Original Article

Effectiveness and safety of combined therapy versus monotherapy based on immune checkpoint inhibitors and/or targeted drugs as salvage treatment for advanced urothelial carcinoma: a systematic review and meta-analysis

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Background: The standard salvage regimen for the patients with advanced urothelial carcinoma (UC) is uncertain, although lots of novel agents are recommended, including immune checkpoint inhibitors (ICIs) and targeted drugs (TDs). We aimed to compare the effectiveness and safety of combined therapy of novel agents (CNA) and monotherapy of novel agents (MNA) as salvage therapy for advanced UC.

Methods: Studies exploring CNA and/or MNA for advanced UC in second-line setting were searched from PubMed, Embase, Cochrane Library, and Web of Science. The data of objective response rate (ORR), disease control rate (DCR), median progression-free survival (PFS), median overall survival (OS), and grade 3-4 adverse effects rate (grade 3-4 AEs%) were pooled for analyses. Cochrane risk of bias tool was applied for the quality judgment of randomized controlled studies (RCTs).

Results: Forty-one arms from 37 studies including 4,691 patients were included. Significant differences were presented in pooled ORR (22.9% versus 12.2%, OR =1.88, P<0.001) and DCR (62.7% versus 37.5%, OR =2.53, P<0.001) between CNA and MNA groups. The pooled median PFS was 3.66 months in CNA group versus 2.16 months in MNA group (WMD =1.50, P=0.028). No significant difference in pooled median OS was found between two groups (7.93 versus 7.50 months, WMD =0.43, P=0.449). 63.7% versus 25.4% of pooled grade 3-4 AEs% could be seen in CNA and MNA groups (OR =3.52, P<0.001). Additionally, the pooled results of PFS-6m and OS-6m in CNA group demonstrated significant advantages over MNA group (31.5% versus 28.7%, OR =1.31, P=0.049; 66.0% versus 56.7%, OR =1.34, P=0.029, respectively). In the subgroup analysis of CNA, use of ICIs, the positive expression of PD-L1 and ECOG-PS =0 were significantly associated with superior clinical outcomes (P<0.05).

Discussion: For advanced UC patients after first line agents, CNA had potential benefits than MNA in terms of ORR, DCR, median PFS, PFS-6m and OS-6m. However, CNA was associated with a significantly higher grade 3-4 AEs%. Furthermore, potential advantages were presented in CNA patients with ICIs usage, positive PD-L1 expression and ECOG-PS =0.

Keywords: Urothelial carcinoma (UC); salvage therapy; novel agents; combined therapy; monotherapy

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Introduction

Platinum-based chemotherapy is one of the first-line agents for advanced urothelial carcinoma (UC), with a median overall survival of 13.8 months in gemcitabine plus cisplatin and 15.1 months in high-dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin (1,2). Nevertheless, the standard regimen is still controversial for patients who failed to chemotherapy.

Monotherapy of novel agents (MNA), including immune checkpoint inhibitors (ICIs) and targeted drugs (TDs), was recommended as rational regimens, which demonstrated objective response rate (ORR) of about 20% in some studies (3,4). Furthermore, dozens of trails reported the combination treatment of novel agents (CNA), presenting more satisfactory outcomes than MNA. CheckMate 032 evaluated the locally advanced or metastatic platinum pretreated UC cohort receiving combined inhibition of PD-1 (nivolumab 1 mg/kg) and cytotoxic T-lymphocyte antigen-4 (ipilimumab 3 mg/kg), which showed notable ORR with a complete response of 6.5% and a partial response of 31.5% (5). The anti-tumor activity was also revealed in the combination treatment of tyrosine kinase inhibitor (pazopanib) plus cytotoxic drug (paclitaxel), which presented a remarkable ORR of 54% and median progression-free survival (PFS) of 6.2 months (6). In addition, the combined treatment regimens of everolimus plus pazopanib and pembrolizumab plus docetaxel/gemcitabine were also recommended because of attractive clinical benefits (7,8). Nonetheless, other studies found that MNA might get more beneficial anti-cancer outcomes in median overall survival (OS) and OS-12m than CNA (3,7), which made this issue still obscure. Additionally, possibly more adverse effects in CNA could not be ignored. Grade 3 or 4 adverse events rate (grade 3-4 AEs%) could be observed in approximate 40% patients for CNA, including fatigue, anemia, neutrophil count decrease, etc. (5,8).

Therefore, we designed this systematic review and meta-analysis to compare the effectiveness and safety between CNA and MNA for the management of advanced UC failing to first-line treatment.

We present the following article in accordance with the PRISMA reporting checklist (9) (available at http://dx.doi.org/10.21037/tcr-20-3354).

Methods

This meta-analysis has been registered (registered number: CRD42020199791).

Search strategy

Eligible studies in English language were searched in the PubMed, Cochrane Library, Embase, and Web of Science from the date of inception up to May 1, 2020. The search strategy included the following terms in title/abstract: ('bladder cancer' OR 'urothelial cancer/carcinoma/neoplasm' OR 'transitional cell cancer/carcinoma') AND ('second line' OR 'previously' OR 'refractory' OR 'resistant' OR 'progressive' OR 'pretreated' OR 'advanced' OR 'metastatic') AND ('pembrolizumab' OR 'nivolumab' OR 'durvalumab' OR 'avelumab' OR 'atezolizumab' OR 'ipilimumab' OR 'tremelimumab' OR 'aflibercept' OR 'sunitinib' OR 'sorafenib' OR 'pazopanib' OR 'ramucirumab' OR 'icrucumab' OR 'vandetanib' OR 'lapatinib' OR 'everolimus' OR 'temsirolimus' OR 'apatorsen' OR 'cetuximab' OR 'SCH66336'). In addition, related references of the acquired literature were reviewed.

Selection criteria

The inclusion criteria were as follows: (I) randomized controlled studies (RCTs) or single-arm studies; (II) patients with advanced UC who were refractory to previous chemotherapy or ICI; (III) patients who were treated by CNA (ICI plus chemotherapy, TD plus chemotherapy, ICI plus TD, dual ICIs, or dual TDs) or MNA (ICI or TD); (IV) studies reporting at least one of outcomes of interest, including ORR, disease control rate (DCR), median PFS, median OS, and grade 3-4 AEs%.

The exclusion criteria were as follows: (I) articles with unrelated topics; (II) papers published as letters, editorials, errata, meta-analyses, reviews, conference abstracts, case-reports, study designs or animal trials; (III) novel agents used as the first choice for advanced UC; (IV) studies with unextractable data, with patient number less than 10, or without full texts.

Data extraction and quality assessment

The data of interest were extracted independently by two investigators. The primary outcomes of interest included ORR, DCR, median PFS, median OS, and grade 3-4 AEs%. ORR was defined as the percentage of patients which had a complete or partial response. DCR was defined as the percentage of patients with a complete response,

partial response, or stable disease. In addition, the second outcomes of interest contained PFS-6m, PFS-12m, OS-6m, OS-12m, OS-24m, and any grade AEs%. If disagreements existed, it would be settled by consensus after discussion with a third investigator.

The Cochrane risk of bias tool was applied for methodological quality judgment of RCTs (10). For single-arm studies, no credible tools were found to assess their quality.

Statistical analysis

All analyses were performed using Stata software version 13.0 (StataCorp, College Station, TX, USA) and RevMan software version 5.3 (The Cochrane Collaboration, Software Update, Oxford). For dichotomous variables, rate and standard error (SE) was used to assess the pooled effect sizes (ESs). For continuous variables, the pooled ESs were evaluated through mean and SE. Fisher exact test and Wilcoxon rank sum test was applied for the comparison of pooled outcomes of dichotomous and continuous variables, respectively (11). Two-sided P<0.05 was considered to be statistically significant. Heterogeneity among studies was assessed by the Cochran Q chi-square test and I^2 statistics, in which P<0.10 was regarded to be significant. Furthermore, the random-effects models were applied when heterogeneity among studies was significant. Otherwise, the fixed-effects models were used. Certain studies which possibly contributed to a high heterogeneity would be excluded for a sensitivity analysis to lower heterogeneity. Publication bias was evaluated by funnel plots and Egger's test.

Furthermore, in CNA group, subgroup analyses were carried out according to agent type, programmed death-ligand 1 (PD-L1) expression, gender, age, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), liver metastases, haemoglobin, Bellmunt risk factor (including liver metastases, haemoglobin <10 g/dL, and ECOG-PS score >0), and tumor site.

