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

Supplementary File

Table S1. Database-specific search strategies

Database	Search strategy	Limits / final search date
PubMed	("clear cell carcinoma" OR "ovarian clear cell carcinoma" OR "gynecologic clear cell carcinoma" OR "ovarian cancer") AND ("immune checkpoint inhibitor" OR immunotherapy OR "PD-1" OR "PD-L1" OR "CTLA-4" OR nivolumab OR pembrolizumab OR atezolizumab OR avelumab OR durvalumab OR ipilimumab OR epacadostat)	Human; English; Jan 2016–Feb 7, 2026
Web of Science	("clear cell carcinoma" OR "ovarian clear cell carcinoma" OR "gynecologic clear cell carcinoma" OR "ovarian cancer") AND ("immune checkpoint inhibitor" OR immunotherapy OR "PD-1" OR "PD-L1" OR "CTLA-4" OR nivolumab OR pembrolizumab OR atezolizumab OR avelumab OR durvalumab OR ipilimumab OR epacadostat)	English; Jan 2016–Feb 7, 2026
Embase	("clear cell carcinoma" OR "ovarian clear cell carcinoma" OR "gynecologic clear cell carcinoma" OR "ovarian cancer") AND ("immune checkpoint inhibitor" OR immunotherapy OR "PD-1" OR "PD-L1" OR "CTLA-4" OR nivolumab OR pembrolizumab OR atezolizumab OR avelumab OR durvalumab OR ipilimumab OR epacadostat)	Human; English; Jan 2016–Feb 7, 2026

Notes: Searches used the prespecified free-text terms entered in the respective database interfaces. Terms within the disease and immunotherapy concepts were combined with OR, and the two concepts with AND. No post hoc terms were added during revision.

Table S2. Pooled objective response rate and estimator sensitivity

Model	Studies	Patients with outcome/ total	Pooled proportion (95% CI)	95% prediction interval	Between-study variance	I^2 (%)	Q (df)	p for Q
Primary: random-intercept logistic GLMM	6	57/181	0.31 (0.20–0.44)	0.06–0.74	0.355	66.1	14.75 (5)	0.011
DerSimonian–Laird			0.32 (0.20–0.45)	0.07–0.74	0.344	66.1	14.75 (5)	0.011
DerSimonian–Laird + Hartung–Knapp			0.32 (0.17–0.52)	0.07–0.74	0.344	66.1	14.75 (5)	0.011
REML			0.31 (0.20–0.46)	0.06–0.76	0.397	66.1	14.75 (5)	0.011
REML + Hartung–Knapp			0.31 (0.16–0.52)	0.06–0.76	0.397	66.1	14.75 (5)	0.011
Paule–Mandel			0.31 (0.19–0.46)	0.05–0.78	0.453	66.1	14.75 (5)	0.011
Paule–Mandel + Hartung–Knapp			0.31 (0.16–0.52)	0.05–0.78	0.453	66.1	14.75 (5)	0.011

Notes: The primary model uses binomial counts in a random-intercept logistic GLMM fitted by maximum likelihood with normal Wald 95% CIs on the logit scale. Inverse-variance models use logit-transformed study proportions and DL, REML, or PM variance estimates, with normal Wald CIs or unmodified Hartung–Knapp t CIs (k−1 df), as labelled. All proportion estimates and limits are back-transformed. 95% prediction intervals use estimate ± t(0.975, k−2) × sqrt(tau2 + classical SE2) on the logit scale (HTS). Q and I2 use the same inverse-variance Cochran Q calculation for all rows.
Abbreviations: CI: Confidence interval; DL: DerSimonian–Laird; GLMM: Generalized linear mixed model; PM: Paule–Mandel; REML: Restricted maximum likelihood.

