Review

Search: Clinical, economic, and/or humanistic outcomes of first-line systemic therapies in patients with unresectable locally advanced/metastatic gastric cancer- A Systematic Review

Citation account (if any): Endnote

Limits: English Language

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Type of publications: phase II and phase III randomized controlled trials

Inclusions:

P- Adults aged ≥ 18 years with stage II – IV gastric cancer

I- First line systemic therapies as approved by NCCN 2022 guidelines

C- First-line systemic therapies and/or best supportive care/placebo

O- Clinical: Overall survival, Progression-free survival, time to progression, objective response rate, Safety: Grade ≥3 treatment related adverse event

Humanistic: Quality of life, utility estimates, where available

Exclusion: Non-English publications, observational, narrative reviews, systematic reviews, meta-analyses, and non-research publications will be excluded. Also, studies that focused exclusively on other line of therapy than first line systemic therapy. Other interventions such as radiotherapy, surgical and total neoadjuvant chemotherapy will be excluded.

Limits: English language and trials conducted among western population or countries.

Search Dates: Inception to May 2022

PubMed

((("Stomach"[Mesh] OR "stomach"[ALL] OR "Gastric"[ALL] OR "Esophagogastric"[ALL] OR "oesophagogastric"[ALL] OR "Gastroesophageal"[ALL] OR "gastrooesophageal"[ALL]) AND ("Neoplasms"[Mesh] OR "Carcino-ma"[Mesh] OR "Stomach Neoplasms"[Mesh] OR "Adenocarcinoma"[Mesh] OR "Cancer*"[ALL] OR "Neo-plasm*"[ALL] OR "Adenocarcinoma*"[ALL] OR "Carcinoma*"[ALL] OR "Tumor*"[ALL] OR "Neoplasm, Stom-ach"[ALL] OR "Stomach Neoplasm"[ALL] OR "Neoplasms, Stomach"[ALL] OR "Gastric Neoplasms"[ALL] OR "Gastric Neoplasm"[ALL] OR "Neoplasm, Gastric"[ALL] OR "Neoplasms, Gastric"[ALL] OR "Cancer of Stom-ach"[ALL] OR "Stomach Cancers"[ALL] OR "Gastric Cancer"[ALL] OR "Cancer, Gastric"[ALL] OR "Cancers, Gas-tric"[ALL] OR "Gastric Cancers"[ALL] OR "Stomach Cancer"[ALL] OR "Cancer, Stomach"[ALL] OR "Cancers, Stomach"[ALL]) AND ("Neoplasm Metastasis"[Mesh] OR "secondary" [Subheading] OR "Advanced"[ALL] OR "Metastatic"[ALL] OR "Metastasis"[ALL] OR "Recurrent"[ALL] OR "Unresectable"[ALL] OR "Inoperable"[ALL] OR "Incurable"[ALL] OR "Neoplasm metastasis"[ALL] OR "Secondary neoplasm*"[ALL] OR "Secondary cancer*"[ALL] OR "Secondary tumor*"[ALL] OR "Stage III"[ALL] OR "Stage IV"[ALL]) AND (("Controlled Clinical Trial" [Publi-cation Type] OR "Clinical Trials as Topic"[Mesh] OR "Clinical Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Randomised"[ALL] OR "Randomized"[ALL] OR "Randomly"[ALL] OR "Random"[ALL] OR "Randomized controlled trial*"[ALL] OR "Controlled clinical trial*"[ALL] OR "Trial*"[ALL] OR "Clinical tri-al*"[ALL] OR "placebo"[ALL])) AND ("Drug Therapy"[Mesh] OR "Antineoplastic Agents"[Mesh] OR "Chemo-therapy, Adjuvant"[Mesh] OR "Combined Modality Therapy"[Mesh] OR "Antineoplastic Combined Chemotherapy Protocols"[Mesh] OR "Palliative Care"[Mesh] OR "Antineoplastic Agents"[ALL] OR "Drug therapy"[ALL] OR "Chemotherapy"[ALL] OR "Adjuvant chemotherapy"[ALL] OR "Antineoplastic combined chemotherapy"[ALL] OR "Palliative care"[ALL] OR "First-line therapy"[ALL] OR "first line"[ALL] OR "Supportive care"[ALL] OR "Antineoplastic Combined Chemotherapy Protocols"[ALL] OR "Systemic therapy"[ALL])

EMBASE

#1)'stomach'/exp OR stomach OR gastric OR Esophagogastric OR oesophagogastric OR Gastroesophageal OR gastrooesophageal