Results

Study identification and characteristics

A total of 821 studies were obtained after removing duplication from initial literature search, and 37 articles were eligible for final meta-analysis, including 4,691 first-line treatment failed patients with advanced UC of bladder, urethra, ureter, or renal pelvis. The flow chart was exhibited in *Figure 1*. Twelve RCTs with 16 arms and 25 single-arm studies were included. Of them, 16 arms reported CNA of ICI plus chemotherapy (n=1), TD plus chemotherapy (n=11), ICI plus TD (n=1), dual ICIs (n=2), and dual TDs (n=1). On the other hand, 25 arms reported MNA of ICI (n=14) and TD (n=11).

The median sample sizes of studies were 33 (range: 12–263) and 59 (range: 11–997) in CNA and MNA groups, respectively. Overall, in CNA group, the median age was 66 years, with 76% of males. In MNA group, the median age was 67 years, with 75% of males. Additionally, 33 studies only enrolled the patients who progressed after platinum-based chemotherapy, and 4 articles contained a few participants failed from 1st line ICIs. Only one study designed the sub-analysis to research the association of outcomes and CNA in 17 patients after 1st line ICIs (12). The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and 1.0 were applied to evaluate ORR and DCR in 28 arms and 13 arms, respectively. The basic characteristics of 41 arms were demonstrated in *Table 1*.

Quality assessment

Methodological quality was evaluated for RCTs, with low risk of blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting in a large proportion of articles, but high or unclear risk of random sequence generation, allocation concealment, or other bias in some studies (Figure S1).

Response and survival outcome

A total of 16 trials in CNA group and 25 trials in MNA group reported outcomes of ORR. The pooled ORR in CNA group could be calculated to be 22.9% (95% CI, 17.3–28.5, I^2=75.4%, *Figure 2A*), while 12.2% (95% CI, 9.4–14.9, I^2=82.5%, *Figure 2B*) in MNA group. The difference between two groups was significant (OR =1.88, P<0.001). After excluding 6 studies (5,18,26,28-30) in MNA and 4 studies (5,6,40,41) in CNA because of large heterogeneity for a sensitivity analysis, the pooled ORRs with lower heterogeneity were presented to be 21.9% (95% CI, 18.9–24.9, I^2=45.9%) in CNA group and 11.1% (95% CI, 8.8–13.4, I^2=63.1%) in MNA group (OR =2.01, P<0.001).

The DCR was available for analysis in 12 trials of CNA group and 23 trials of MNA group. The pooled DCR was

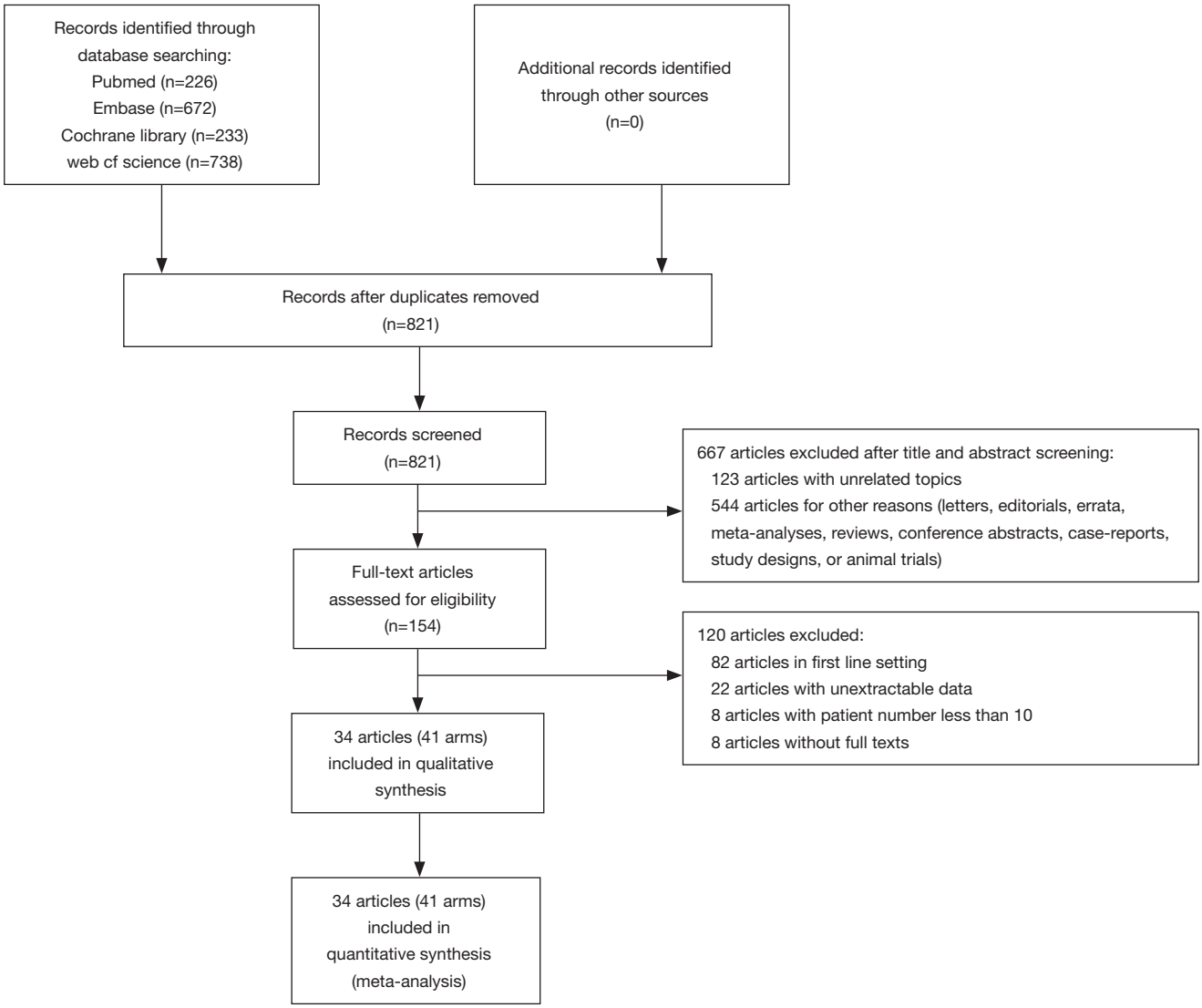

Figure 1 The flow chart of study identification.

62.7% (95% CI, 51.0–71.4, I^2=82.6%, *Figure 2C*) in CNA and 37.5% (95% CI, 33.9–41.2, I^2=74.5%, *Figure 2D*) in MNA, with a significant difference (OR =2.53, P<0.001). The results after omitting 4 studies (5,17,21,29) of MNA and 2 studies (6,37) of CNA for a sensitivity analysis revealed that the modified pooled DCR in CNA was still significantly higher than that in MNA (59.2% versus 36.4%, OR =2.35, P<0.001).

Ten studies in CNA and 20 studies in MNA reported the median PFS. The Pooled data demonstrated that the median PFS in CNA group was significantly longer than that in MNA group [3.66 versus 2.16 months, weighted mean difference (WMD) =1.50, P=0.028, *Figure 3A*,*B*]. After omitting 4 studies (14,16,19,30) of MNA and 3 studies (6,13,37) of CNA, the modified result of sensitivity analysis showed that the difference between two groups was still significant (3.76 versus 2.12 months, WMD =1.64, P=0.002). Additionally, there was significant difference between CNA and MNA in PFS-6m (31.5% versus 28.7%, OR =1.31, P=0.049), but not in PFS-12m (14.4% versus 16.7%, OR =0.87, P=0.384).