Table S3. Generalized linear mixed model sensitivity and leave-one-out analyses

Outcome	Analysis	Studies	Patients with outcome/total	Pooled proportion (95% CI)	95% prediction interval	I^2 (%)
Grade ≥3 AE	Primary: verified counts, all six studies	6	45/189	0.24 (0.12–0.40)	0.02–0.81	78.1
	Counts as submitted to EJMO	6	46/191	0.24 (0.13–0.40)	0.03–0.79	76.9
	MOCCA counted as 4 AE terms rather than 3 patients	6	46/189	0.25 (0.13–0.41)	0.03–0.79	76.8
	NRG-GY016 as 7/14, assuming the probably-related grade 5 death is a seventh patient	6	46/189	0.25 (0.13–0.42)	0.02–0.84	79.6
	CTCAE v5.0 studies only	5	42/158	0.28 (0.15–0.46)	0.02–0.87	77.7
	Excluding MoST-CIRCUIT (immune-related AE only)	5	35/161	0.21 (0.10–0.41)	0.01–0.88	81.6
	Excluding NRG-GY016 (grade 3 only, attribution ambiguous)	5	39/175	0.21 (0.10–0.39)	0.01–0.86	81.1
	Restricted to the 4 studies with unambiguous grade ≥3 TRAE	4	29/147	0.18 (0.07–0.38)	0.00–0.96	84.5
	Leave-one-out: omitting Ngoi *et al.*[1] (LARA)	5	31/162	0.19 (0.10–0.34)	0.02–0.75	70.5
	Leave-one-out: omitting Gao *et al.*[2] (MoST-CIRCUIT)	5	35/161	0.21 (0.10–0.41)	0.01–0.88	81.6
	Leave-one-out: omitting Kristeleit *et al.*[3] (PEACOCC)	5	36/141	0.25 (0.11–0.46)	0.01–0.91	80.3
	Leave-one-out: omitting Gien *et al.*[4] (NRG-GY016)	5	39/175	0.21 (0.10–0.39)	0.01–0.86	81.1
	Leave-one-out: omitting Ngoi *et al.*[5] (MOCCA)	5	42/158	0.28 (0.15–0.46)	0.02–0.87	77.7
	Leave-one-out: omitting Peng *et al.*[6] (INOVA)	5	42/148	0.29 (0.17–0.45)	0.03–0.83	73.6
ORR	Primary: source-defined efficacy populations	6	57/181	0.31 (0.20–0.44)	0.06–0.74	66.1
	All treated; excluded efficacy patients assumed nonresponders	6	57/189	0.29 (0.20–0.41)	0.08–0.67	59.6
	LARA post-hoc ORR at any timepoint (11/25) instead of the 24-week endpoint	6	58/181	0.31 (0.20–0.45)	0.06–0.75	67.6
	Leave-one-out: omitting Ngoi *et al.*[1] (LARA)	5	47/156	0.29 (0.16–0.45)	0.03–0.82	71.9
	Leave-one-out: omitting Gao *et al.*[2] (MoST-CIRCUIT)	5	43/155	0.27 (0.17–0.39)	0.06–0.68	57.2
	Leave-one-out: omitting Kristeleit *et al.*[3] (PEACOCC)	5	45/133	0.32 (0.18–0.49)	0.04–0.84	68.2
	Leave-one-out: omitting Gien *et al.*[4] (NRG-GY016)	5	54/167	0.32 (0.20–0.47)	0.05–0.82	70.9
	Leave-one-out: omitting Ngoi *et al.*[5] (MOCCA)	5	54/150	0.36 (0.27–0.47)	0.15–0.65	47.4

Notes: All rows use binomial random-intercept logistic GLMMs fitted by ML with normal Wald 95% CIs on the logit scale, back-transformed. HTS prediction intervals use $k-2$ df and the classical SE. The all-treated ORR scenario assumes every treated patient outside the efficacy population had no confirmed response; this is not a reconstructed ITT analysis. The safety rows vary one extraction or definitional choice at a time against the six-study primary model. The restricted row keeps only the four studies reporting an unambiguous patient-level grade ≥3 treatment-related count. The NRG-GY016 7/14 row assumes the grade 5 death occurred in a patient not already among the six with grade 3 events; the source paper does not report the overlap.

