Supplementary

Table S1 Search Strategy

Number	String
#10	Search: ((((((((((((((((((Programmed Cell Death 1 Receptor[MeSH Terms]) OR (PD-1[Title/Abstract])) OR (PDCD1[Title/Abstract])) OR (nivolumab[Title/Abstract])) OR (pembrolizumab[Title/Abstract])) OR (cemiplimab[Title/Abstract])) OR (dostarlimab[Title/Abstract])) OR (Toripalimab[Title/Abstract])) OR (Camrelizumab[Title/Abstract])) OR (Sintilimab[Title/Abstract])) OR (Tislelizumab[Title/Abstract])) OR (Penpulimab[Title/Abstract])) OR (Opdivo[Title/Abstract])) OR (Keytruda[Title/Abstract])) OR (Libtayo[Title/Abstract])) OR (Jemperli[Title/Abstract])) AND (((Stomach Neoplasms[MeSH Terms]) OR (Gastric Neoplasms[MeSH Terms])) OR ((Stomach Cancer [Title/Abstract] OR Gastric Cancer [Title/Abstract] OR Gastric Carcinoma [Title/Abstract] OR Gastric Neoplasms [Title/Abstract]) OR (cancer of the stomach[Title/Abstract])))) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT (humans[mh] AND animals[mh])))) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]))
#9	Search: (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh])
#8	Search: (Efficacy [Title/Abstract] OR Effectiveness [Title/Abstract] OR Outcome [Title/Abstract] OR Response [Title/Abstract]) OR (Safety [Title/Abstract] OR Adverse Effects [Title/Abstract] OR Side Effects [Title/Abstract] OR Toxicity [Title/Abstract])
#7	Search: ((Stomach Neoplasms[MeSH Terms]) OR (Gastric Neoplasms[MeSH Terms])) OR ((Stomach Cancer [Title/Abstract] OR Gastric Cancer [Title/Abstract] OR Gastric Carcinoma [Title/Abstract] OR Gastric Neoplasms [Title/Abstract]) OR (cancer of the stomach[Title/Abstract]))
#6	Search: (Stomach Cancer [Title/Abstract] OR Gastric Cancer [Title/Abstract] OR Gastric Carcinoma [Title/Abstract] OR Gastric Neoplasms [Title/Abstract]) OR (cancer of the stomach[Title/Abstract])
#5	Search: Gastric Neoplasms[MeSH Terms]
#4	Search: Stomach Neoplasms[MeSH Terms]
#3	Search: ((((((((((((((((Programmed Cell Death 1 Receptor[MeSH Terms]) OR (PD-1[Title/Abstract])) OR (PDCD1[Title/Abstract])) OR (nivolumab[Title/Abstract])) OR (pembrolizumab[Title/Abstract])) OR (cemiplimab[Title/Abstract])) OR (dostarlimab[Title/Abstract])) OR (Toripalimab[Title/Abstract])) OR (Camrelizumab[Title/Abstract])) OR (Sintilimab[Title/Abstract])) OR (Tislelizumab[Title/Abstract])) OR (Penpulimab[Title/Abstract])) OR (Opdivo[Title/Abstract])) OR (Keytruda[Title/Abstract])) OR (Libtayo[Title/Abstract])) OR (Jemperli[Title/Abstract])
#2	Search: (PD-1[Title/Abstract])) OR (PDCD1[Title/Abstract])) OR (nivolumab[Title/Abstract])) OR (pembrolizumab[Title/Abstract])) OR (cemiplimab[Title/Abstract])) OR (dostarlimab[Title/Abstract])) OR (Toripalimab[Title/Abstract])) OR (Camrelizumab[Title/Abstract])) OR (Sintilimab[Title/Abstract])) OR (Tislelizumab[Title/Abstract])) OR (Penpulimab[Title/Abstract])) OR (Opdivo[Title/Abstract])) OR (Keytruda[Title/Abstract])) OR (Libtayo[Title/Abstract])) OR (Jemperli[Title/Abstract])
