ACCSCIENCE PUBLISHING

Eurasian Journal of Medicine and Oncology

ORIGINAL RESEARCH ARTICLE

Immune checkpoint inhibitor-based therapy in gynecologic clear cell carcinoma: A systematic review and meta-analysis

Hwisu Jung, Hye Lim Jung, Younga Kwon, Kyoung-Chul Chun, Young Ah Kim, Jae Whoan Koh, Jung Yeol Han, and Dong Won Hwang*

Department of Obstetrics and Gynecology, Inje University Ilsan Paik Hospital, Goyang, Gyeonggi, Republic of Korea

Abstract

Introduction: Gynecologic clear cell carcinoma (CCC) is an uncommon histologic entity for which therapeutic options remain limited, and the clinical activity of immune checkpoint inhibitor (ICI)-based treatment has not been clearly defined.
Objective: To synthesize the available evidence on efficacy and safety of ICI-containing regimens in gynecologic CCC.
Methods: We performed a Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020-guided systematic review and meta-analysis. PubMed, Web of Science, and Embase were searched for peer-reviewed full-text studies published between January 2016 and February 7, 2026 that investigated ICI-based treatment in gynecologic CCC. Studies were eligible if they included objective response rate (ORR), grade ≥3 adverse events (AEs), or both. Pooled proportions were obtained through a binomial random-intercept generalized linear mixed model (GLMM); subgroup and sensitivity analyses were exploratory.
Results: Six studies included 181 patients in the efficacy analysis and 189 in the safety analysis. The GLMM estimate for ORR was 0.31 (95% confidence interval [CI], 0.20–0.44; I^2 = 66.1%), and the 95% prediction interval was 0.06–0.74. By treatment strategy, exploratory pooled ORRs were 0.17 (95% CI: 0.07–0.39) for ICI monotherapy and 0.42 (95% CI: 0.32–0.52) for combination regimens. The conventional subgroup comparison yielded p = 0.040, whereas Knapp–Hartung-adjusted meta-regression yielded p = 0.094. For study-defined grade ≥ 3 AEs, the pooled proportion was 0.24 (95% CI: 0.12–0.40; I^2 = 78.1%) with a 95% prediction interval of 0.02–0.81. Corresponding exploratory safety estimates were 0.31 for combination therapy and 0.15 for monotherapy ($p_{between}$ = 0.160).
Conclusion: ICI-containing therapy shows variable antitumor activity across gynecologic CCC cohorts. Combination cohorts had numerically higher response and severe-toxicity rates, but these nonrandomized across-study contrasts were sensitive to small-sample adjustment and confounded by differences in regimens and populations. Overall certainty of the evidence was very low.

Keywords: Gynecologic cancer; Clear cell carcinoma; Immune checkpoint inhibitor; Immunotherapy; Meta-analysis

***Corresponding author:**
Dong Won Hwang
(l0571@paik.ac.kr)

Citation: Jung H, Jung HL, Kwon Y, *et al*. Immune checkpoint inhibitor-based therapy in gynecologic clear cell carcinoma: A systematic review and meta-analysis. *Eurasian J Med Oncol*.
doi: 10.36922/EJMO026260313

Received: June 27, 2026

Revised: September 11, 2026

Accepted: September 16, 2026

Published online: September 23, 2026

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1. Introduction

Gynecologic clear cell carcinoma (CCC) is a distinct but infrequent histologic subtype. It may originate in the ovary, endometrium, or cervix, with ovarian disease representing the most frequent presentation.[1] Ovarian CCC (OCCC) accounts for roughly 5–10% of epithelial ovarian cancers in Western series and approximately 20–25% in East Asian populations, indicating marked geographic variation.[2-4] Its clinicopathologic and molecular profile differs from that of high-grade serous carcinoma, and relative platinum resistance becomes particularly important in recurrent disease.[5-7] Although outcomes can be favorable after surgery for early-stage tumors, advanced or recurrent CCC generally responds poorly to conventional systemic treatment and is associated with worse survival.[8,9]

These therapeutic limitations have prompted investigation of non-cytotoxic approaches, including immune checkpoint blockade and molecularly targeted treatment. Biological characteristics of CCC, including recurrent disruption of chromatin-remodeling pathways such as AT-rich interaction domain 1A (ARID1A) and prominent angiogenic signaling, support testing immunotherapy alone or in combination.[10-12] Clinical studies have consequently examined agents targeting the programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) pathway, as monotherapy or with anti-angiogenic or other immunomodulatory agents, in gynecologic CCC.[13-18] Reported activity, however, has varied considerably between cohorts, leaving the expected magnitude of benefit uncertain, particularly for OCCC.[19,20]

The evidence base remains small and methodologically heterogeneous despite increasing interest in immune checkpoint inhibitor (ICI)-based treatment for gynecologic CCC. Most available data arise from limited phase II cohorts that differ in tumor composition, prior therapy, treatment regimen, and outcome definitions. We therefore sought to summarize both antitumor response and severe toxicity using pooled objective response rates (ORRs) and study-defined grade ≥3 adverse events. Noronha *et al.*[21] recently reported a broader meta-analysis that incorporated conference abstracts as well as full publications. Our review was intended to complement that work by restricting inclusion to peer-reviewed full-text reports available by a prespecified cutoff, thereby permitting more detailed extraction of study-level efficacy and safety definitions. That choice improves depth of outcome characterization but may omit preliminary evidence available only in abstract form. We also examined treatment-strategy and tumor-scope subgroups and tested the stability of pooled estimates across alternative random-effects methods and sensitivity scenarios. The objective was therefore not only to estimate overall efficacy and toxicity, but also to characterize the uncertainty and heterogeneity surrounding those estimates.

2. Materials and methods

2.1. Literature search strategy

The review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines. Because only published aggregate data were analyzed, institutional review board review was not required. The protocol was not prospectively registered in PROSPERO.

PubMed, Web of Science, and Embase were searched for eligible reports published from January 2016 through February 7, 2026. The strategy relied on free-text concepts for gynecologic CCC/OCCC and immune checkpoint blockade. Disease terms included "clear cell carcinoma," "ovarian clear cell carcinoma," "gynecologic clear cell carcinoma," and "ovarian cancer." Immunotherapy terms included "immune checkpoint inhibitor," "immunotherapy," "PD-1," "PD-L1," "CTLA-4," and the agent names nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, ipilimumab, and epacadostat. Disease and treatment concepts were linked with AND, with alternative terms joined by OR as appropriate for each database. Searches were restricted to human studies in English. Database-specific expressions and the final search date are shown in Table S1.