Abbreviations: AE: Adverse event; CI: Confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; GLMM: Generalized linear mixed model; HTS: Higgins–Thompson–Spiegelhalter; ITT: Intention-to-treat; ML: Maximum likelihood; ORR: Objective response rate; SE: Standard error; TRAE: Treatment-related adverse event.

Table S4. Exploratory subgroup analyses

Analysis	Subgroup	Studies	Patients with outcome/ total	Proportion (95% CI)	CI method	I^2 (%)	*p* for within-subgroup *Q*	$Q_{between}$ (df)	$p_{between}$
ORR: treatment strategy	Monotherapy	2	15/79	0.17 (0.07–0.39)	REML, normal Wald	62.7	0.101	4.23 (1)	0.040
	Combination	4	42/102	0.42 (0.32–0.52)	–	20.8	0.285	–	–
ORR: tumor scope	Ovarian-only	3	21/82	0.23 (0.09–0.47)	–	73.6	0.023	1.19 (1)	0.275
	Mixed	3	36/99	0.38 (0.23–0.56)	–	66.8	0.049	–	–
Grade ≥3 AE: treatment strategy	Monotherapy	2	12/79	0.15 (0.08–0.27)	–	14.1	0.281	1.97 (1)	0.160
	Combination	4	33/110	0.31 (0.13–0.57)	–	78.3	0.003	–	–
Grade ≥3 AE: tumor scope	Ovarian-only	3	12/86	0.16 (0.04–0.44)	–	78.8	0.009	1.40 (1)	0.237
	Mixed	3	33/103	0.34 (0.18–0.55)	–	76.2	0.015	–	–
Grade ≥3 AE: regimen class (exploratory)	ICI monotherapy	2	12/79	0.15 (0.08–0.27)	–	14.1	0.281	–	–
	ICI + anti-angiogenic	2	17/68	0.23 (0.02–0.80)	–	92.6	$p < 0.001$	–	–
	Dual checkpoint blockade	1	10/28	0.36 (0.19–0.56)	Exact binomial (single study)	–	–	–	–
	ICI + IDO1 inhibitor	1	6/14	0.43 (0.18–0.71)	–	–	–	–	–

Notes: Multiple-study subgroups use logit inverse-variance REML models with separate subgroup variances and normal Wald 95% CIs. A single study uses its observed proportion and an exact Clopper–Pearson CI, with no heterogeneity estimate. $Q_{between}$ tests use random-effects subgroup estimates (chi-squared, groups−1 df). Regimen-class strata include two single-study groups and are descriptive; no class-difference test is reported. All safety subgroups use the verified six-study counts. Comparisons are across studies, not randomized.

Abbreviations: AE: Adverse event; CI: Confidence interval; ICI: Immune checkpoint inhibitor; IDO1: Indoleamine 2,3-dioxygenase 1; ORR: Objective response rate; REML: Restricted maximum likelihood.

Table S5. Exploratory study-level moderator comparisons

Outcome	Contrast	Studies	$Q_{between}$ (df = 1)	p ($Q_{between}$)	OR, GLMM (95% CI)	*p* (GLMM)	OR, Knapp–Hartung (95% CI)	*p* (Knapp–Hartung)
ORR	Combination versus monotherapy	6	4.23	0.040	2.99 (1.50–5.94)	0.002	2.95 (0.75–11.65)	0.094
	Mixed versus ovarian-only		1.19	0.275	2.05 (0.68–6.14)	0.200	2.04 (0.34–12.42)	0.335
Grade ≥3 AE	Combination versus monotherapy		1.97	0.160	2.82 (0.68–11.82)	0.155	2.82 (0.25–32.26)	0.302
	Mixed versus ovarian-only		1.40	0.237	2.87 (0.77–10.68)	0.115	2.70 (0.27–26.83)	0.297

GLMM: binomial random-intercept logistic model, ML variance, normal Wald 95% CI and two-sided *z* test. Knapp–Hartung: logit inverse-variance REML meta-regression, unmodified variance adjustment, *t* CI/test with $k-2$ df. These meta-regressions estimate one residual variance across groups; $Q_{between}$ uses separately estimated subgroup variances, so the tests have different assumptions. *p*-values are exploratory and unadjusted for multiplicity.