#1	Search: Programmed Cell Death 1 Receptor[MeSH Terms]

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Table S2 Characteristics of studies and subjects included in the review

Study	Country/Region	Subjects (intervention/ control)	Sex (male/female) (intervention/control)	Mean age (intervention/ control)	Type of disease	HER2	Intervention detail			Outcomes	
							Intervention group		Control group		
Chen *et al.* (2019)	Japen, South Korea, Taiwan	493 (330/163)	229/101 *vs.* 119/44	62±11.1 *vs.* 61±11.1	Unresectable advanced or recurrent/metastatic gastric or gastroesophageal junction adenocarcinoma	NA	PD-1 Monotherapy	Nivolumab 3 mg/kg IV every 2 weeks until disease progression, unacceptable toxicity, or withdrawal	Placebo	Matching placebo IV every 2 weeks, same treatment duration criteria	OS, PFS, ORR, DCR, ≥3 AE
Janjigian *et al.* (2021)	Multinational study	1581 (789/792)	540/249 *vs.* 560/232	62±11.1 *vs.* 61±11.1	Unresectable advanced or metastatic gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma	Negative	PD-1 + Chemotherapy	Nivolumab 360 mg IV q3 weeks or 240 mg IV q2 weeks, plus XELOX: capecitabine 1000 mg/m^2 bid d1–14 + oxaliplatin 130 mg/m^2 d1 q3 weeks or FOLFOX: leucovorin 400 mg/m^2 d1 + 5-FU 400 mg/m^2 d1 & 1200 mg/m^2 d2 + oxaliplatin 85 mg/m^2 d1 q2 weeks	Chemotherapy	Chemotherapy alone: XELOX: capecitabine 1000 mg/m^2 bid d1–14 + oxaliplatin 130 mg/m^2 d1 q3 weeks or FOLFOX: leucovorin 400 mg/m^2 d1 + 5-FU 400 mg/m^2 d1 & 1200 mg/m^2 d2 + oxaliplatin 85 mg/m^2 d1 q2 weeks	ORR, DCR, ≥3 AE
Satoh *et al.* (2019)	Japen, South Korea, Taiwan	412 (271/141)	182/89 *vs.* 99/42	62±15.8 *vs.* 61±14.3	Unresectable or metastatic (≥ third-line) gastric or gastroesophageal junction adenocarcinoma	NA	PD-1 Monotherapy	Nivolumab 3 mg/kg IV every 2 weeks until progression or unacceptable toxicity	Placebo	Placebo IV every 2 weeks under the same schedule	ORR, DCR, ≥3 AE
Kato *et al.* (2018)	Japen	226 (152/74)	111/41 *vs.* 57/17	65±15.8 *vs.* 66±12.8	Unresectable advanced or recurrent gastric or gastro-oesophageal junction adenocarcinoma refractory to, or intolerant of, ≥2 prior chemotherapy regimens	NA	PD-1 Monotherapy	Nivolumab 3 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity	Placebo	Matching placebo IV every 2 weeks on the same schedule	OS, PFS, ORR, DCR, ≥3 AE
Liu *et al.* (2022)	China	208 (99/109)	64/35 *vs.* 75/34	61±15 *vs.* 60±16	Advanced unresectable stomach or gastroesophageal cancer	Negative	PD-1 + Chemotherapy	Nivolumab 360 mg IV q3 weeks or 240 mg IV q2 weeks, plus XELOX: capecitabine 1 000 mg/m^2 bid d1–14 + oxaliplatin 130 mg/m^2 d1 q3 weeks or FOLFOX: leucovorin 400 mg/m^2 d1 + 5-FU 400 mg/m^2 d1 & 1 200 mg/m^2 d2 + oxaliplatin 85 mg/m^2 d1 q2 weeks	Chemotherapy	Chemotherapy alone: XELOX: capecitabine 1000 mg/m^2 bid d1–14 + oxaliplatin 130 mg/m^2 d1 q3 weeks or FOLFOX: leucovorin 400 mg/m^2 d1 + 5-FU 400 mg/m^2 d1 & 1200 mg/m^2 d2 + oxaliplatin 85 mg/m^2 d1 q2 weeks	OS, PFS, ORR, ≥3 AE