2.2. Study selection

A study qualified for inclusion if it enrolled patients with gynecologic CCC (including OCCC), evaluated an ICI-containing regimen either alone or with another agent, provided extractable ORR and/or grade ≥3 adverse-event data, and used a prospective clinical trial or retrospective cohort design.

We excluded reviews, case reports and case series, reports without ICI exposure, studies lacking extractable efficacy or safety outcomes, mixed-histology studies from which clear-cell-specific results could not be separated, and studies of non-gynecologic malignancies. Two investigators independently screened titles and abstracts and subsequently assessed potentially eligible full texts; disagreements were settled by consensus. Only peer-reviewed full-text publications were included so that study design, follow-up, response definitions, and safety outcomes could be evaluated in sufficient detail. Conference-only reports without peer reviews were not included.

2.3. Data extraction

Two reviewers independently recorded study data using a standardized collection form. Extracted information comprised publication and design characteristics (author, year, phase, and study design), tumor population (OCCC-only or mixed gynecologic CCC), treatment regimen and combination class, efficacy and safety denominators, objective response, and grade ≥3 adverse events. ORR was taken according to the response criteria used in each source report. When a publication contained several treatment groups, only the cohort relevant to the ICI-based regimen of interest was entered into the meta-analysis.

2.4. Definition of treatment strategies

For this review, an ICI-based regimen was defined as a regimen that included an antibody against PD-1, PD-L1, or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Regimens were classified as combinations when checkpoint blockade was administered with another immunomodulatory drug (including a second checkpoint inhibitor or an indoleamine 2,3-dioxygenase 1 [IDO1] inhibitor) or with anti-angiogenic therapy. Regimens without such concomitant agents were categorized as ICI monotherapy.

2.5. Outcomes

Pooled ORR was the primary efficacy endpoint, while the primary safety endpoint was the pooled proportion of patients with study-defined grade ≥3 adverse events or toxicities.

Exploratory subgroup analyses considered two study-level factors: tumor scope (OCCC-only versus mixed gynecologic CCC) and treatment strategy (ICI monotherapy versus ICI-based combination therapy).

For each efficacy analysis, we used the response-evaluable, modified intention-to-treat, or intention-to-treat population defined by the source publication. Safety analyses used the corresponding study-defined safety set, which generally included patients receiving at least one treatment dose. Consequently, efficacy and safety denominators could differ within the same trial.

Safety was synthesized using the severe-toxicity measure reported by each study rather than assuming a fully uniform treatment-related endpoint. We therefore extracted and reported differences in attribution rules, adverse event definitions, Common Terminology Criteria for Adverse Events (CTCAE) version, and safety population separately. Sensitivity analyses then excluded studies with less comparable safety definitions, including reports limited to immune-related events or those with unclear treatment attribution.

2.6. Statistical analysis

Objective response and severe adverse event proportions from single-arm cohorts were synthesized using random-effects models. The primary analysis used maximum-likelihood binomial random-intercept logistic regression, modeling event counts directly rather than relying on a normal approximation after logit transformation. Summary estimates were converted back to the proportion scale. Wald 95% confidence intervals were derived on the logit scale for pooled estimates, whereas exact Clopper–Pearson intervals were used for individual studies.

Given the small evidence base (six studies), each overall meta-analysis was also repeated with inverse-variance models on the logit scale using three estimators of between-study variance: DerSimonian–Laird, restricted maximum likelihood (REML), and Paule–Mandel. Each estimator was evaluated both with and without Hartung–Knapp adjustment, using a t distribution with $k-1$ degrees of freedom. Cochran's Q and I^2 were used to describe heterogeneity. Prediction intervals at the 95% level were calculated using the Higgins–Thompson–Spiegelhalter approach with a t distribution and $k-2$ degrees of freedom.

Because response assessment varied in timing, assessor, and analysis set, these features were tabulated by study. REML was used for subgroup pooling, while the primary generalized linear mixed model (GLMM) was retained for sensitivity and leave-one-out analyses. Prespecified subgroup contrasts were monotherapy versus combination therapy and ovarian-only versus mixed gynecologic clear-cell cohorts. Differences between subgroups were evaluated using Cochran's between-group Q statistic and study-level meta-regression. The latter was fitted both as a random-intercept logistic model and as a logit-scale random-effects model with Knapp–Hartung adjustment. Regimen-class safety analyses included two strata represented by only one study; those strata were therefore summarized with exact binomial intervals and no formal between-class comparison. All subgroup contrasts were ecological, across-study comparisons rather than randomized treatment comparisons.

Sensitivity analyses tested several extraction and definition choices. For safety, these included alternative event counts, exclusion of studies with less comparable attribution, restriction by CTCAE version, and restriction to studies reporting an unambiguous patient-level grade ≥3 treatment-related event count. For efficacy, we examined an alternative LARA response definition and an all-treated denominator scenario, and both outcomes underwent leave-one-out analysis. In the all-treated ORR

scenario, patients outside the source efficacy population were assumed not to have a confirmed response; this scenario was not treated as a reconstructed intention-to-treat analysis. Funnel plots were inspected descriptively. Because fewer than 10 studies were available, no statistical test for funnel asymmetry was performed, and publication bias could not be assessed reliably. Statistical tests were two-sided with $p < 0.05$ as the nominal significance level. Analyses were conducted in R version 4.6.1 using the "meta" and "metafor" packages.

2.7. Risk of bias and certainty of evidence

For the five non-randomized single-arm phase II studies, risk of bias was evaluated with the non-comparative Methodological Index for Non-Randomized Studies (MINORS), which scores eight domains from 0 to 2 (maximum 16). MOCCA, the randomized trial, was evaluated separately with Cochrane RoB 2 across its five domains, and judgments were made independently for tumor response and grade ≥3 treatment-related adverse events. Because the meta-analysis used only the durvalumab arm, RoB 2 domains concerning randomization and deviations from intended intervention characterize the parent trial rather than the extracted single-arm proportion. Two reviewers performed the assessments independently and reached consensus on disagreements. MINORS scores were presented descriptively without converting totals into qualitative categories.

Certainty was appraised for pooled ORR and grade ≥3 adverse events using a Grading of Recommendations, Assessment, Development, and Evaluation framework that considered risk of bias, inconsistency, indirectness, imprecision, and publication bias.