Abbreviations: AE: Adverse event; CI: Confidence interval; GLMM: Generalized linear mixed model; ML: Maximum likelihood; OR: Odds ratio; ORR: Objective response rate; REML: Restricted maximum likelihood.

Table S6. Safety extraction audit and outcome definitions

Study	Safety population	Submitted	Verified	Source-defined grade ≥3 endpoint	CTCAE	Comment
Ngoi *et al.*[1] (LARA)	27 treated	14/27	14/27	Grade 3–4 treatment-related AEs	v5.0	Unambiguous patient-level count
Gao *et al.*[2] (MoST-CIRCUIT)	28 treated	10/29	10/28	Grade ≥3 immune-related AEs	v5.0	Immune-related AEs only
Kristeleit *et al.*[3] (PEACOCC)	48 treated	9/47	9/48	Grade 3 treatment-related AEs	v5.0	Unambiguous patient-level count
Gien *et al.*[4] (NRG-GY016)	14 treated	6/14	6/14	Grade 3 AEs; attribution ambiguous	v5.0	Grade 4 and grade 5 SAEs reported separately; overlap unresolved
Ngoi *et al.*[5] (MOCCA)	31 durvalumab	4/31	3/31	Grade 3–4 treatment-related AEs	v4.0	Patient-level percentage used, not number of AE terms
Peng *et al.*[6] (INOVA)	41 treated	3/43	3/41	Grade 3 treatment-related AEs	v5.0	Unambiguous patient-level count

Note: Verified counts sum to 45/189 and are used in the primary safety analysis.
Abbreviations: AE: Adverse event; CTCAE: Common Terminology Criteria for Adverse Events.

Table S7. Pooled grade ≥3 adverse events and estimator sensitivity

Model	Studies	Patients with outcome/total	Pooled proportion (95% CI)	95% prediction interval	Between-study variance	I^2(%)	Q (df)	p for Q
Primary: random-intercept logistic GLMM	6	45/189	0.24 (0.12–0.40)	0.02–0.81	0.737	78.1	22.85 (5)	$p < 0.001$
DerSimonian–Laird			0.25 (0.13–0.42)	0.02–0.82	0.753	78.1	22.85 (5)	$p < 0.001$
DerSimonian–Laird + Hartung–Knapp			0.25 (0.10–0.50)	0.02–0.82	0.753	78.1	22.85 (5)	$p < 0.001$
REML			0.25 (0.12–0.43)	0.02–0.84	0.843	78.1	22.85 (5)	$p < 0.001$
REML + Hartung–Knapp			0.25 (0.10–0.50)	0.02–0.84	0.843	78.1	22.85 (5)	$p < 0.001$
Paule–Mandel			0.25 (0.12–0.43)	0.02–0.85	0.877	78.1	22.85 (5)	$p < 0.001$
Paule–Mandel + Hartung–Knapp			0.25 (0.10–0.50)	0.02–0.85	0.877	78.1	22.85 (5)	$p < 0.001$

Notes: The primary model uses binomial counts in a random-intercept logistic GLMM fitted by maximum likelihood with normal Wald 95% CIs on the logit scale. Inverse-variance models use logit-transformed study proportions and DL, REML, or PM variance estimates, with normal Wald CIs or unmodified Hartung–Knapp t CIs (k–1 df), as labeled. All proportion estimates and limits are back-transformed. 95% prediction intervals use estimate ± $t(0.975, k–2) \times \text{sqrt}(\text{tau}^2 + \text{classical SE}^2)$ on the logit scale (HTS). Q and I^2 use the same inverse-variance Cochran Q calculation for all rows.
Abbreviations: CI: Confidence interval; DL: DerSimonian–Laird; GLMM: Generalized linear mixed model; HTS: Higgins–Thompson–Spiegelhalter; PM: Paule–Mandel; REML: Restricted maximum likelihood; SE: Standard error.