The OS was available for analysis from 12 trials in CNA and 15 trials in MNA. However, the pooled median OS was insignificantly different between two groups (WMD =0.43, P=0.449, *Figure 3C*,*D*). After omitting 5 studies (4,16,28,30,34) from MNA with high heterogeneity, the

Table 1 Baseline characteristics of 41 arms for meta-analysis

Author	Study type	Treatment	Patients, n	Median age, years	ORR, % (95% CI)	DCR, % (95% CI)	Median PFS, months (95% CI)	Median OS, months (95% CI)	Grade 3-4 AEs, % (95% CI)
MNA									
Necchi, 2012 (4)	P	Paz	41	67.0	17.1 (7.2–32.1)	51.2 (35.1–67.1)	2.6 (1.7–3.7)	4.7 (4.2–7.3)	29.2 (NA)
Sharma, 2019 (5)	P	Niv	78	65.5	25.6 (16.4–36.8)	52.6 (NA)	2.8 (1.5 to 5.3)	9.9 (7.3–21.1)	26.9 (NA)
Wong, 2012 (13)	P	Cet	11	71.0	0.0 (NA)	0.0 (NA)	NA	1.9 (1.5–NR)	NA
Fradet, 2019 (14)	P	Pem	270	67.0	21.1 (16.4–26.5)	38.5 (NA)	2.1 (2.0–2.2)	10.1 (8.0–12.3)	16.5 (NA)
Yasuoka, 2019 (15)	R	Pem	40	69.0	20.6 (NA)	NA	4.2	10.0 (NA)	10.0 (NA)
Tamura, 2020 (16)	R	Pem	41	70.0	14.6 (NA)	56.4 (NA)	2.5 (1.4–6.2)	11.9 (4.9–NA)	4.9 (NA)
Petrylak, 2018 (17)	P	Ate	95	66.0	26.3 (NA)	45.3 (NA)	2.7 (1.4–4.3)	10.1 (7.3–17.0)	9.5 (NA)
Powles, 2018 (18)	P	Ate	467	67.0	13.4 (10.5–16.9)	33.3 (NA)	2.1 (2.1–2.2)	8.6 (7.8–9.6)	19.8 (NA)
Pal, 2018 (19)	P	Ate	214	69.0	14.9 (NA)	49.1 (NA)	NA	NA	7.9 (NA)
Sternberg, 2019 (20)	P	Ate	997	68.0	13.0 (11.0–16.0)	40.0 (37.0–43.0)	2.2 (2.1–2.4)	8.7 (7.8–9.9)	44.9 (NA)
Rosenberg, 2016 (21)	P	Ate	310	66.0	15.0 (11.0–19.0)	33.5 (NA)	2.7 (2.1–3.9)	7.9 (6.6–9.3)	16.1 (NA)
Apolo, 2017 (22)	P	Ave	44	68.0	18.2 (8.2–32.7)	52.3 (NA)	2.9 (1.5–4.4)	13.7 (8.5–NE)	6.8 (NA)
Patel, 2018 (23)	P	Ave	249	68.0	17.0 (11.0–24.0)	39.8 (NA)	1.6 (1.5–2.5)	6.5 (4.8–9.5)	8.4 (NA)
Ohyama, 2019 (24)	P	Niv	270	66.0	20.4 (15.7–25.7)	41.5 (NA)	1.9 (1.9–2.3)	8.6 (6.1–11.3)	22.6 (NA)
Powles, 2017 (25)	P	Dur	191	67.0	17.8 (12.7–24.0)	36.6 (29.8–43.9)	1.5 (1.4–1.9)	18.2 (8.1–NE)	6.8 (NA)
Twardowski, 2010 (26)	P	Afl	22	67.0	4.5 (0.1–22.8)	36.4 (NA)	2.79 (1.7-3.9)	NA	NA
Wülfing, 2009 (27)	P	Lap	59	64.0	2.0 (0.0–9.1)	32.2 (NA)	2.2[c] (2.0–2.8)	4.5 (3.3–7.6)	NA
Dreicer, 2009 (28)	P	Sor	22	66.0	0.0 (NA)	13.6 (NA)	2.2[b] (1.8–3.7)	6.8 (5.7–8.5)	NA
Gallagher, 2010 (29)	P	Sun	77	NA	5.2 (NA)	28.6 (NA)	NA	NA	74.0 (NA)
Sharma, 2020 (30)	P	Tre	32	66.5	18.8 (7.2–36.4)	28.1 (NA)	2.6 (NA)	10.3 (NA)	28.1 (NA)
Pili, 2013 (31)	P	Paz	18	65.6	0.0 (NA)	NA	1.9 (NA)	NA	38.9 (NA)
Jones, 2017 (32)	P	Paz	66	69.0	4.5 (NA)	36.4	3.1[a] (2.7–4.6)	4.7[a] (4.2–6.4)	37.9 (NA)
Seront, 2012 (33)	P	Eve	37	63.0	5.4 (NA)	27.0 (NA)	2.0 (1.6–2.1)	3.4 (2.7–4.3)	NA
Milowsky, 2013 (34)	P	Eve	45	66.0	5.4 (NA)	37.8 (NA)	2.6 (1.8–3.5)	8.3 (5.5–12.1)	64.4 (NA)
Pulido, 2018 (35)	P	Tem	54	65.0	6.7 (NA)	48.9 (NA)	2.8 (1.8–3.7)	7.2 (5.2–9.5)	52.8 (NA)

Table 1 (*continued*)

Table 1 (*continued*)

Author	Study type	Treatment	Patients, n	Median age, years	ORR, % (95% CI)	DCR, % (95% CI)	Median PFS, months (95% CI)	Median OS, months (95% CI)	Grade 3-4 AEs, % (95% CI)
CNA									
Sharma, 2019 (5)	P	N3I1	104	63.0	26.9 (18.7–36.5)	50.0 (NA)	2.6 (1.4– 3.9)	7.4 (5.6–11.0)	30.8 (NA)
Sharma, 2019 (5)	P	N1I3	92	64.0	38.0 (28.1–48.8)	63.0 (NA)	4.9 (2.7– 6.6)	15.3 (10.1–27.6)	39.1 (NA)
Narayanan, 2016 (6)	P	PP	32	67.0	53.6 (NA)	92.9 (NA)	6.2 (5.6–7.6)	10.0 (5.7–16.0)	NA
Bellmunt, 2018 (7)	P	EP	19	69.0	21.1 (NA)	63.2 (NA)	3.6 (1.8–5.6)	9.1 (6.2–13.1)	73.7 (NA)
Parikh, 2018 (8)	P	PD/PG	12	66.0	41.7 (NA)	58.3 (NA)	4.8 (NA)	NA	58.3 (NA)
Petrylak, 2020 (12)	P	RD	263	65.0	25.9 (20.6–31.1)	65.4 (59.7–71.1)	4.1 (3.3–4.8)	9.4 (7.9–11.4)	47.7 (NA)
Wong, 2012 (13)	P	CP	28	69.0	25.0 (11.0–45.0)	NA	4.1 (3.0–6.3)	10.5 (7.6–19.5)	NA
Petrylak, 2016 (36)	P	RD	46	67.5	24.0 (12.6–38.8)	78.0 (63.6–89.1)	5.4 (3.1–6.9)	10.4 (7.0– 15.1)	82.6 (NA)
Petrylak, 2016 (36)	P	ID	49	66.0	12.0 (4.6–24.8)	45.0 (30.7–59.8)	1.6 (1.4– 2.9)	6.7 (4.5–8.5)	83.7 (NA)
Herbst, 2019 (37)	P	RP	24	63.0	13.0 (2.7–32.4)	50.0 (29.1–70.9)	1.9 (1.2–2.8)	6.4 (2.5–18.7)	NA
Rosenberg, 2018 (38)	P	AD	99	68.0	16.1 (11.5–21.9)	NA	1.8 (NA)	6.4 (NA)	82.8 (NA)
Miyata, 2015 (39)	P	SGP	20	74.0	5.0 (NA)	NA	NA	7.0 (NA)	NA
Choueiri, 2012 (40)	P	VD	70	NA	11.4 (NA)	51.4 (NA)	2.6 (NA)	5.9 (NA)	60.0 (NA)
Niegisch, 2015 (41)	P	PE	27	63.0	12.5 (NA)	58.3 (NA)	2.9 (1.9–4.2)	5.6 (4.8–10.2)	80.0 (NA)
Theodore, 2005 (42)	P	SG	34	63.6	32.3 (17.0–51.0)	NA	7.0 (NA)	11.5 (NA)	NA
Shah, 2019 (43)	P	SV	22	62.5	41.2 (NA)	70.6 (NA)	4.5 (NA)	7.0 (NA)	NA

CNA, combined therapy based on novel agents; MNA, monotherapy of novel agents; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; AEs%, adverse effects rate; CI, confidence interval; P, prospective; R, retrospective; [a], 80% CI; [b], 90% CI; [c], time to progression; NR, not reached; NA, not available; NE, not estimable; Paz, pazopanib; Niv, nivolumab; Cet, cetuximab; Pem, pembrolizumab; Ate, atezolizumab; Ave, avelumab; Dur, durvalumab; Afl, Aflibercept; Lap, lapatinib; Sor, sorafenib; Sun, sunitinib; Tre, tremelimumab; Eve, everolimus; Tem, temsirolimus; N3I1, nivolumab 3 mg/kg, ipilimumab 1 mg/kg; N1I3, nivolumab 1 mg/kg, ipilimumab 3 mg/kg; PP, pazopanib, paclitaxel; EP, everolimus, pazopanib; PD, pembrolizumab, docetaxel; PG, pembrolizumab, gemcitabine; RD, ramucirumab, docetaxel; ID, icrucumab, docetaxel; RP, ramucirumab, pembrolizumab; CP, cetuximab, paclitaxel; AD, apatorsen, docetaxel; SGP, sorafenib, gemcitabine, paclitaxel; VD, vandetanib, docetaxel; PE, paclitaxel, everolimus; SG, SCH66336, gemcitabine; SV, sorafenib, vinflunine.