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#2) 'neoplasm'/exp OR 'carcinoma'/exp OR 'stomach tumor'/exp OR 'adenocarcinoma'/exp OR 'malignant neoplasm'/exp OR 'stomach cancer'/exp OR 'neoplasms' OR 'carcinoma' OR 'stomach neoplasms' OR 'adenocarcinoma' OR 'cancer*' OR 'neoplasm*' OR 'adenocarcinoma*' OR 'carcinoma*' OR 'tumor*' OR 'neoplasm, stomach' OR 'stomach neoplasm' OR 'neoplasms, stomach' OR 'gastric neoplasms' OR 'gastric neoplasm' OR 'neoplasm, gastric' OR 'neoplasms, gastric' OR 'cancer of stomach' OR 'stomach cancers' OR 'gastric cancer' OR 'cancer, gastric' OR 'cancers, gastric' OR 'gastric cancers' OR 'stomach cancer' OR 'cancer, stomach' OR 'cancers, stomach'

#3) 'metastasis'/exp OR 'secondary'/exp OR 'advanced cancer'/exp OR 'inoperable cancer'/exp OR 'incurable cancer'/exp OR "Neoplasm Metastasis" OR "secondary" "Advanced" OR "Metastatic" OR "Metastasis" OR "Recurrent" OR "Unresectable" OR "Inoperable" OR "Incurable" OR "Neoplasm metastasis" OR "Secondary neoplasm*" OR "Secondary cancer*" OR "Secondary tumor*" OR "Stage III" OR "Stage IV"

#4)'controlled clinical trial'/exp OR 'clinical trial'/exp OR 'randomized controlled trial'/exp OR 'trial'/exp OR 'placebo'/exp OR "Controlled Clinical Trial" OR "Clinical Trials as Topic" OR "Clinical Trial" OR "Randomized Controlled Trials as Topic" OR "Randomised" OR "Randomized" OR "Randomly" OR "Random" OR "Randomized controlled trial*" OR "Controlled clinical trial*" OR "Trial*" OR "Clinical trial*" OR "placebo"

#5) 'drug therapy'/exp OR 'antineoplastic agent'/exp OR 'chemotherapy'/exp OR 'adjuvant chemotherapy'/exp OR 'multimodality cancer therapy'/exp OR 'palliative therapy'/exp OR 'chemotherapy'/exp OR 'first line therapy'/exp OR 'supportive care'/exp OR 'systemic therapy'/exp OR "Drug Therapy" OR "Antineoplastic Agents" OR "Chemotherapy, Adjuvant" OR "Combined Modality Therapy" OR "Antineoplastic Combined Chemotherapy Protocols" OR "Palliative Care" OR "Antineoplastic Agents" OR "Drug therapy" OR "Chemotherapy" OR "Adjuvant chemotherapy" OR "Antineoplastic combined chemotherapy" OR "Palliative care" OR "First-line therapy" OR "first line" OR "Supportive care" OR "Antineoplastic Combined Chemotherapy Protocols" OR "Systemic therapy"

#1 AND #2 AND #3 AND #4 AND #5

SCOPUS

(TITLE-ABS-KEY (stomach OR gastric OR Esophagogastric OR gastrooesophageal)) AND (TITLE-ABS-KEY (neoplasm OR carcinoma OR tumor OR adenocarcinoma OR cancer)) AND (TITLE-ABS-KEY (metastasis OR advanced OR {stage III} OR {stage IV})) AND (TITLE-ABS-KEY ({controlled clinical trial} OR {clinical trial} OR {randomized controlled trial} OR trial OR placebo)) AND (TITLE-ABS-KEY ({antineoplastic agent} OR chemotherapy OR {palliative therapy} OR {multimodality cancer therapy} OR {systemic therapy}))

COCHRANE CENTRAL REGISTER OF CONTROLLED TRIALS

(neoplasm OR carcinoma OR tumor OR adenocarcinoma OR cancer) AND (stomach OR gastric OR esophagogastric OR gastrooesophageal) AND (metastasis OR advanced OR "stage III" OR "stage IV") AND ("controlled clinical trial" OR "clinical trial" OR "randomized controlled trial" OR trial OR placebo) AND ("antineoplastic agent" OR chemotherapy OR "palliative therapy" OR "multimodality cancer therapy" OR "systemic therapy")

CLINICAL TRIAL.GOV

(Stomach cancer OR gastric cancer OR “stomach adenocarcinoma” OR “STOMACH CANCER, STAGE 3” OR “STOMACH CANCER, STAGE 4” OR “Gastroesophageal TUMOR” OR “Gastroesophageal CANCER” OR “Gastroesophageal NEOPLASM” OR “Esophageal Cancer”) AND (metastasis OR advanced OR "stage III"

OR "stage IV") AND ("antineoplastic agent" OR chemotherapy OR "palliative therapy" OR "multimodality cancer therapy" OR "systemic therapy") Filters: Phase 3 , 4

ASCO MEETING LIBRARY

(Keywords:advanced gastric cancer OR Keywords:metastatic gastric cancer) AND (Keywords:first line AND Keywords: systemic therapies)

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