Table S8. Grading of Recommendations Assessment, Development and Evaluation-style certainty of evidence for the two pooled outcomes

Outcome	Domain	Judgement	Certainty
Objective response rate	Starting certainty	Low: pooled single-arm proportion with no comparator, including one isolated randomized trial arm	Very low
	Risk of bias	Serious: no control arm and open-label investigator-assessed response in five of six studies; all six prespecified a sample size	
	Inconsistency	Serious: I^2: 66%, 95% prediction interval: 0.06–0.74	
	Indirectness	Not serious: populations, regimens and RECIST 1.1 assessment matches the review question, though response windows differ	
	Imprecision	Serious: 57 events in 181 patients, 95% CI: 0.31 (0.20–0.44)	
	Publication bias	Not assessable: only six studies were available; formal tests of funnel-plot asymmetry were not performed, and publication bias cannot be excluded	
Grade ≥3 adverse events	Starting certainty	Low: pooled single-arm proportion with no comparator, including one isolated randomized trial arm	
	Risk of bias	Serious: investigator attribution of relatedness, no control arm, open-label collection	
	Inconsistency	Serious: I^2: 78%, 95% prediction interval: 0.02–0.81	
	Indirectness	Serious: MoST-CIRCUIT reports immune-related AEs only; NRG-GY016 reports grade 3 with ambiguous attribution; MOCCA uses CTCAE v4.0	
	Imprecision	Serious: 45 events in 189 patients, 95% CI: 0.24 (0.12–0.40)	
	Publication bias	Not assessable: only six studies were available; formal tests of funnel-plot asymmetry were not performed, and publication bias cannot be excluded	

Notes: Certainty for a pooled single-arm proportion starts at low because the estimate is not comparative, and is rated down further for the domains marked serious. Numerical summaries come from the primary GLMM with HTS prediction intervals. Risk-of-bias judgements follow the MINORS domains reported in the manuscript and should be confirmed against the authors' own assessment.
Abbreviations: AE: Adverse event; CI: Confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; GLMM: Generalized linear mixed model; HTS: Higgins–Thompson–Spiegelhalter; MINORS: Methodological Index for Non-Randomized Studies; RECIST: Response Evaluation Criteria in Solid Tumors.

Table S9. Small-study effects assessment

Outcome	Studies	Assessment	Reason
Objective response rate	6	No formal funnel-asymmetry test	Fewer than 10 studies; low power. Funnel plots are descriptive only
Grade ≥3 adverse events	6	–	–

Notes: Neither Peters nor Egger regression is performed. Publication bias cannot be excluded. Descriptive funnel plots study logits against their standard errors. Methodological basis: Cochrane Handbook, chapter 13, recommendations on funnel-plot asymmetry tests.