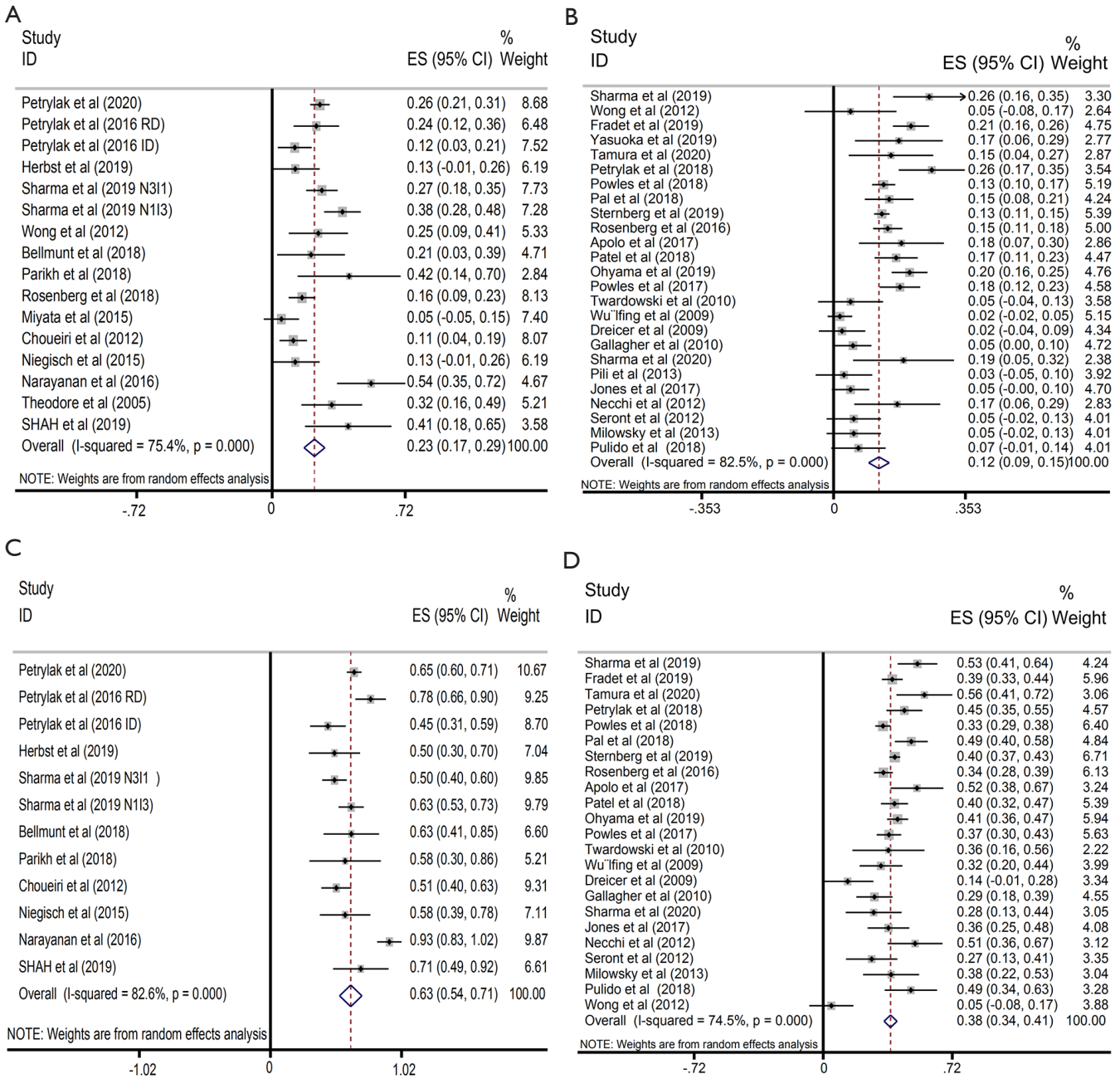

Figure 2 Forest plots of response outcomes of CNA and MNA. (A) Pooled ORR of CNA. (B) Pooled ORR of MNA. (C) Pooled DCR of CNA. (D) Pooled DCR of MNA. CNA, combined therapy of novel agents; MNA, monotherapy of novel agents; ORR, objective response rate; DCR, disease control rate.

difference was insignificant as well (WMD =–0.18, P=0.843). Furthermore, CNA was significantly associated with higher OS-6m (66.0% versus 56.7%, OR =1.34, P=0.029) and lower OS-24m (17.7% versus 28.3%, OR =0.55, P<0.001), but insignificant lower OS-12m (39.5% versus 42.8%, OR =0.94, P=0.47), compared with MNA (*Table 2*).

Toxicity

Ten trials of CNA and 20 trials of MNA reported the grade

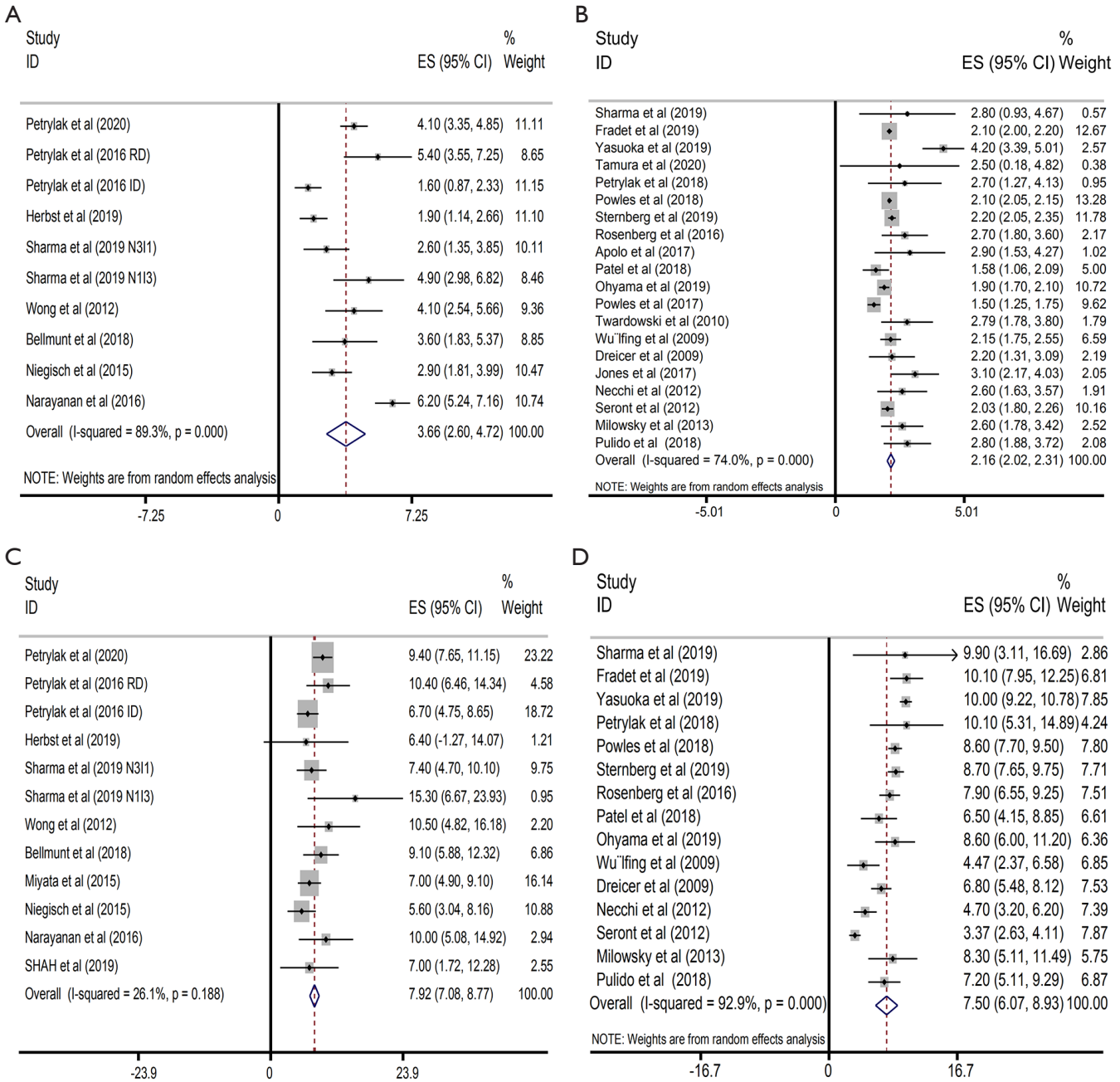

Figure 3 Forest plots of survival outcomes of CNA and MNA. (A) Pooled median PFS of CNA. (B) Pooled median PFS of MNA. (C) Pooled median OS of CNA. (D) Pooled median OS of MNA. CNA, combined therapy of novel agents; MNA, monotherapy of novel agents; PFS, progression-free survival; OS, overall survival.