3. Results

3.1. Study selection

Database searching identified 268 records. After removing 34 duplicates, 234 unique records remained for title/abstract screening; 217 were excluded at that stage. Full texts were obtained for 17 reports, of which 11 did not contain extractable clear-cell-specific ORR or grade ≥3 adverse-event data under the prespecified eligibility criteria. Six studies remained for quantitative synthesis (Figure 1). Reports available only as conference abstracts were excluded by the full-text publication criterion.

3.2. Study characteristics

Table 1 summarizes the six eligible studies. Each was a prospective phase II trial: five used non-randomized single-arm designs, whereas MOCCA was randomized and contributed only its durvalumab arm. Three studies enrolled OCCC exclusively and three included more than one gynecologic clear-cell primary site. Across studies, treatment consisted of either ICI monotherapy or combinations with anti-angiogenic agents, dual checkpoint blockade, or other immunomodulators. The source-defined efficacy populations and response assessments were not identical, particularly regarding the analysis population, assessment window, and assessor; these details are shown in Table 1.

A total of 181 patients contributed objective-response data. The primary GLMM produced a pooled ORR of 0.31 (95% CI: 0.20–0.44). Between-study variability was substantial ($I^2 = 66.1\%$; Cochran's $Q = 14.75$, df = 5, $p = 0.011$), and the 95% prediction interval extended from 0.06 to 0.74 (Figure 2). Individual study estimates ranged from 0.10 to 0.54. Alternative random-effects estimators yielded pooled point estimates between 0.31 and 0.32 (Table S2). Results of leave-one-out analyses are provided in Table S3 and Figure S1.

When studies were grouped by treatment strategy, the exploratory REML estimate for ORR was 0.17 (95% CI: 0.07–0.39) for monotherapy and 0.42 (95% CI: 0.32–0.52) for combination regimens (Figure 3). The conventional between-group test yielded $Q_{between} = 4.23$ (df = 1, $p = 0.040$), whereas Knapp–Hartung-adjusted meta-regression yielded $p = 0.094$. Tables S4 and S5 provide the complete subgroup and moderator results.

3.3. Subgroup analysis by cancer type

For the tumor-scope analysis, pooled ORR was 0.23 (95% CI: 0.09–0.47) among ovarian-only cohorts and 0.38 (95% CI: 0.23–0.56) among mixed gynecologic clear-cell cohorts. The between-group statistic was $Q_{between} = 1.19$ (df = 1, $p = 0.275$), providing no statistically significant subgroup difference (Figure 4).

3.4. Grade ≥3 adverse events

Safety analyses included 189 patients and 45 study-defined grade ≥3 events. Tables 2 and S6 detail the safety sets, event definitions, attribution rules, and CTCAE versions used by each study. The primary GLMM yielded a pooled severe-event proportion of 0.24 (95% CI: 0.12–0.40), with substantial heterogeneity ($I^2 = 78.1\%$; $Q = 22.85$, df = 5, $p < 0.001$). The corresponding 95% prediction interval was 0.02–0.81 (Figure 5), while study-level rates ranged from 0.07 to 0.52. Alternative random-effects estimators produced similar point estimates (Table S7). Sensitivity and leave-one-out findings are reported in Table S3 and Figure S2.

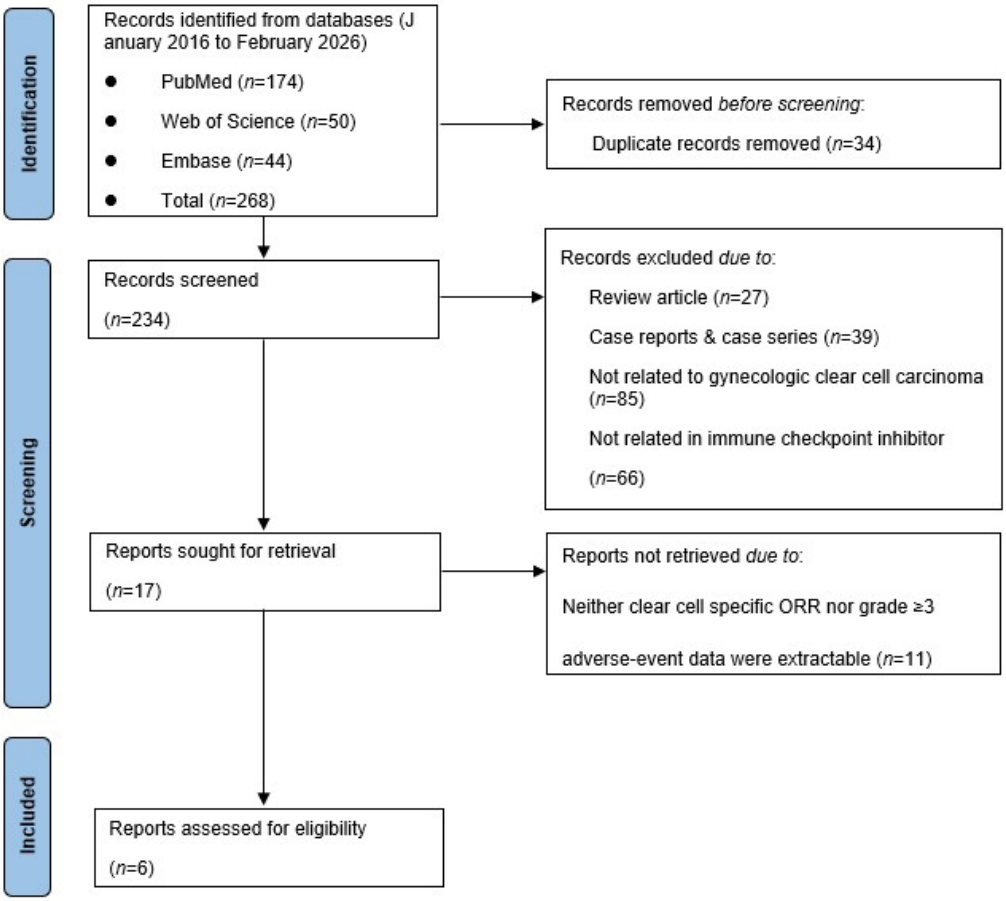


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram of literature search and study selection