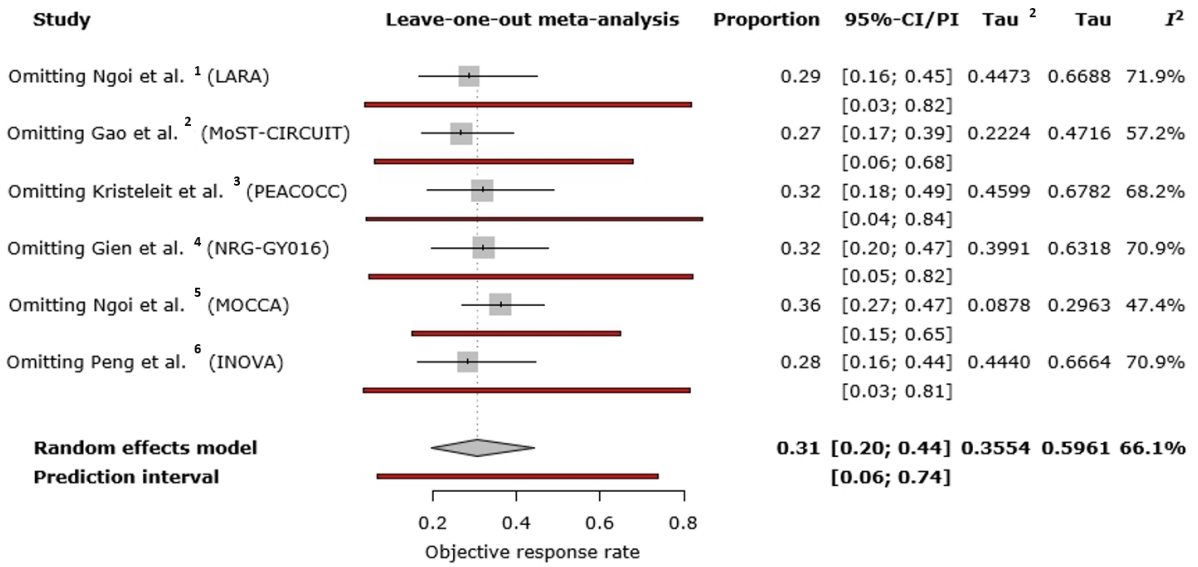

Figure S1. Leave-one-out analysis of objective response rate. Leave-one-out sensitivity analysis using the primary binomial random-intercept generalized linear mixed model.

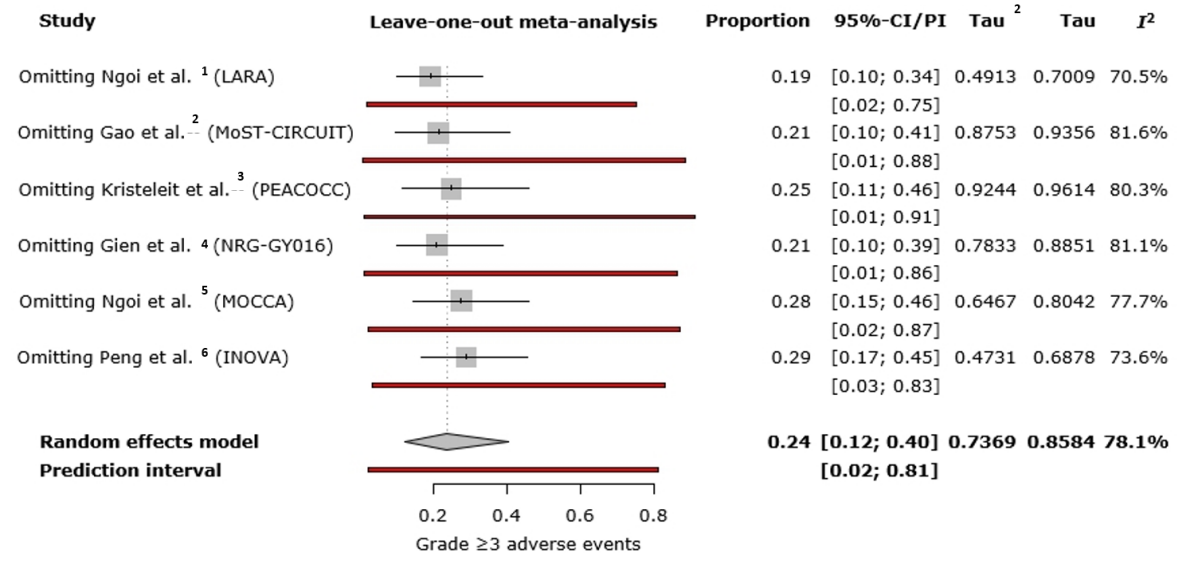

Figure S2. Leave-one-out analysis of grade ≥3 adverse events. Leave-one-out sensitivity analysis using the primary binomial random-intercept generalized linear mixed model.