3-4 AEs%. The pooled results presented that there was significantly higher grade 3-4 AEs% in CNA than MNA (63.7% versus 25.4%, OR =3.52, P<0.001, *Figure 4A*,*B*). The results of sensitivity analysis suggested that omitting any one study did not obviously decrease the heterogeneity.

And the most frequent grade 3-4 AEs in CNA were neutropenia (16.6%), leukopenia (10.8%), fatigue (9.8%), anemia (6.5%), diarrhea (4.5%), hypertension (3.3%), stomatitis (3.3%), elevated ALT (3.0%), elevated AST (2.9%), renal failure (2.7%), and rash (2.6%). In addition,

Table 2 Summary of the pooled outcomes of effectiveness between CNA and MNA

Groups	Cohorts, n	Event, % (95% CI)	Time, months (95% CI)	I^2	OR	WMD	P value
ORR							
CNA	16	22.9 (17.3–28.5)	–	75.4%	1.88	–	<0.001
MNA	25	12.2 (9.4–14.9)	–	82.5%			
DCR							
CNA	12	62.7 (51.0–71.4)	–	82.6%	2.53	–	<0.001
MNA	23	37.5 (33.9–41.2)	–	74.5%			
mPFS							
CNA	10	–	3.66 (2.61–4.72)	89.3%	–	1.50	0.028
MNA	20	–	2.16 (2.02–2.31)	74.0%			
PFS-6m							
CNA	6	35.1 (27.7–35.2)	–	44.5%	1.31	–	0.049
MNA	4	28.7 (20.7–36.7)	–	71.0%			
PFS-12m							
CNA	6	14.4 (8.4–20.3)	–	74.1%	0.87	–	0.384
MNA	5	16.7 (14.2–19.2)	–	0.0%			
mOS							
CNA	12	–	7.93 (7.08–8.77)	26.1%	–	0.43	0.449
MNA	15	–	7.50 (6.07–8.93)	92.9%			
OS-6m							
CNA	3	66.0 (60.7–71.3)	–	35.4%	1.34	–	0.029
MNA	5	56.7 (50.7–62.8)	–	66.0%			
OS-12m							
CNA	9	39.5 (33.9–45.1)	–	50.0%	0.94	–	0.470
MNA	11	42.8 (39.5–46.1)	–	59.1%			
OS-24m							
CNA	3	17.7 (13.7–21.6)	–	0.0%	0.55	–	<0.001
MNA	3	28.3 (24.8–31.8)	–	0.0%			

CI, confidence interval; CNA, combined therapy based on novel agents; MNA, monotherapy of novel agents; ORR, objective response rate; DCR, disease control rate; mPFS, median progression-free survival; mOS, median overall survival; OR, odds ratio; WMD, weighted mean difference.

similar significance could be found in any grade AEs% between the two groups (87.9% versus 66.9%, OR =2.15, P<0.001) (*Table 3*).

Subgroup analyses in CNA group

In CNA group, the statistical difference could be found between ICIs and TDs in pooled ORR (32.2% versus 21.0%, OR =1.68, P=0.003), but not in pooled median PFS (3.63 versus 3.95 months, WMD =–0.32, P=0.769) and OS (10.24 versus 7.92 months, WMD =2.32, P=0.345).

Furthermore, the ORR of participants with positive PD-L1 expression was significantly higher than those negative (36.9% versus 24.7%, OR =1.97, 95% CI, 1.20–

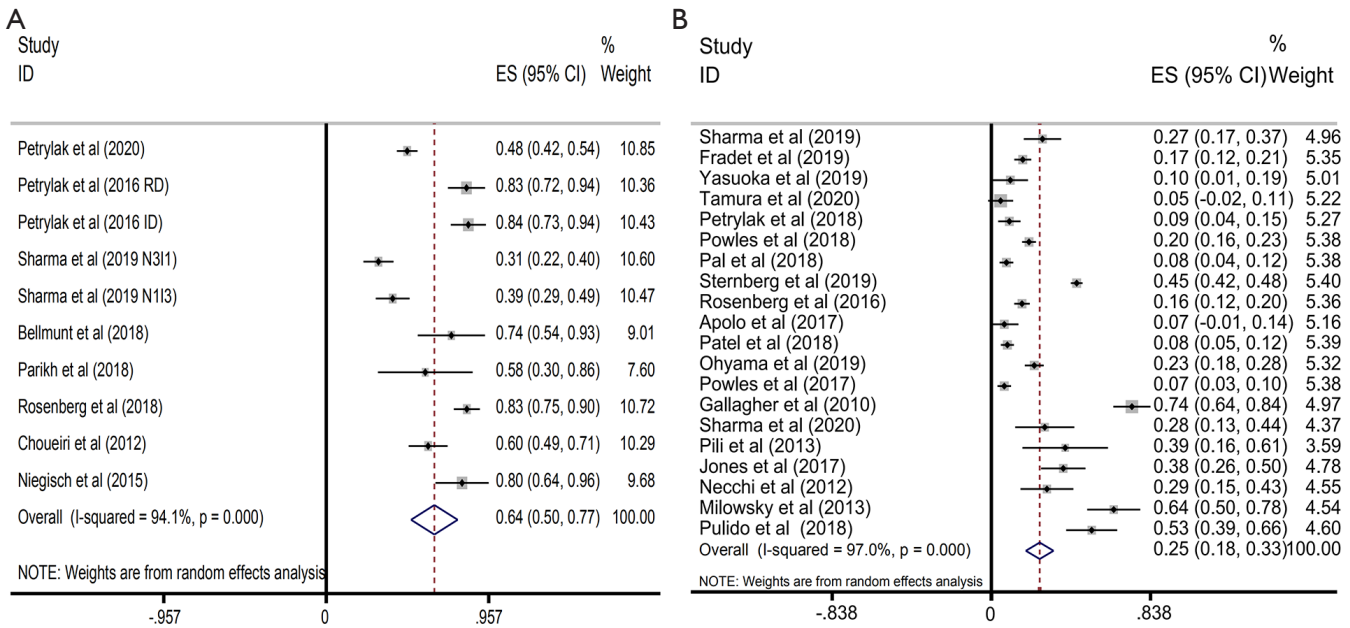

Figure 4 Forest plots of toxicity of CNA and MNA. (A) Pooled grade 3-4 AEs% of CNA. (B) Pooled grade 3-4 AEs% of MNA. CNA, combined therapy of novel agents; MNA, monotherapy of novel agents; grade 3-4 AEs%, grade 3 or 4 adverse events rate.

3.24, P=0.008, I^2=41.9%, *Figure 5A*), and the statistical superiority could be also found in DCR (68.6% versus 50.9%, OR =1.81, 95% CI, 1.13–2.91, P=0.014, I^2=0.0%, *Figure 5B*). However, the median PFS and median OS between participants with PD-L1 (+) and PD-L1 (-) were insignificantly different (4.28 versus 3.12 months, WMD =1.05, 95% CI, 0.42–2.51, P=0.162, I^2=0.0%; 8.15 versus 6.76 months, WMD =0.81, 95% CI, −3.19–4.81, P=0.69, I^2=0.0%). Additionally, the patients of ECOG-PS =0 suggested statistically better ORR than those of ECOG-PS ≥1 (46.7% versus 18.3%, OR =5.55, 95% CI, 1.33–23.22, P=0.019, I^2=40.9%, *Figure 5C*). And the pooled results of other prognostic indicators demonstrated superior clinical outcomes and revealed the trends of significant differences (Tables S1-S3).

Sensitivity analysis and publication bias diagnosis

All sensitivity analyses were presented in Figure S2. No obvious publication bias existed by funnel plot and Egger's test for most outcomes in CNA and MNA groups. The details of all publication bias were provided in Figure S3.

Discussion

Platinum-based chemotherapy or ICI was the first-line treatment for advanced UC (1,2,44). However, it was still inconclusive for the patients with progressive or relapsed disease after first-line regimens. Although MNA including ICIs and TDs, was proved to be a considerable salvage choice for these patients (4,16), CNA demonstrated better results (8,12). Nevertheless, up to now, there was little study comparing the effectiveness and safety of CNA and MNA as salvage treatment for this condition.