Kang *et al.* (2022)	Japen, South Korea, Taiwan	724 (362/362)	253/109 *vs.* 270/92	64±15.3 *vs.* 65±15.5	Untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction adenocarcinoma	Negative	PD-1 + Chemotherapy	Nivolumab 360 mg IV every 3 weeks, plus Oxaliplatin-based chemotherapy every 3 weeks: SOX: S-1 40 mg/m^2 orally bid on days 1–14 + oxaliplatin 130 mg/m^2 IV on day 1 or CAPOX: Capecitabine 1 000 mg/m^2 orally bid on days 1–14 + oxaliplatin 130 mg/m^2 IV on day 1	Chemotherapy	SOX: S-1 40 mg/m^2 orally bid on days 1–14 + oxaliplatin 130 mg/m^2 IV on day 1 or CAPOX: Capecitabine 1 000 mg/m^2 orally bid on days 1–14 + oxaliplatin 130 mg/m^2 IV on day 1	OS, PFS, ORR
Kim *et al.* (2022)	South Korea	45 (28/17)	21/7 *vs.* 13/4	60±13.3 *vs.* 59±10.3	Unresectable or metastatic, histologically confirmed advanced gastric or gastroesophageal junction adenocarcinoma	NA	PD-1 Monotherapy	Nivolumab 3 mg/kg IV every 2 weeks (one cycle = 6 weeks) until disease progression or unacceptable toxicity	Placebo	Matching placebo IV every 2 weeks under the same schedule and discontinuation rules	OS, PFS, ORR
Boku *et al.* (2021)	Japan, South Korea, Taiwan	146 (109/37)	78/31 *vs.* 30/7	NA	Unresectable advanced or recurrent gastric/gastroesophageal junction adenocarcinoma refractory to ≥2 prior chemotherapy lines	NA	PD-1 Monotherapy	Nivolumab 3 mg/kg IV every 2 weeks; one cycle = 6 weeks; continued until progression or unacceptable toxicity.	Placebo	Matching placebo IV every 2 weeks under the same schedule and discontinuation rules	OS, PFS, ORR, DCR, ≥3 AE
Chung *et al.* (2022)	China, Malaysia, South Korea, Taiwan	94 (47/47)	32/15 *vs.* 37/10	61 ± 12.1 *vs.* 65 ± 9.8	Locally advanced unresectable or metastatic gastric/GEJ adenocarcinoma	Negative	PD-1 Monotherapy	Pembrolizumab 200 mg IV q3weeks, up to 2 years/35 cycles	Chemotherapy	Paclitaxel 80mg/m^2 IV, q1week (D1/8/15) every 4 weeks	ORR
Shitara *et al.* (2020)	Multinational study	763 (256/257/250)	180/76 *vs.* 195/62 *vs.* 179/71	56.25±10.5 *vs.* 57.25±10.17 *vs.* 58.75±10.67	Locally advanced/unresectable or metastatic gastric/GEJ adenocarcinoma	Negative	(a) PD-1 Monotherapy (b) PD-1 + Chemotherapy	(a) Pembrolizumab 200 mg IV every 3 weeks for up to 35 doses (approximately 2 years) until disease progression, unacceptable toxicity, or patient withdrawal (b) Pembrolizumab + Cisplatin 80mg/m^2 d1 + 5-FU 800mg/m^2/d d1–5 or Capecitabine 1000 mg/m^2 bid d1–14	Chemotherapy	Cisplatin 80 mg/m^2 d1 + 5-FU 800 mg/m^2/d d1–5 or Capecitabine 1000 mg/m^2 bid d1–14	OS, PFS, ORR, DCR, ≥3 AE