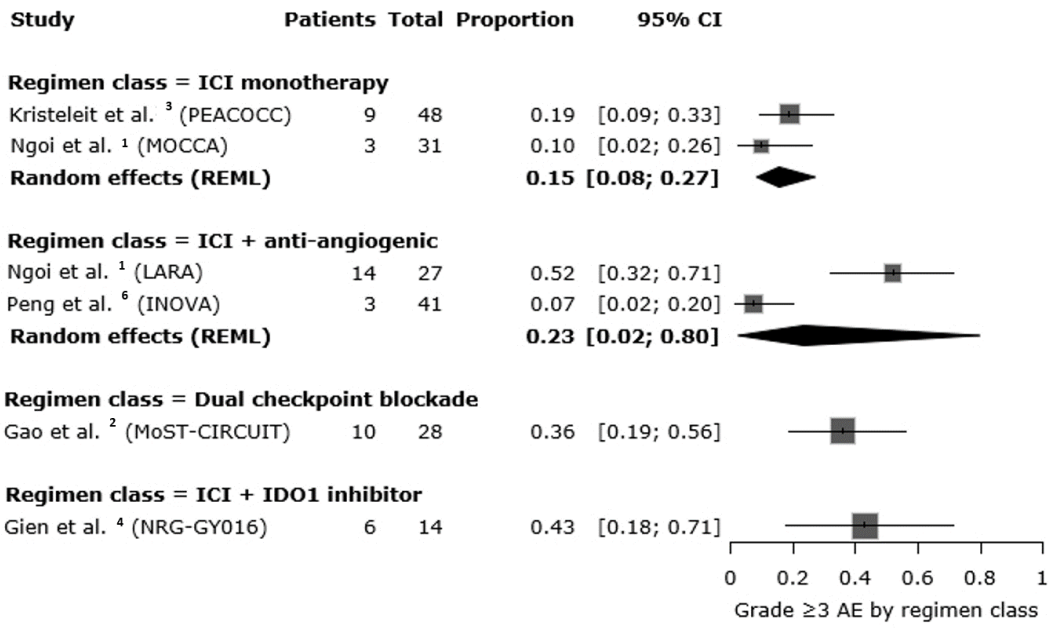

Figure S3. Exploratory grade ≥3 adverse events by regimen class. Regimen-class strata included two single-study groups; estimates are descriptive, and no between-class test was performed.