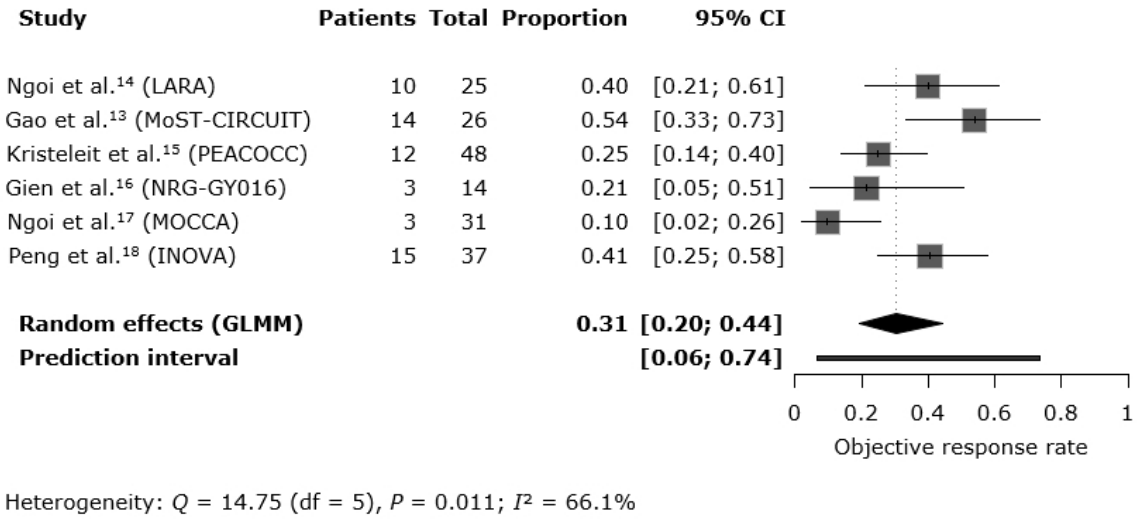


Figure 2. Primary random-effects generalized linear mixed model (GLMM) of objective response rate across the six included studies. The pooled ORR was 0.31 (95% confidence interval [CI]: 0.20–0.44), with a 95% prediction interval of 0.06–0.74; heterogeneity was $I^2 = 66.1\%$ ($Q = 14.75$, df = 5, $p = 0.011$).

Table 1. Study characteristics and objective response rates

Study	Regimen	Design	Efficacy population	ORR definition	Responders/ total	ORR, % (95% CI)
Ngoi *et al.*[14] (LARA)	Pembrolizumab + lenvatinib	Phase 2, single-arm	mITT, confirmed ORR within 24 weeks	Confirmed ORR within 24 weeks, investigator (RECIST 1.1)	10/25	40.0 (21.1–61.3)
Gao *et al.*[13] (MoST-CIRCUIT)	Nivolumab + ipilimumab	Phase 2, single-arm (basket substudy)	Response-evaluable (26 of 28 treated)	ORR in response-evaluable patients, investigator (RECIST 1.1)	14/26	53.8 (33.4–73.4)
Kristeleit *et al.*[15] (PEACOCC)	Pembrolizumab	Phase 2, single-arm	All eligible and treated; best ORR	Best ORR at any time point, investigator (RECIST 1.1)	12/48	25.0 (13.6–39.6)
Gien *et al.*[16] (NRG-GY016)	Pembrolizumab + epacadostat	Phase 2, single-arm (stage 1)	All enrolled initiated therapy; ORR within 7 months	ORR within 7 months of enrolment, investigator (RECIST 1.1)	3/14	21.4 (4.7–50.8)
Ngoi *et al.*[17] (MOCCA)	Durvalumab	Phase 2, randomized (durvalumab arm)	ITT, durvalumab arm	ORR, investigator (RECIST 1.1 and modified RECIST)	3/31	9.7 (2.0–25.8)
Peng *et al.*[18] (INOVA)	Sintilimab + bevacizumab	Phase 2, single-arm	Activity analysis (≥1 post-baseline assessment)	ORR by independent central review (RECIST 1.1)	15/37	40.5 (24.8–57.9)

Abbreviations: CI: Confidence interval; ITT: Intention-to-treat; mITT: Modified intention-to-treat; ORR: Objective response rate; RECIST: Response Evaluation Criteria in Solid Tumors.

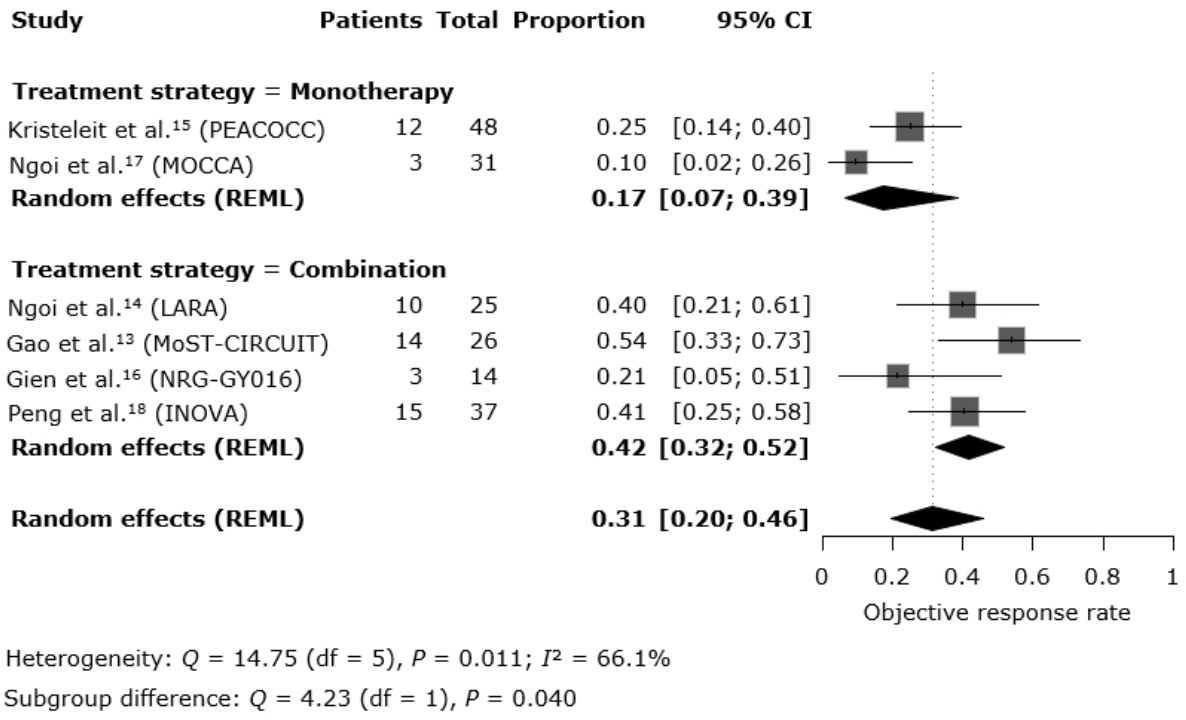


Figure 3. Exploratory subgroup analysis of objective response rate by treatment strategy. Restricted maximum likelihood (REML) pooled objective response rate was 0.17 (95% confidence interval [CI]: 0.07–0.39) for monotherapy and 0.42 (95% CI: 0.32–0.52) for combination therapy; $Q_{between} = 4.23$ (df = 1, $p = 0.040$).