This meta-analysis demonstrated significant advantages of CNA over MNA in terms of ORR, DCR, PFS, PFS-6m, and OS-6m. The statistical differences remained after sensitivity analyses. However, it could not be ignored that CNA was associated with higher grade 3-4 AEs%. In the subgroup analyses of CNA, ICIs presented better ORR than TDs, and the prognosis was superior in the patients with PD-L1(+) and ECOG-PS =0.

Programmed death 1 (PD-1) receptor was extensively expressed on activated and exhausted T cells, macrophages, dendritic cells, and B cells, resulting in tumor immune escape by the combination with PD-L1 expressing on tumor cells (45). Somatic mutations and increased immunogenicity were previously observed in UC cells, which suggested that UC was a kind of immune-responsive tumors and monoclonal antibody of immune checkpoints could be a probably rational choice for the treatment of UC (46).

On the other hand, a myriad of molecular targets had

Table 3 Summary of the pooled outcomes of safety between CNA and MNA

Groups	Cohorts, n	Event, % (95% CI)	I^2	OR	P value
Grade 3-4 AEs%					
CNA	10	63.7 (50.0–77.4)	94.1%	3.52	<0.001
MNA	20	25.4 (18.1–32.7)	97.0%		
Any grade AEs%					
CNA	7	87.9 (80.9–94.8)	92.5%	2.15	<0.001
MNA	15	66.9 (59.2–74.5)	95.9%		
Anemia					
CNA	15	6.5 (3.8–9.3)	79.0%	2.72	<0.001
MNA	15	1.9 (0.9–2.9)	69.7%		
Neutropenia					
CNA	11	16.6 (9.6–23.6)	86.2%	22.06	<0.001
MNA	10	0.5 (0.1–1.0)	0.0%		
Leukopenia					
CNA	7	10.8 (3.3–18.4)	87.2%	12.55	<0.001
MNA	6	0.2 (–0.1–0.5)	31.9%		
Thrombocytopenia					
CNA	11	0.7 (0.0–1.3)	47.3%	0.66	0.242
MNA	8	2.8 (0.5–5.0)	57.3%		
Nausea					
CNA	12	1.2 (0.4–2.0)	0.0%	2.48	0.022
MNA	17	0.3 (0.1–0.4)	0.3%		
Vomiting					
CNA	8	1.3 (0.3–2.2)	0.0%	3.16	0.009
MNA	11	0.4 (0.1–0.7)	0.0%		
Decreased appetite					
CNA	5	0.8 (0.1–1.5)	0.0%	1.27	0.76
MNA	10	0.4 (0.2–0.6)	0.0%		
Diarrhea					
CNA	14	4.5 (3.1–5.8)	0.0%	6.28	<0.001
MNA	22	0.6 (0.3–0.8)	0.0%		
Constipation					
CNA	3	0.5 (–0.2–1.3)	3.8%	7.43	0.013
MNA	7	0.2 (–0.0–0.4)	0.0%		
Fatigue					
CNA	15	9.8 (6.1–13.6)	82.5%	4.34	<0.001
MNA	21	1.7 (0.9–2.5)	68.3%		

Table 3 (*continued*)

Table 3 (*continued*)

Groups	Cohorts, n	Event, % (95% CI)	I^2	OR	P value
Neuropathy					
CNA	7	1.6 (−0.2–3.5)	55.0%	23.82	<0.001
MNA	6	0.2 (−0.0–0.5)	0.0%		
Renal failure					
CNA	5	2.7 (−0.4–5.8)	50.3%	2.40	0.068
MNA	4	0.8 (0.3–1.2)	0.0%		
Hypertension					
CNA	10	3.3 (1.9–4.8)	0.0%	2.12	0.008
MNA	10	1.2 (0.7–1.7)	33.2%		
Dyspnoea					
CNA	8	1.4 (0.5–2.3)	22.2%	2.87	0.005
MNA	6	0.7 (0.3–1.1)	0.0%		
Pneumonia					
CNA	7	1.6 (0.5–2.8)	19.4%	2.47	0.018
MNA	10	1.0 (0.5–1.6)	0.0%		
Alopecia					
CNA	4	0.6 (−1.0–2.2)	55.2%	4.45	0.222
MNA	3	0.2 (−0.3–0.7)	0.0%		
Stomatitis					
CNA	2	3.3 (1.2–5.4)	0.0%	4.60	0.006
MNA	6	0.3 (−0.1–0.7)	0.0%		
Hypothyroidism					
CNA	3	0.6 (−0.4–1.5)	0.0%	10.28	0.170
MNA	9	0.1 (−0.0–0.3)	0.0%		
Rash					
CNA	8	2.6 (0.4–4.8)	57.5%	7.45	<0.001
MNA	16	0.4 (0.2–0.6)	0.0%		
Elevated ALT					
CNA	6	3.0 (0.4–5.7)	57.6%	1.31	0.573
MNA	8	0.8 (0.2–1.4)	42.9%		
Elevated AST					
CNA	5	2.9 (0.9–4.9)	0.0%	2.49	0.038
MNA	8	0.8 (0.2–1.3)	0.0%		

CNA, combined therapy based on novel agents; MNA, monotherapy of novel agents; AEs%, adverse effects rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; OR, odds ratio.

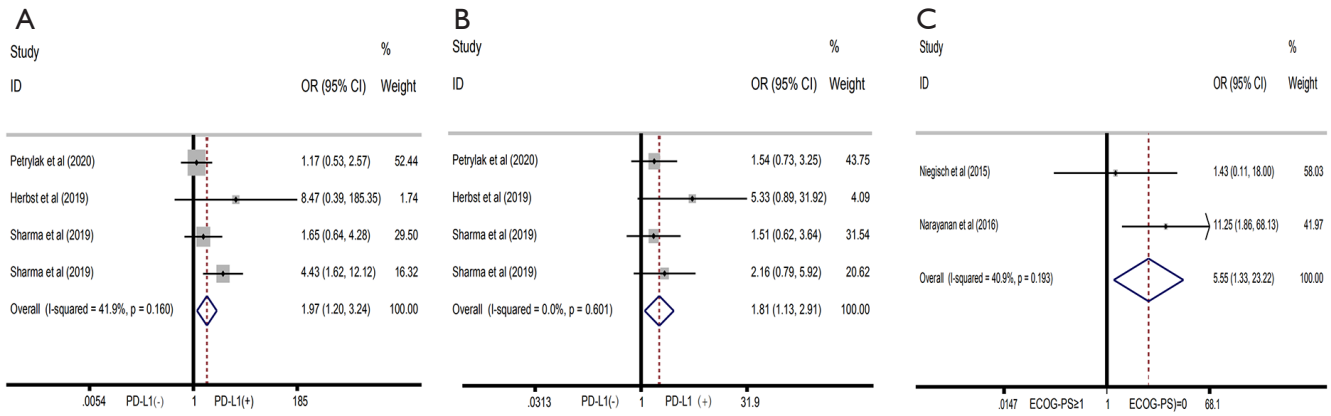

Figure 5 Forest plots of the subgroup analyses in CNA group. (A) ORR of PD-L1(+) *vs.* PD-L1(-). (B) DCR of PD-L1(+) *vs.* PD-L1(-). (C) ORR of ECOG-PS =0 *vs.* ECOG-PS ≥1. CNA, combined therapy of novel agents; ORR, objective response rate; DCR, disease control rate; PD-L1, programmed death-ligand 1; ECOG-PS, Eastern Cooperative Oncology Group Performance Status.

been also found on the surface of UC cells, demonstrating the potential of TDs. Vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) of UC could induce cell proliferation and migration when binding to VEGF and EGF. Additionally, mammalian target of rapamycin (mTOR) pathway was detected in UC, which was associated with poor prognosis. The inhibitors of VEGFR, EGFR and mTOR pathway presented remarkable anti-cancer efficacy (27,28,33).

Furthermore, it had been proved that chemotherapy-induced immunogenic modulation could enhance the anti-tumor activity cytotoxic T lymphocytes through increasing tumor's sensitivity (47). Cytotoxic drugs inhibited angiogenesis through increasing microtubule dynamics in endothelial cells, impairing interphase microtubule functions, and degrading heat shock protein 90, etc. (48). Tumor immune microenvironment could be adjusted by the use of ramucirumab, so that ICIs might lead to better outcomes with the adding of antiangiogenic drugs (12). Combined use of immunological agents could stimulate an anti-cancer immunological joint memory, resulting in improved response rate and prolonged duration of response (49). The activation of mTOR had been proved to increase the proliferation of tumor cells and promote their angiogenesis, which demonstrated that antiangiogenic agents could obtain better effects when accompanying with the mTOR inhibitor (7).