Hegewisch-Becker *et al.* (2024)	Multinational study	274 (138/136)	94/44 *vs.* 98/38	56.75±9.17 *vs.* 58.25±10.17	Unresectable locally advanced or metastatic gastric cancer (GC)/ gastroesophageal junction cancer (GEJC) adenocarcinoma	Negative	PD-1 + LAG-3 + Chemotherapy	Nivolumab 360 mg + Relatlimab 120 mg IV on days 1 and 22, every 6 weeks; Oxaliplatin 130 mg/m^2 IV on days 1 and 22; Capecitabine 1,000 mg/m^2 PO bid on days 1–14 and 22–35	PD-1 + Chemotherapy	Nivolumab alone (360 mg or 480 mg, given at the same time points as the intervention arm but without relatlimab) combined with FOLFOX, XELOX, or SOX	ORR, DCR, ≥3 AE
Janjigian *et al.* (2021)	Multinational study	434 (217/217)	179/38 *vs.* 174/43	56.75±10.83 vs 60.25±8.50	Unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma	Positive	PD-1 + LAG-3 + Chemotherapy	Pembrolizumab 200 mg IV q3 weeks + trastuzumab (8 mg/kg loading, then 6 mg/kg q3 weeks) + investigator's choice of chemotherapy (5-FU/cisplatin or capecitabine/oxaliplatin)	Placebo + Chemotherapy	Placebo IV q3 weeks + identical trastuzumab and chemotherapy regimens.	OS, PFS, ORR, DCR, ≥3 AE
Wei *et al.* (2024)	China	51 (25/26)	17/8 vs 19/7	55.10±8.00 *vs.* 55.90±8.33	Advanced/metastatic gastric or esophagogastric junction adenocarcinoma	Negative	PD-1 + Anti-angiogenic	Toripalimab 240 mg IV day 1 q3 weeks + Apatinib 250 mg orally daily	Chemotherapy	Physician's choice of single-agent chemotherapy	OS, PFS, ORR, DCR, ≥3 AE
Qiu *et al.* (2024)	Multinational study	997 (501/496)	346/155 *vs.* 346/150	59.75±2.17 *vs.* 61.00±2.33	Locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma	Negative	PD-1 + Chemotherapy	Tislelizumab 200 mg IV q3weeks, plus chemotherapy (investigator's choice)	Placebo + Chemotherapy	Placebo 200 mg IV q3 weeks, plus chemotherapy (investigator's choice)	OS, PFS, ORR, DCR, ≥3 AE
Xu *et al.* (2023)	China	650 (327/323)	483/167	59.07±6.21	Unresectable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma	Negative	PD-1 + Chemotherapy	Sintilimab 3 mg/kg (<60 kg) or 200 mg (≥60 kg) IV on day 1 of each 3-week cycle, combined with XELOX (capecitabine 1 000 mg/m^2 bid d1–14 + oxaliplatin 130 mg/m^2 IV d1) for up to 6 cycles, then maintenance sintilimab + capecitabine up to 2 years	Placebo + Chemotherapy	Placebo IV q3weeks + XELOX 6cycles + capecitabine maintenance	OS, PFS, ORR, DCR
Chao *et al.* (2021a)	Multinational study	27 (15/12)	NA	67±10 *vs.* 63±8	Microsatellite instability–high advanced gastric or gastroesophageal junction adenocarcinoma	NA	PD-1 Monotherapy	Pembrolizumab 200 mg IV every 3 weeks	Chemotherapy	Paclitaxel monotherapy (80 mg/m^2 IV weekly)	OS, PFS, ORR, DCR
Chao *et al.* (2021b)	Multinational study	50 (14/17/19)	NA	62±8.75 *vs.* 67±6 *vs.* 69±13.5	Microsatellite instability–high advanced gastric or gastroesophageal junction adenocarcinoma	NA	PD-1 Monotherapy	Pembrolizumab 200 mg IV every 3 weeks	Chemotherapy	Chemotherapy alone: Cisplatin 80 mg/m^2 IV on day 1 + 5-fluorouracil 800 mg/m^2/day IV on days 1–5, every 3 weeks or Capecitabine 1 000 mg/m^2 orally twice daily on days 1–14, every 3 weeks	OS, PFS, ORR, DCR, ≥3 AE