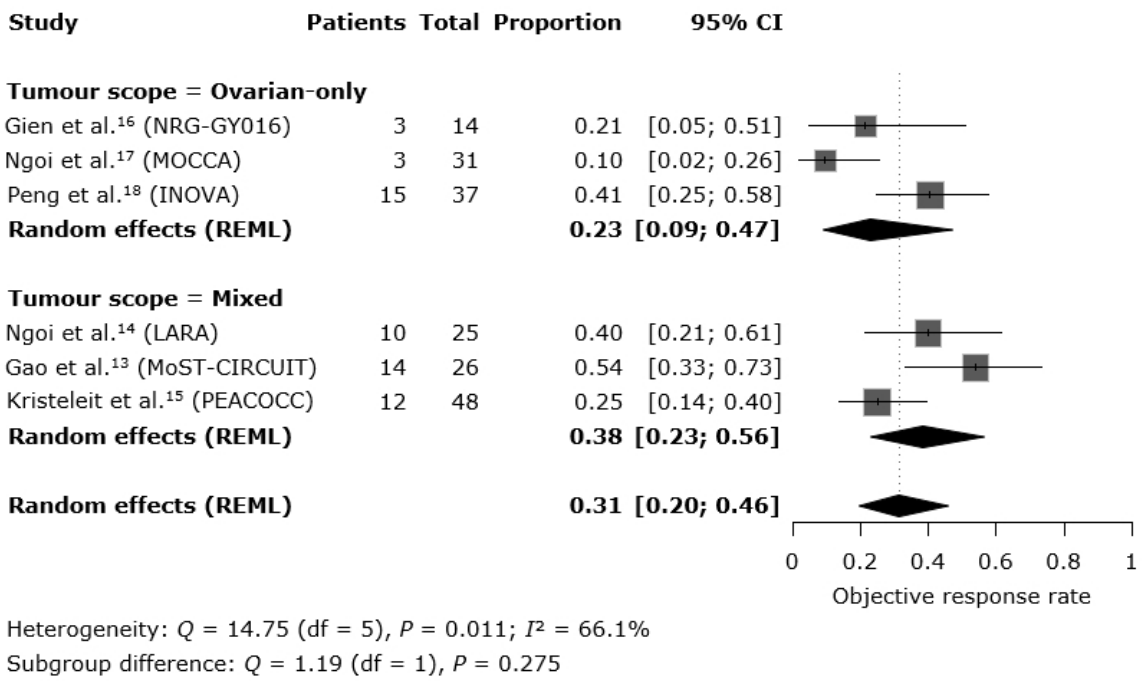


Figure 4. Exploratory subgroup analysis of objective response rate (ORR) by tumor scope (ovarian-only vs mixed gynecologic clear-cell cohorts). Restricted maximum likelihood (REML) pooled ORR was 0.23 (95% confidence interval [CI]: 0.09–0.47) and 0.38 (95% CI: 0.23–0.56), respectively; $Q_{between} = 1.19$ (df = 1, $p = 0.275$).

Table 2. Study-level safety populations and grade ≥3 adverse-event definitions

Study	Regimen	Safety population	Safety definition	CTCAE	Events/total	Proportion, % (95% CI)
Ngoi 2026 (LARA)[14]	Pembrolizumab + lenvatinib	All who received ≥1 dose	Grade 3–4 treatment-related AEs	v5.0	14/27	51.9 (31.9–71.3)
Gao 2025 (MoST-CIRCUIT)[13]	Nivolumab + ipilimumab	All who received ≥1 dose	Grade ≥3 immune-related AEs	v5.0	10/28	35.7 (18.6–55.9)
Kristeleit 2025 (PEACOCC)[15]	Pembrolizumab	All eligible and treated	Grade 3 treatment-related AEs	v5.0	9/48	18.8 (8.9–32.6)
Gien 2024 (NRG-GY016)[16]	Pembrolizumab + epacadostat	All treated	Grade 3 AEs; attribution ambiguous	v5.0	6/14	42.9 (17.7–71.1)
Ngoi 2025 (MOCCA)[17]	Durvalumab	Durvalumab arm, all randomized and treated	Grade 3–4 treatment-related AEs	v4.0	3/31	9.7 (2.0–25.8)
Peng 2024 (INOVA)[18]	Sintilimab + bevacizumab	All who received ≥1 dose	Grade 3 treatment-related AEs	v5.0	3/41	7.3 (1.5–19.9)

Note: CIs are 95% exact Clopper–Pearson binomial intervals.
Abbreviations: AE: Adverse event; CTCAE: Common Terminology Criteria for Adverse Events; irAE: Immune-related adverse event; TRAE: Treatment-related adverse event.