Based on these theories, CNA might be superior to MNA in anti-cancer effectiveness. Clinically, adding pemetrexed and carboplatin chemotherapy to gefitinib significantly prolonged PFS and OS compared with gefitinib alone in advanced non-small-cell lung cancer (50). First-line treatment with dabrafenib plus trametinib led to long-term benefit in the patients who had unresectable or metastatic melanoma (51). Additionally, notable response and survival outcomes had also been revealed in urological cancers. The combination of everolimus and bevacizumab had been suggested for the treatment of advanced non-clear cell renal cell carcinoma (52). For patients with metastatic castration-resistant prostate cancer, durvalumab plus olaparib demonstrated satisfactory efficacy of median PFS and PFS-12m (53).

It's worth noting that the pooled grade 3-4 AEs% in CNA group (63.7%) was significantly higher than that in MNA (25.4%), which might limit the application of combined regimens. Therefore, prevention measures were demanded to decrease the treatment-related adverse effects of CNA. Vitamin E and G-CSF were recommended for the prophylaxis of chemotherapy-induced peripheral neuropathy and neutropenia, respectively (54,55). And immunosuppressants were suggested when severe diarrhea and colitis occurred caused by ICIs (56). Though a lot of methods had been applied, the prevention and treatment for adverse effects generated by CNA need to be further explored.

However, several limitations in our study should be concentrated. Firstly, there was the lack of head-to-head RCTs comparing CNA and MNA, which could largely affect the quality of our study. Secondly, the heterogeneous modality of 1st line chemotherapy and ICIs might affect the outcomes despite the particularly small proportion of 1st line ICIs patients. Thirdly, we enrolled advanced UC

patients treated with different second-line novel agents, which would possibly lead to a selective bias and contribute to some conflicting results in our study, such as OS-12mo and OS-24mo. Finally, though sensitivity analyses were carried out in our study, heterogeneities among studies could not be eliminated.

Conclusions

In conclusion, CNA showed significantly more effectiveness than MNA for patients with advanced UC failed to the first-line treatment. However, the treatment related toxicity of CNA must be carefully noticed. Particularly, for CNA, the regimens of ICIs could be more suitable than TDs, and the patients with PD-L1 (+) and ECOG-PS =0 would have a superior prognosis. However, our results should be further confirmed because of poor quality, publication bias, and significant heterogeneity among included studies.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

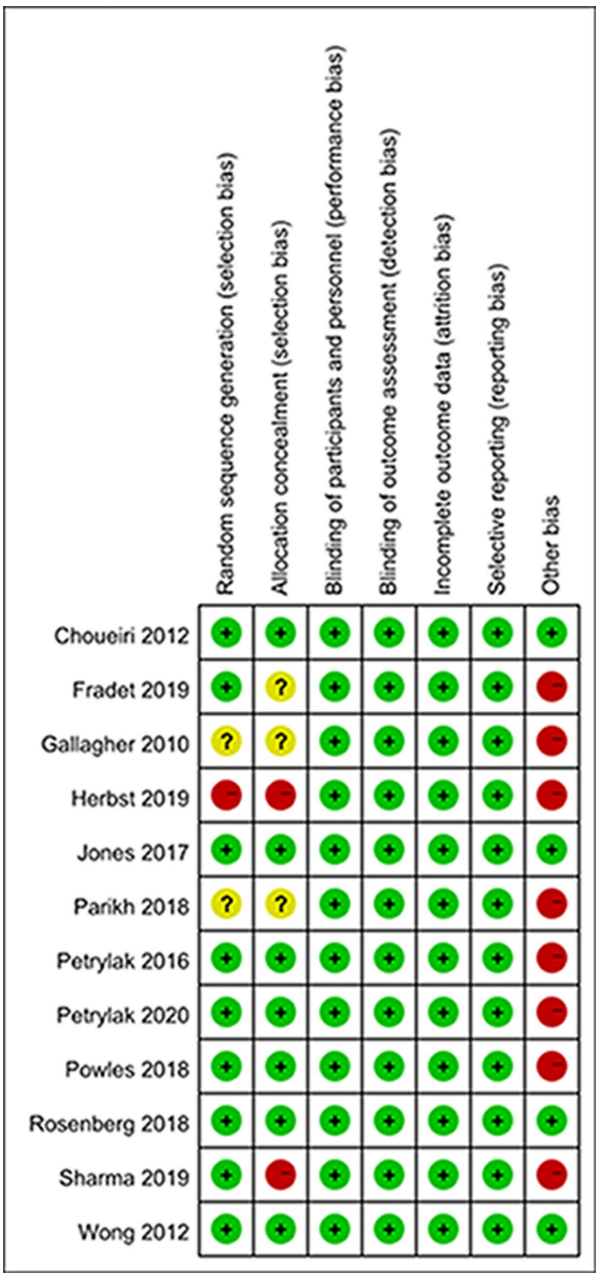

Figure S1 The quality assessment by Cochrane risk of bias tool.

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Table S1 Meta-analysis of the relationship between prognostic indicators and OS event in the subgroup analysis of CNA group

Groups	OS event, %	OR (95% CI)	P value	I^2
Male	73.8% versus 76.0%	1.30 (0.73–2.30)	0.372	0.0%
Versus				
Female				
Age (years) <65	75.6% versus 71.3%	1.29 (0.80–2.06)	0.300	0.0%
Versus				
Age (years) ≥65				
ECOG-PS =0	68.5% versus 77.5%	0.64 (0.40–1.04)	0.069	0.0%
Versus				
ECOG-PS ≥1				
Liver metastases	83.2% versus 70.6%	1.57 (0.92–2.68)	0.099	0.0%
Versus				
Non-Liver metastases				
Haemoglobin <10 (g/dL)	84.8% versus 72.2%	2.17 (0.93–5.06)	0.072	0.0%
Versus				
Haemoglobin ≥ 10 (g/dL)				

CNA, combined therapy based on novel agents; CI, confidence interval; OR, odds ratio; OS, overall survival; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; OS event was defined as death.

Table S2 Meta-analysis of the relationship between prognostic indicators and PFS event in the subgroup analysis of CNA group

Groups	PFS event, %	OR (95% CI)	P value	I^2
Male	80.7% versus 76.5%	1.38 (0.43–4.44)	0.593	0.0%
Versus				
Female				
Age (years) < 65	92.3% versus 73.1%	2.89 (0.88–9.54)	0.081	0.0%
Versus				
Age (years) ≥ 65				
ECOG-PS = 0	77.8% versus 80.4%	0.91 (0.33–2.49)	0.85	0.0%
Versus				
ECOG-PS ≥ 1				
Liver metastases	87.1% versus 77.4%	2.16 (0.65–7.15)	0.206	0.0%
Versus				
Non-Liver metastases				
Haemoglobin < 10 (g/dL)	89.0% versus 77.7%	3.23 (0.39–26.51)	0.274	0.0%
Versus				
Haemoglobin ≥ 10 (g/dL)				

CNA, combined therapy based on novel agents; CI, confidence interval; OR, odds ratio; PFS, progression-free survival; ECOG-PS, Eastern Cooperative Oncology Group Performance Statust; PFS event was defined as disease progression or death.

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Table S3 Meta-analysis of the relationship between prognostic indicators and ORR in the subgroup analysis of CNA group

Groups	ORR, %	OR (95% CI)	P value	I^2
Male	26.1% versus 27.0%	0.75 (0.20–2.76)	0.666	0.0%
Versus				
Female				
ECOG-PS =0	46.7% versus 18.3%	5.55 (1.33–23.22)	0.019	40.9%
Versus				
ECOG-PS ≥1				
Liver metastases	33.3% versus24.5%	1.81 (0.48–6.75)	0.379	0.0%
Versus				
Non-Liver metastases				
Bellmunt risk factors (n) =0	48.0% versus 22.8%	4.11 (0.94–18.06)	0.061	46.3%
Versus				
Bellmunt risk factors (n) ≥1				
UT	17.7% versus 43.3%	0.31 (0.94–18.06)	0.066	0.0%
Versus				
LT				

CNA, combined therapy based on novel agents; CI, confidence interval; OR, odds ratio; ORR, objective response rate; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; UT, upper urinary tract; LT, lower urinary tract.