Fuchs *et al.* (2022)	Multinational study	395 (196/199)	146/50 *vs.* 140/59	62.5±15 *vs.* 60.0±16.5	Locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma (PD-L1 CPS ≥1)	Positive/ Negative	PD-1 Monotherapy	Pembrolizumab 200 mg IV q3 weeks, ≤35 cycles (≈2 years), or until progression/toxicity/ withdrawal	Chemotherapy	Paclitaxel 80 mg/m^2 IV on days 1, 8, 15 of each 28-day cycle, until progression/toxicity/ withdrawal	OS, PFS, ORR, DCR, ≥3 AE
Rha *et al.* (2023)	Multinational study	1579 (790/789)	527/263 *vs.* 544/245	61±11.1 *vs.* 62±12.6	Locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma	Negative	PD-1 + Chemotherapy	Pembrolizumab 200 mg IV on day 1 q3 weeks × up to 35 cycles, plus investigator's choice chemotherapy (fluorouracil 800 mg/m^2/day d1–5 + cisplatin 80 mg/m^2 d1 or capecitabine 1000 mg/m^2 bid d1–14 + oxaliplatin 130 mg/m^2 d1)	Placebo + Chemotherapy	Placebo IV on day 1 q3 weeks × up to 35 cycles, plus same chemotherapy regimens as intervention	OS, PFS, ORR, DCR, ≥3 AE
Satake *et al.* (2023)	Multinational study	187 (62/64/61)	46/16 *vs.* 50/14 *vs.* 41/20	64.5±13.8 *vs.* 65.0±12.3 *vs.* 67.0±12.0	Locally advanced, unresectable or metastatic gastric cancer and gastroesophageal junction adenocarcinoma (PD-L1 CPS ≥1)	Negative	(a) PD-1 Monotherapy (b) PD-1 + Chemotherapy	(a) Pembrolizumab monotherapy: 200 mg IV every 3 weeks, up to 35 doses (2 years), until progression/toxicity/withdrawal (b) Pembrolizumab + chemotherapy: Pembrolizumab 200 mg IV Q3W plus investigator's choice of cisplatin 80 mg/m^2 IV on day 1 Q3W + 5-fluorouracil 800 mg/m^2/day IV on days 1–5 Q3W or capecitabine 1 000 mg/m^2 orally twice daily on days 1–14 Q3W	Placebo + Chemotherapy	Placebo + chemotherapy: Placebo IV Q3W plus the same chemotherapy options (cisplatin + 5-FU or capecitabine regimens as above), until progression/toxicity/ withdrawal	OS, PFS, ORR, DCR, ≥3 AE
Shitara *et al.* (2018)	Multinational study	592 (296/296)	202/94 *vs.* 208/88	62.5±11.9 *vs.* 60.0±11.1	Advanced or metastatic gastric or gastroesophageal junction adenocarcinoma	Positive/ Negative	PD-1 Monotherapy	Pembrolizumab 200 mg IV on day 1 every 3 weeks, up to 35 cycles (2 years)	Chemotherapy	Paclitaxel 80 mg/m^2 IV on days 1, 8, and 15 of each 28-day cycle, until progression/ toxicity/withdrawal	OS, PFS, ORR, DCR, ≥3 AE

RCT, randomized controlled trial; PD-1, programmed death-1; ICI, immune checkpoint inhibitor; q2W (q2w), every 2 weeks; q3W (q3w), every 3 weeks; IV, intravenous; PO, per os (oral); bid, bis in die (twice daily); XELOX, capecitabine + oxaliplatin; FOLFOX, leucovorin + 5-fluorouracil + oxaliplatin; SOX, S-1 + oxaliplatin; CAPOX, capecitabine + oxaliplatin; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; DCR, disease control rate; AE, adverse event; TRAEs, treatment-related adverse events; HER2, human epidermal growth factor receptor 2; GEJ, gastroesophageal junction; m, months; w, weeks; NA, not available.