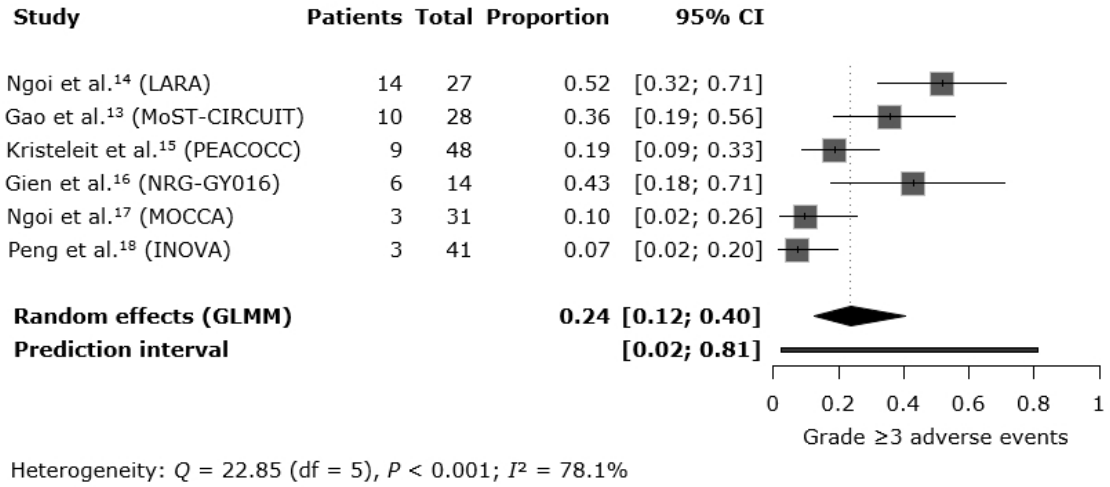


Figure 5. Primary random-effects generalized linear mixed model (GLMM) of study-defined grade ≥3 adverse events across the six included studies. The pooled proportion was 0.24 (95% confidence interval [CI]: 0.12–0.40), with a 95% prediction interval of 0.02–0.81; heterogeneity was $I^2 = 78.1\%$ ($Q = 22.85$, df = 5, $p < 0.001$).

3.5. Subgroup analysis by treatment strategy

Exploratory pooling by treatment strategy yielded a grade ≥3 adverse-event proportion of 0.15 (95% CI: 0.08–0.27) for monotherapy and 0.31 (95% CI: 0.13–0.57) for combination regimens. The subgroup contrast was not statistically significant ($Q_{between} = 1.97$, df = 1, $p = 0.160$); Knapp–Hartung-adjusted meta-regression similarly gave $p = 0.302$ (Figure 6; Tables S4 and S5). In the regimen-class analysis, two studies contributed ICI monotherapy, two contributed ICI plus anti-angiogenic therapy, and the dual-checkpoint and ICI-plus-IDO1 strata each consisted of one study. Because two classes were single-study strata, class-specific estimates were displayed descriptively without a formal between-class test (Figure S3).

3.6. Risk of bias, certainty of evidence, and publication bias

Risk-of-bias results are summarized in Tables 3 and 4 and Figure 7. MINORS totals for the five single-arm studies were 13/16 (LARA),[14] 13/16 (MoST-CIRCUIT),[13] 15/16 (PEACOCC), 14/16 (NRG-GY016),[16] and 13/16 (INOVA);[18] each had a prespecified sample-size calculation. For MOCCA,[17] RoB 2 produced an overall high-risk judgment for both tumor response and grade ≥3 treatment-related adverse events, mainly because of concerns in the outcome-measurement domain. Missing outcome data were judged as some concerns for tumor response and low risk for safety. Because only the durvalumab arm was included in the meta-analysis, the randomization and deviation domains referred to the parent randomized trial. GRADE certainty was very low for both pooled outcomes because the evidence was predominantly non-comparative and showed important inconsistency and imprecision; heterogeneous safety definitions added indirectness for the adverse-event endpoint (Table S8). With only six studies, publication bias could not be evaluated meaningfully. We therefore did not perform formal funnel-asymmetry testing and retained funnel plots for description only (Table S9; Figures S4 and S5).

4. Discussion

Across six prospective phase II studies, 181 patients contributed efficacy data and 189 contributed safety data. The primary GLMM estimated an ORR of 0.31 (95% CI: 0.20–0.44) and a study-defined grade ≥3 adverse-event proportion of 0.24 (95% CI: 0.12–0.40). Both outcomes showed wide prediction intervals (0.06–0.74 for ORR and 0.02–0.81 for severe AEs), underscoring considerable uncertainty between cohorts. Combination-treatment studies had a higher pooled response estimate than monotherapy studies, but the nominal conventional subgroup result did not remain significant after Hartung–Knapp small-sample adjustment. This pattern should therefore not be interpreted as proof that combination therapy is more effective. Regimens grouped as "combination" differed markedly in mechanism, and the underlying studies also differed in prior treatment, tumor site, biomarker composition, patient selection, and design. The same caution applies to toxicity: although the pooled severe-event rate was numerically higher in combination cohorts, the between-subgroup contrast was not statistically significant, and the data cannot quantify

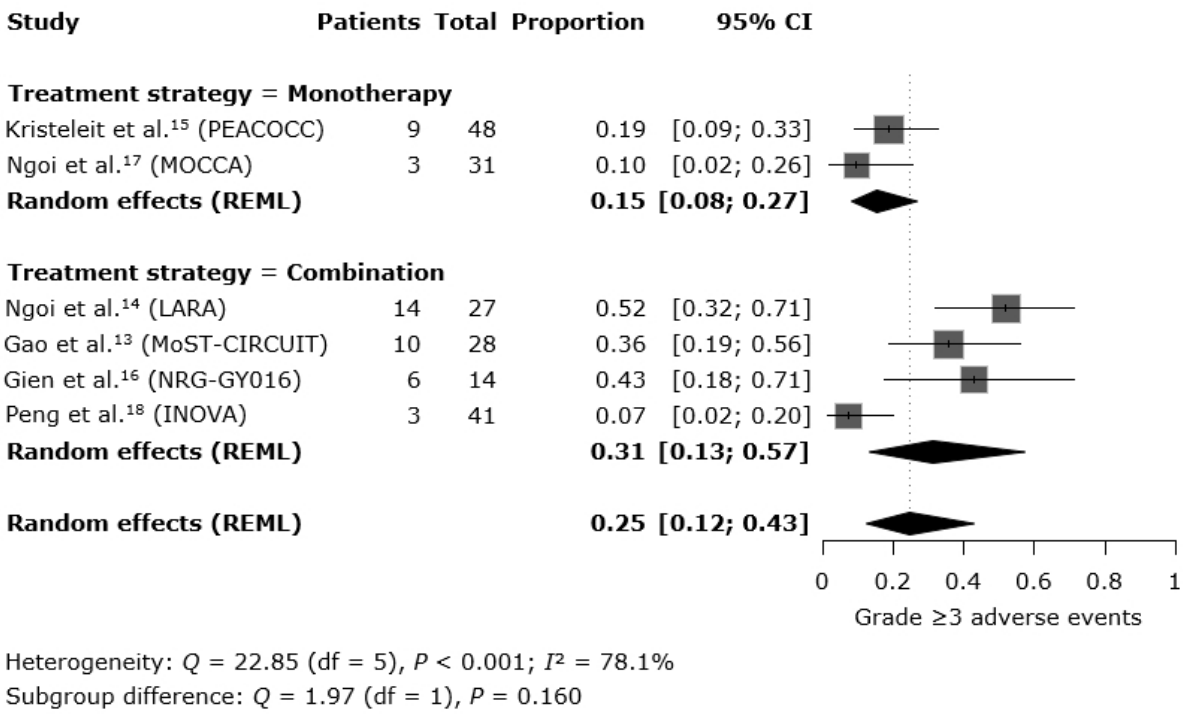


Figure 6. Exploratory subgroup analysis of study-defined grade ≥3 adverse events by treatment strategy. Restricted maximum likelihood (REML) pooled proportions were 0.15 (95% confidence interval [CI]: 0.08–0.27) for monotherapy and 0.31 (95% CI: 0.13–0.57) for combination therapy; $Q_{between} = 1.97$ (df = 1, $p = 0.160$).