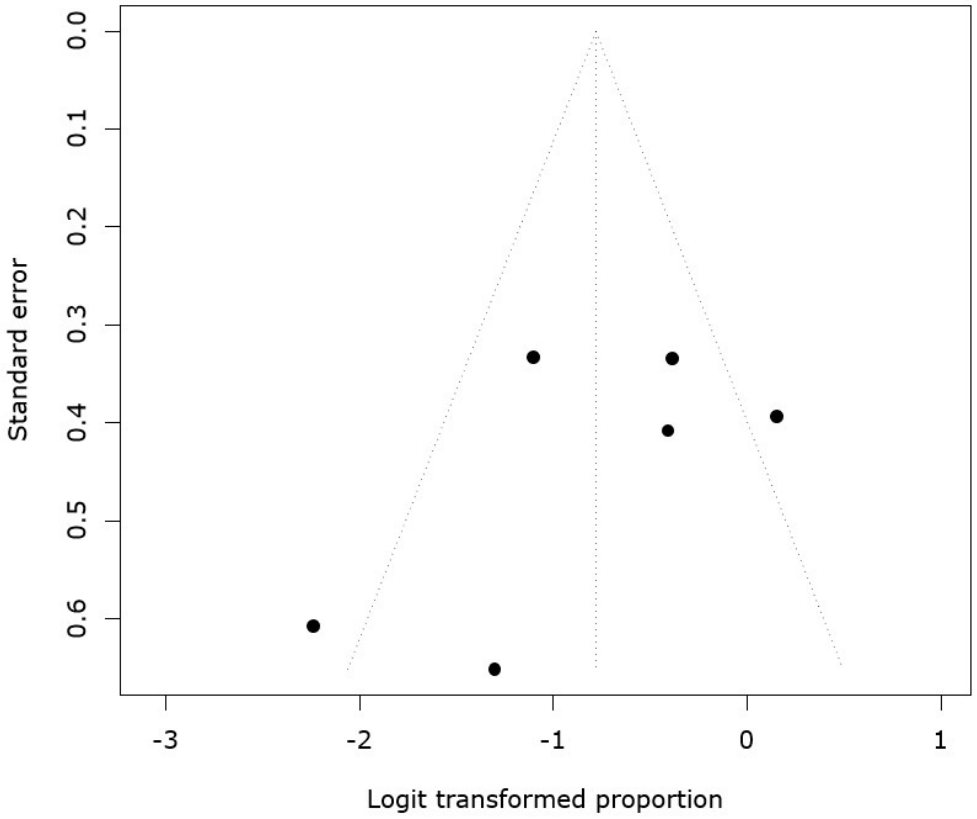

Figure S4. Descriptive funnel plot for objective response rate. Funnel plot shown descriptively only. Formal asymmetry testing was not performed because fewer than 10 studies were available.

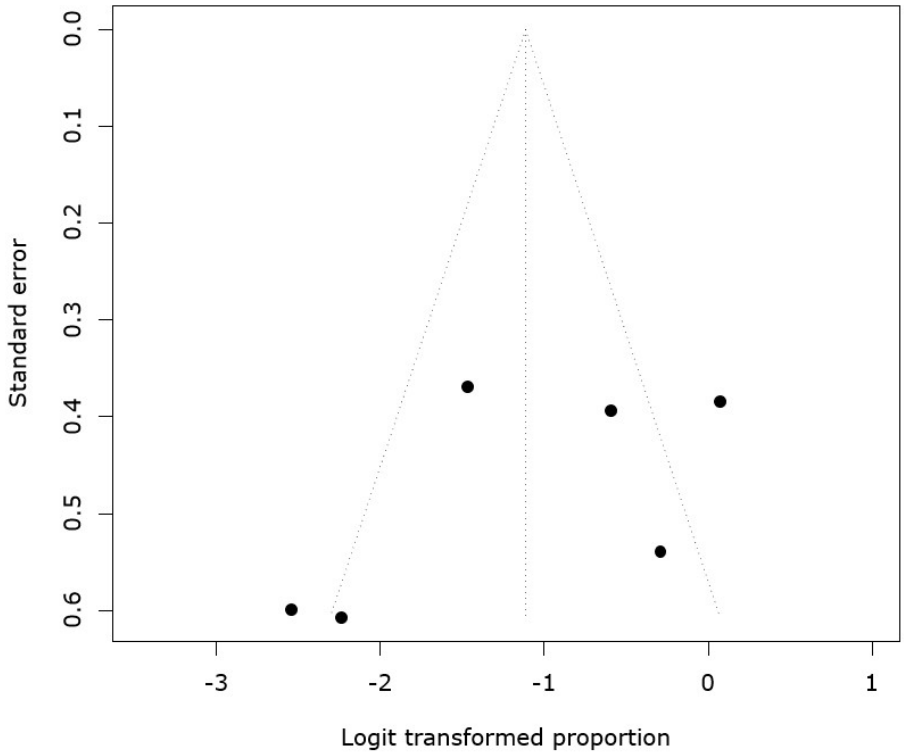

Figure S5. Descriptive funnel plot for grade ≥3 adverse events. Funnel plot shown descriptively only. Formal asymmetry testing was not performed because fewer than 10 studies were available.

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