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Table S3 Node splitting method results of ≥3 TRAEs

Side		Direct		Indirect		Difference		P>|z|	tau
		Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.		
A	B	0.4275384	0.1463438	1.268113	0.4888128	-0.8405745	0.5074924	0.098	0.2317576
A	C	-1.779665	0.2151881	-1.874731	0.4935885	0.0950663	0.5360305	0.859	0.341632
B	C	-2.574379	0.2990387	-2.024852	0.2889869	-0.5495277	0.4132442	0.184	0.2899841
B	E	0.369198	0.4084939	-0.2976546	0.4152513	0.6668526	0.5824954	0.252	0.3183652
B	G	-0.2979441	0.1818097	0.3165647	0.483529	-0.6145088	0.5165803	0.234	0.3102313
C	F	-0.921471	0.3121709	3.127866	117.656	-4.049337	117.6561	0.973	0.3237265
C	G	2.02544	0.5443556	2.102051	0.3276897	-0.0766112	0.6337406	0.904	0.3415095
E	G	0.0108109	0.3729719	-0.6560063	0.4474313	0.6668173	0.5824971	0.252	0.3183658

Table S4 Risk of bias

Author	Bias arising from the randomization process	Bias due to deviations from intended intervention	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall
Chen *et al.* (2019)	Low	Low	Low	Low	Low	Low
Janjigian *et al.* (2021)	Low	Low	Low	Low	Low	Low
Satoh *et al.* (2019)	Low	Low	Low	Some Concerns	Low	Some Concerns
Kato *et al.* (2018)	Some Concerns	Low	Low	Low	Low	Some Concerns