Table 3. Corrected MINORS assessment of the five non-randomized single-arm trials

Study	Aim	Consecutive patients	Prospective data	Appropriate endpoint	Unbiased assessment	Follow-up	Loss <5%	Sample-size calculation	Total /16
Ngoi *et al.*[14] (LARA)	2	2	2	1	1	2	1	2	13
Gao *et al.*[13] (MoST-CIRCUIT)	2	2	2	1	1	2	1	2	13
Kristeleit *et al.*[15] (PEACOCC)	2	2	2	2	1	2	2	2	15
Gien *et al.*[16] (NRG-GY016)	2	2	2	2	1	2	1	2	14
Peng *et al.*[18] (INOVA)	2	2	2	1	1	2	1	2	13

Notes: MINORS items are scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). No categorical quality thresholds were applied. All five trials had prospective sample-size calculations.

Table 4. Cochrane RoB 2 assessment of the randomized MOCCA trial

Outcome	D1 Randomization	D2 Deviations	D3 Missing data	D4 Outcome measurement	D5 Reported result	Overall
Tumor response	Low	Some concerns	Some concerns	High	Some concerns	High
Grade ≥3 treatment-related AEs	Low	Some concerns	Low	High	Some concerns	High

Notes: RoB 2 judgments are outcome-specific. Because only the durvalumab arm was extracted for this meta-analysis, D1 and D2 describe the parent randomized trial, whereas D3–D5 are more directly relevant to the extracted single-arm proportions. The high overall judgment for tumor response was driven primarily by uncertainty regarding blinded/independent outcome assessment; for grade ≥3 treatment-related adverse events (AEs), investigator attribution of relatedness in an open-label trial drove the high measurement-domain judgment.

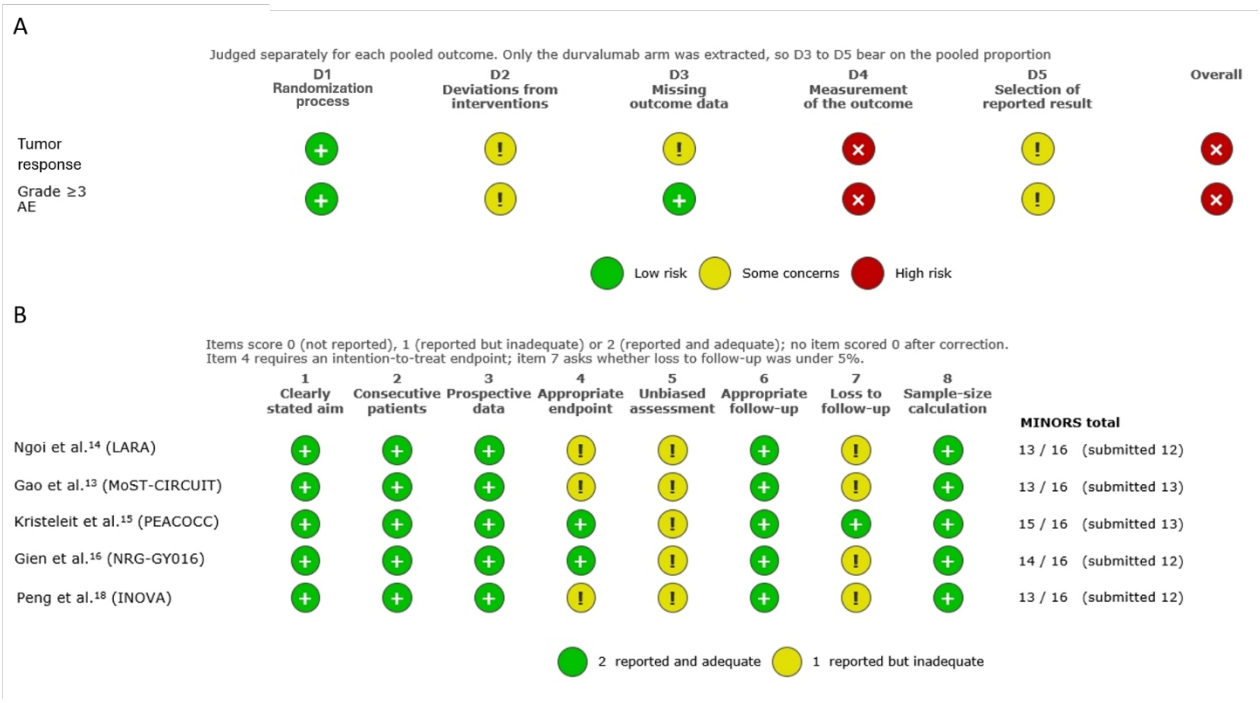


Figure 7. Risk-of-bias assessment using RoB 2 for the (A) randomized MOCCA trial and (B) corrected MINORS assessment for the five single-arm trials. RoB 2 judgments were conducted separately for tumor response and grade ≥3 treatment-related adverse events.

incremental toxicity attributable to combination therapy as a unified class. The broad prediction intervals further indicate that the pooled means should not be treated as fixed rates expected for every ICI regimen; results in a future cohort could differ substantially according to regimen and clinical population.

Comparison with the recent literature helps place these estimates in context. Noronha *et al.*[21] combined 15 studies and reported a pooled ORR of 24.5%, drawing on a wider evidence base that also included conference abstracts. Our analysis instead used peer-reviewed full-text reports available by the prespecified cutoff. The two strategies emphasize different priorities: abstract inclusion broadens evidence capture, whereas full publications permit more complete assessment of methods, follow-up, outcome definitions, and safety. The latter approach is not inherently superior and may miss negative or immature findings that remain unpublished in full, thereby increasing susceptibility to publication or time-lag bias. Historical ICI monotherapy studies in unselected recurrent epithelial ovarian cancer, including KEYNOTE-100, generally reported response rates below 15%. Such external comparisons are indirect, however, and cannot demonstrate differential benefit in clear-cell disease.