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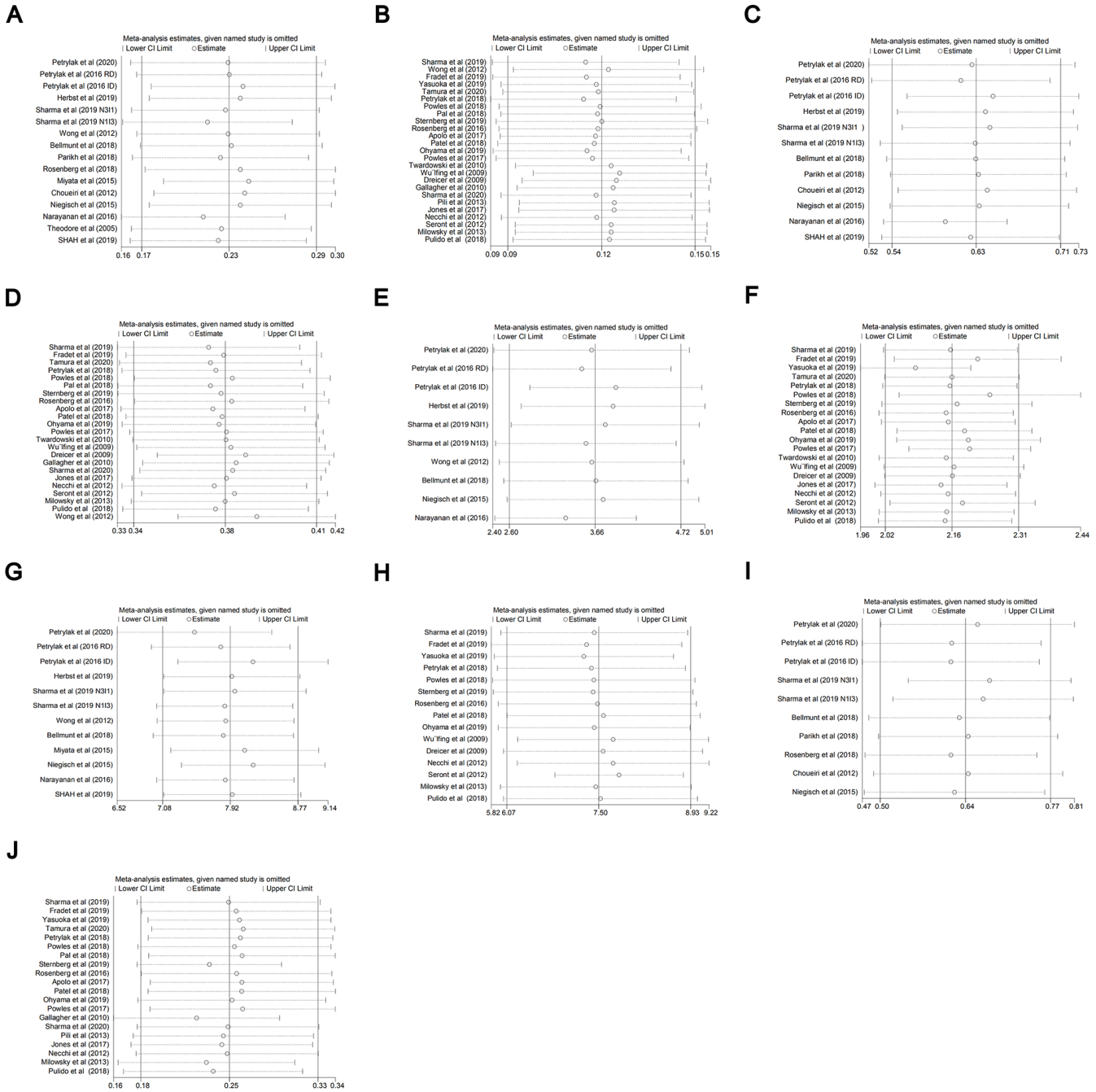

Figure S2 Sensitivity analyses. (A) ORR of CNA. (B) ORR of MNA. (C) DCR of CNA. (D) DCR of MNA. (E) median PFS of CNA. (F) median PFS of MNA. (G) median OS of CNA. (H) median OS of MNA. (I) grade 3-4 AEs% of CNA. (J) grade 3-4 AEs% of MNA. CNA, combined therapy of novel agents; MNA, monotherapy of novel agents; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; grade 3-4 AEs%, grade 3 or 4 adverse events rate.

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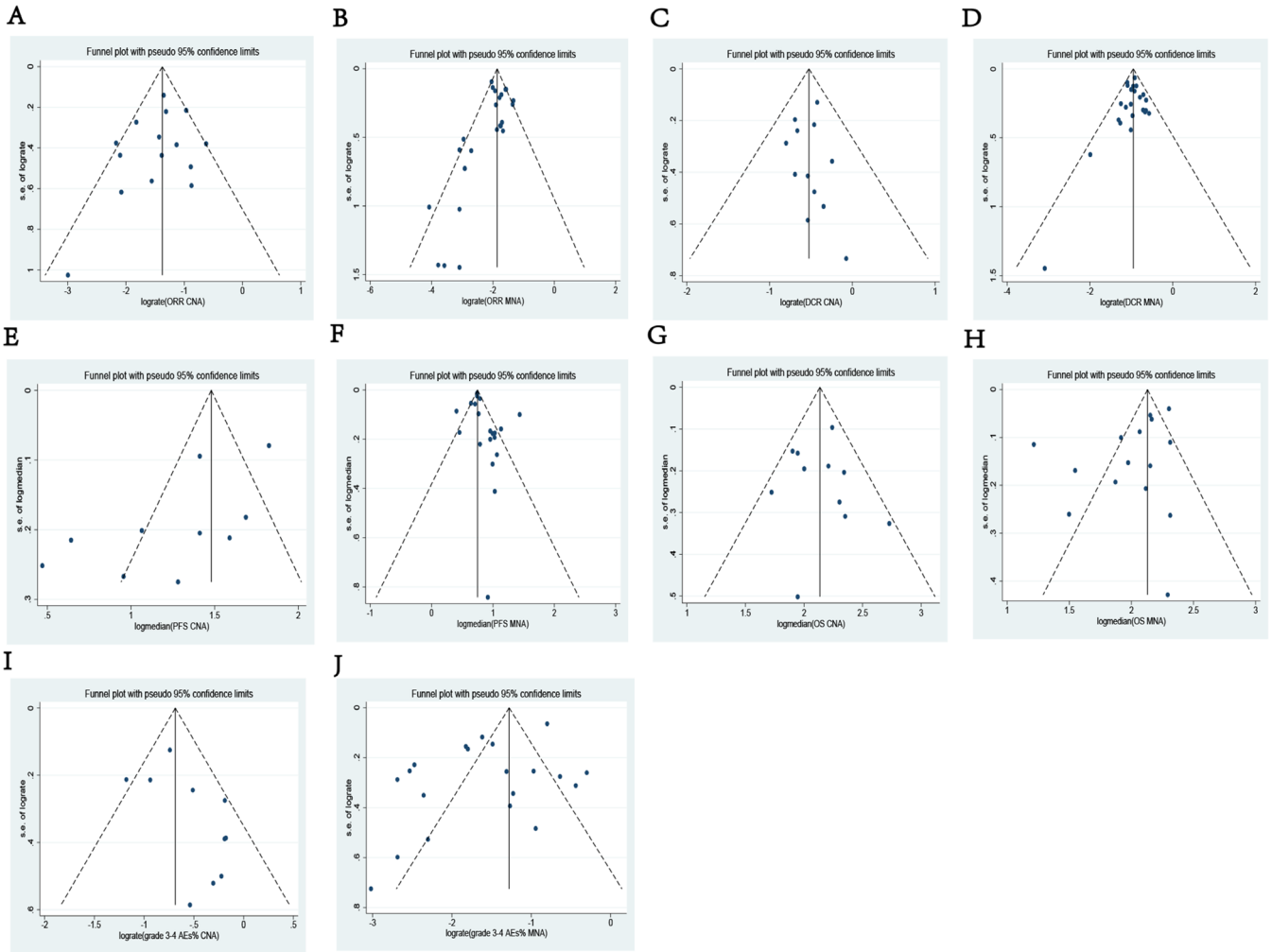

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Quantitative assessment for publication bias					
	ORR	DCR	median PFS	median OS	Grade 3-4 AEs%
Number of studies					
CNA	16	12	10	12	10
MNA	25	23	20	15	20
P value for Egger's tests					
CNA	0.641	0.123	0.039	0.269	0.494
MNA	0.011	0.588	0.607	0.003	P<0.001

CNA, combined therapy based on novel agents; MNA, monotherapy of novel agents; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; AEs%, adverse effects rate.

Figure S3 Publication bias diagnoses. (A) ORR of CNA. (B) ORR of MNA. (C) DCR of CNA. (D) DCR of MNA. (E) median PFS of CNA. (F) median PFS of MNA. (G) median OS of CNA. (H) median OS of MNA. (I) grade 3-4 AEs% of CNA. (J) grade 3-4 AEs% of MNA. (K) Egger' tests. CNA, combined therapy of novel agents; MNA, monotherapy of novel agents; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; grade 3-4 AEs%, grade 3 or 4 adverse events rate.

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