Liu *et al.* (2022)	Low	Low	Low	Low	Low	Low
Kang *et al.* (2022)	Low	Low	Low	Low	Low	Low
Kim *et al.* (2022)	Low	Low	Low	Low	Low	Low
Boku *et al.* (2021)	Low	Low	Some Concerns	Low	Low	Some Concerns
Chung *et al.* (2022)	Some Concerns	Low	Some Concerns	Low	Low	Some Concerns
Shitara *et al.* (2020)	Low	Low	Low	Low	Low	Low
Hegewisch-Becker *et al.* (2024)	Low	Low	Low	Low	Low	Low
Janjigian *et al.* (2021)	Low	Low	Low	Low	Low	Low
Wei *et al.* (2024)	High	High	High	Low	Low	High
Qiu *et al.* (2024)	Low	Low	Low	Low	Low	Low
Xu *et al.* (2023)	Low	Low	Some Concerns	Low	Low	Some Concerns
Chao *et al.* (2021)	Some Concerns	Low	Some Concerns	Low	Low	Some Concerns
Fuchs *et al.* (2022)	Some Concerns	Some Concerns	Some Concerns	Low	Low	Some Concerns
Rha *et al.* (2023)	Low	Some Concerns	Low	Low	Low	Some Concerns
Satake *et al.* (2023)	Low	Low	Low	Low	Low	Low
Shitara *et al.* (2018)	Some Concerns	Low	Low	Low	Low	Some Concerns

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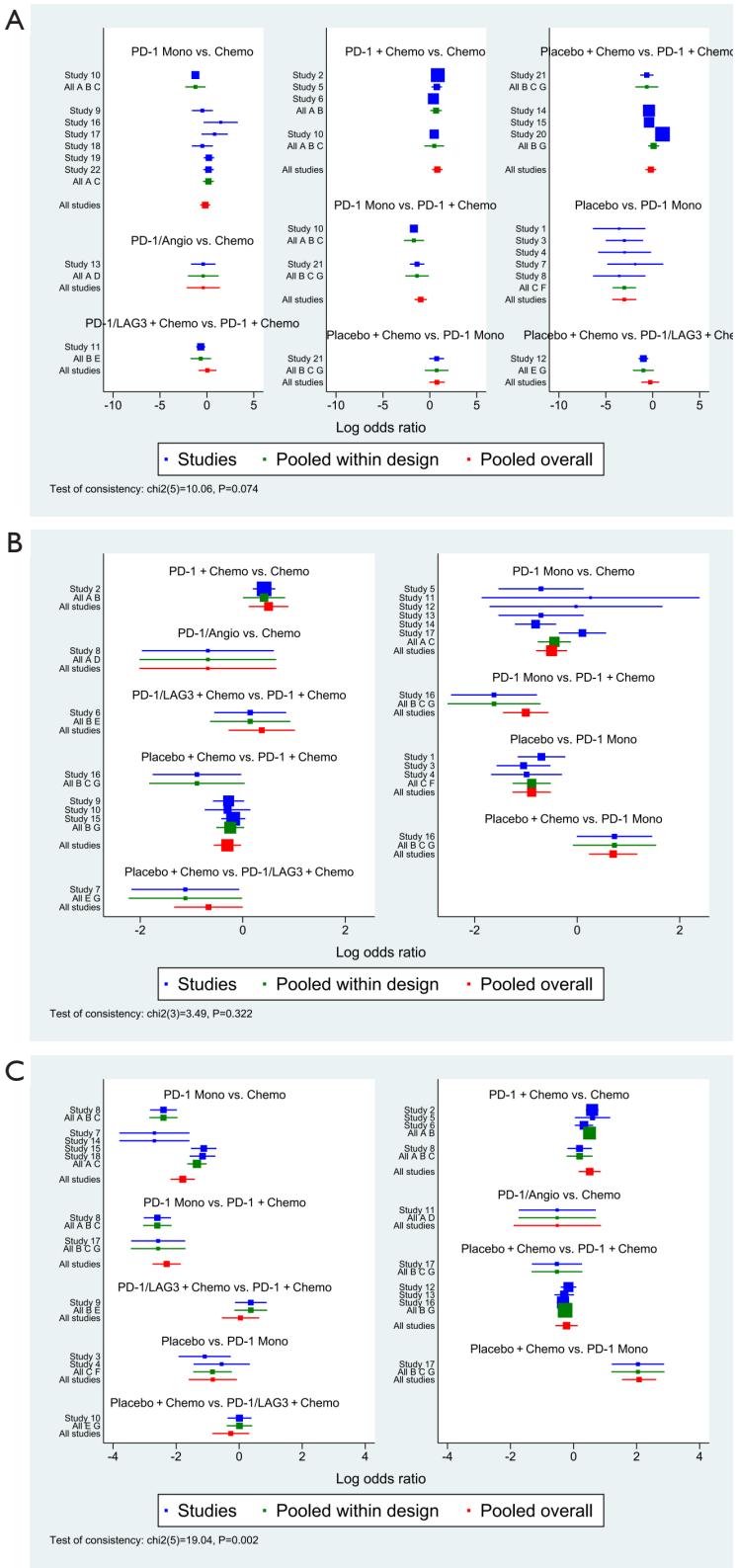

Figure S1 Forest plots. (A) The forest plot of ORR. The result of inconsistency test showed the P=0.074. (B) The forest plot of DCR. The result of inconsistency test showed the P=0.322. (C) The forest plot of ≥3 TRAEs. The result of inconsistency test showed the P=0.002.