Clinical heterogeneity was apparent at the individual-study level, with ORRs ranging from 0.10 to 0.54. Differences in regimen, prior therapy, eligibility, primary tumor site, and trial design are all plausible contributors. The combination studies themselves did not represent a single therapeutic strategy: two paired ICI therapy with anti-angiogenic agents, one used dual checkpoint blockade, and one added an IDO1 inhibitor. Checkpoint blockade may interact biologically with angiogenic signaling and the tumor immune milieu, but these mechanisms were not measured consistently enough in the included cohorts to explain observed response differences. Because some regimen classes were represented by only one study, their estimates are best viewed as descriptive signals rather than comparative evidence. This diversity also weakens any simple interpretation of the pooled monotherapy-versus-combination contrast.

The tumor-scope analysis warrants similar restraint. Ovarian-only studies yielded a pooled ORR of 0.23 and mixed gynecologic clear-cell studies 0.38, but the difference between these study groups was not significant ($Q_{between}$ = 1.19, p = 0.275). The two sets of studies also differed in regimen, prior treatment, patient selection, biomarker distributions, and design. The observed numerical difference therefore cannot be assigned to primary tumor site, and results from mixed clear-cell cohorts should not be regarded as direct estimates for an OCCC-only population.

Potential biomarkers provide biologically relevant hypotheses but cannot be resolved by this meta-analysis. ARID1A alteration may affect chromatin regulation and antitumor immune signaling, while mismatch-repair deficiency, microsatellite instability, and, in selected tumors, POLE-associated hypermutation can increase neoantigen load. PD-L1 expression, tumor mutational burden, immune-cell infiltration, and angiogenic/vascular endothelial growth factor (VEGF) features are additional candidate modifiers of ICI activity, especially for regimens combining checkpoint blockade with anti-angiogenic therapy. Yet these variables were measured and reported inconsistently, and patient-level biomarker-response data were unavailable, precluding identification or validation of a predictive marker. Experimental data further support immune-modulatory effects of ARID1A or SWI/SNF perturbation,[22,23] and the angiogenic phenotype of clear-cell tumors provides a rationale for pairing checkpoint blockade with VEGF-pathway inhibition.[24] These mechanistic observations remain hypothesis-generating: they were not captured uniformly in the six cohorts and cannot be inferred to mediate the pooled clinical responses.

Interpretation of the safety estimate is also limited by nonuniform source definitions. Although the pooled proportion of study-defined grade ≥3 events was 0.24, the studies differed in event attribution, safety population, CTCAE version, and the type of toxicity reported. Combination cohorts had a numerically higher pooled rate than monotherapy cohorts (0.31 versus 0.15), but this difference was not statistically significant, and the combination regimens represented distinct toxicity profiles. Results were broadly similar when less comparable safety definitions were excluded, supporting robustness of the overall signal while not creating a fully harmonized endpoint. MoST-CIRCUIT, for example, focused on immune-related adverse events, whereas NRG-GY016 reported grade 3 events with ambiguous attribution; MOCCA used CTCAE version 4.0, compared with version 5.0 in most other studies. Accordingly, the pooled value best reflects a summary of study-defined severe toxicity rather than a precise treatment-related adverse event rate shared across regimens.

Overall, the data support antitumor activity with ICI-based therapy in gynecologic CCC, but they do not show that one treatment strategy is superior or identify a biomarker-defined group that derives greater benefit. The small, predominantly non-comparative evidence base, together with substantial heterogeneity and very low certainty, argues for prospective histology-specific studies using standardized efficacy, safety, and biomarker assessments.

Several limitations affect interpretation. The evidence base consisted of only six phase II studies, five with non-randomized single-arm designs, so comparative inference is inherently limited. MOCCA was randomized, but only one randomized arm was used in the pooled single-arm analysis; RoB 2 nevertheless identified high overall risk for the extracted response and safety outcomes, mainly because blinded outcome assessment or attribution could not be established from the report. Considerable variation in regimens, enrolled populations, response assessment, and safety definitions adds further uncertainty. Efficacy and safety denominators were study-defined and not identical across trials, and individual patient data were unavailable. Biomarker reporting was too inconsistent for formal biomarker-treatment interaction analyses. Restricting eligibility to peer-reviewed full-text publications may also have reduced comprehensiveness and introduced publication or time-lag bias; with six studies, publication bias itself could not be assessed meaningfully. The dedicated DART report of gynecologic CCC was published on February 11, 2026, four days after our February 7 search cutoff, and therefore did not meet the temporal eligibility criterion.[25] NRG-GY003 evaluated nivolumab with or

without ipilimumab in recurrent ovarian cancer but did not report extractable clear-cell-specific outcomes for this synthesis.[26] In addition, the review was not prospectively registered in PROSPERO. Although the review question, eligibility criteria, and outcomes were defined before quantitative synthesis, the lack of prospective public registration reduces transparency about protocol adherence. Finally, GRADE certainty was very low, so pooled estimates should be interpreted as exploratory summaries rather than definitive comparative treatment effects.

5. Conclusion

Immune checkpoint inhibitor-based treatment demonstrates variable antitumor activity across gynecologic CCC studies. Combination cohorts showed numerically higher response and severe-toxicity estimates, but these study-level comparisons were exploratory, sensitive to small-sample adjustment, and confounded by important differences in regimens and populations. Because certainty of evidence remains very low, the analysis does not establish causal superiority of any treatment strategy. Prospective, histology-specific trials incorporating standardized biomarker evaluation are needed.

Acknowledgments

None.

Funding

This work was supported by the 2024 Inje University research grant.

Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Hwisu Jung, Dong Won Hwang
Data curation: Hwisu Jung, Hye Lim Jung, Younga Kwon, Kyoung-Chul Chun, Young Ah Kim, Jae Whoan Koh, Jung Yeol Han
Formal analysis: Hwisu Jung
Funding acquisition: Dong Won Hwang
Investigation: Hwisu Jung, Hye Lim Jung, Younga Kwon, Kyoung-Chul Chun, Young Ah Kim, Jae Whoan Koh, Jung Yeol Han
Methodology: Hwisu Jung
Project administration: Dong Won Hwang
Supervision: Dong Won Hwang
Writing–original draft: Hwisu Jung
Writing–review & editing: Dong Won Hwang

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

All data generated or analyzed during this study are included in this published article and its supplementary file.

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