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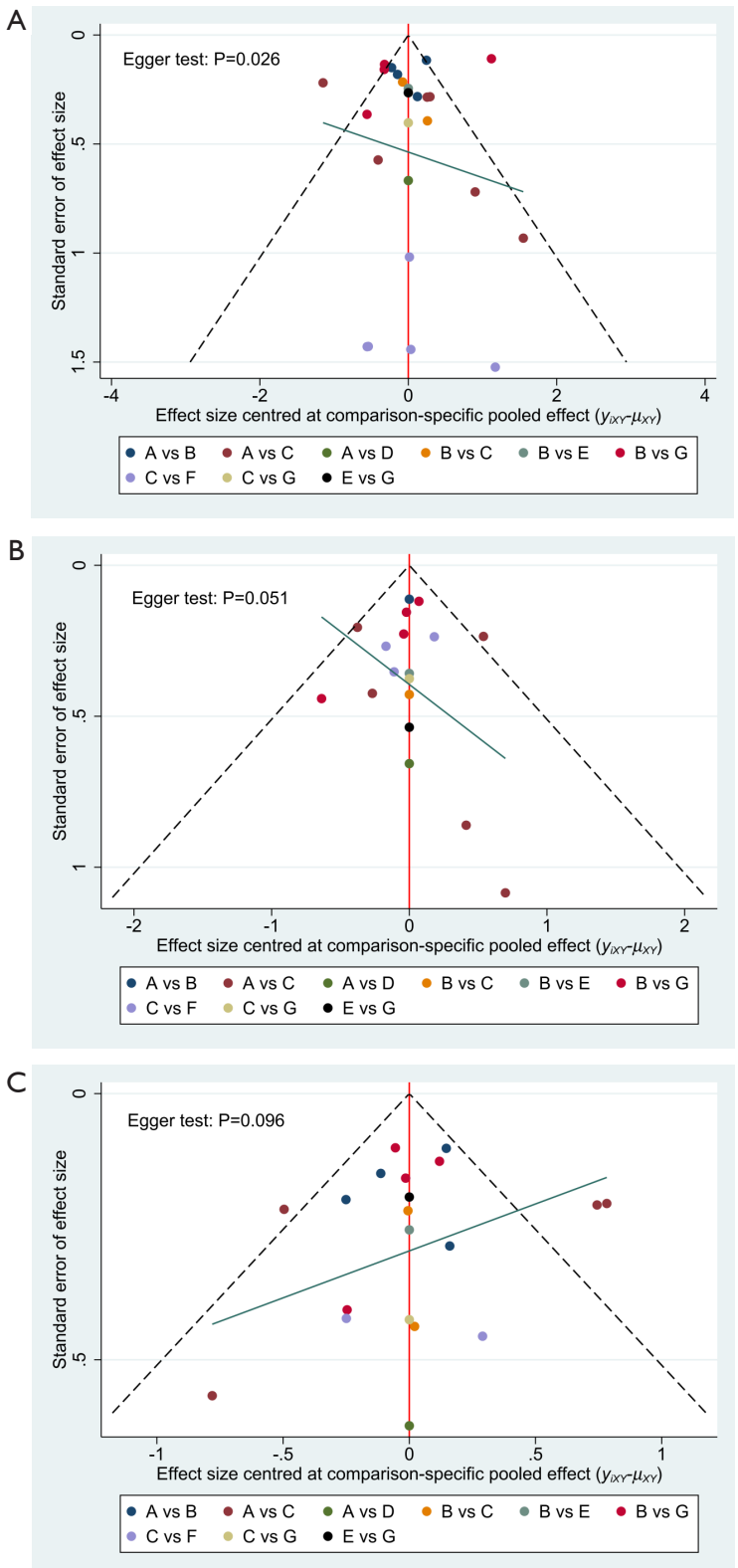

Figure S2 Funnel plots of publication bias. (A) The funnel plot of ORR. The result of Egger test showed the P=0.026. (B) The funnel plot of DCR. The result of Egger test showed the P=0.051. (C) The funnel plot of ≥3 TRAEs. The result of Egger test showed the P=0.096.

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