Supplementary Online Content

Erickson AW, Brastianos PK, Das S. Assessment of effectiveness and safety of osimertinib for patients with intracranial metastatic disease: a systematic review and meta-analysis. *JAMA Netw Open*. 2020;3(3):e201617. doi:10.1001/jamanetworkopen.2020.1617

This supplementary material has been provided by the authors to give readers additional information about their work.

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eMethods. Supplementary Methods

Search and selection criteria

A literature search was conducted on September 20, 2019, using the following search query in MEDLINE and EMBASE databases: (osimertinib OR mereletinib OR tagrisso OR tamarix OR azd9291) AND (brain metastases OR intracranial metastatic disease OR cns). Only articles and abstracts published in English were considered, and all years considered from database inception to search date. Study authors were not contacted. Retrieved records were screened by abstract for reference to osimertinib as treatment for IMD. Case reports, case series, and reviews were excluded. Records reporting intracranial outcomes were included in the analysis.

Data extraction

The following outcomes were extracted from included studies: CNS objective response rate (ORR), CNS disease control rate (DCR), CNS progression-free survival (PFS), CNS duration of response (DoR), CNS time to response (TTR), best change in intracranial lesion size, complete response rate, overall survival (OS), follow-up length, and follow-up completeness. Data for each outcome were directly extracted according to the original authors' outcome definitions, and not modified following extraction. Where available, results were extracted from data from specified subgroups of patients whose CNS disease was evaluable for response (cEFR). Safety data were extracted for adverse events grade 3 or higher according to the Common Terminology Criteria for Adverse Events (CTCAE). Additionally, the following trial characteristics were extracted: author, year, number of patients, study phase, trial name, publication type, therapy line, and pharmaceutical industry funding.

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Statistical analysis

Meta-analyses of proportions were conducted to pool estimates for outcomes reported by more than five studies, which included CNS ORR and CNS DCR, reported effectively in ten and nine of the included fifteen studies, respectively. The random-effects model was used for weighted synthesis on the assumption that the included studies represented a sample of studies whose true effect sizes followed a normal distribution. This model was estimated using the restricted maximum likelihood method. Statistical tests included the Q-statistic for heterogeneity, τ^2 for between-study variance, and I^2 statistic developed by Higgins et al. as a "signal-to-noise ratio" to assess the percentage of observed variance attributable to variance between studies.[1,2] An I^2 value of 0% was interpreted to indicate all heterogeneity was due to sampling error, and 100% to indicate all variance was due to true differences between studies, with 0–50% as a benchmark for low heterogeneity and 50–100% for high heterogeneity. Initial synthesis of values for CNS ORR generated an I^2 value indicating high heterogeneity. This prompted leave-out-one and influence analyses to identify outlier studies, which were removed to produce the final model. Subgroup analyses were conducted to reveal sources of additional heterogeneity by stratifying studies based on trial characteristics as: retrospective vs. prospective; article vs. abstract; first vs. second vs. any line osimertinib therapy; and pharmaceutical industry funding yes vs. no vs. not reported. Funnel plots were generated to assess for publication bias and unweighted Egger's regression tests performed to assess funnel plot asymmetry. Additionally, a comparative meta-analysis was conducted to calculate risk ratios for CNS ORR and CNS DCR by aggregating results from the two RCTs.[3,4]

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All statistical analyses were conducted using the R programming language (v3.6.1; R Core Team, 2019) and the R packages *meta* (v4.9-6; Schwarzer, 2019) and *metafor* (v2.1-0; Viechtbauer, 2019).[5-7]

Assessment of study quality

Phase III trials were assessed using the Cochrane Risk of Bias Tool (RoB 2).[8] Phase II and retrospective trials were assessed using a modified version of the Newcastle-Ottawa scale for cohort studies.[9] To modify the scale, three questions were removed—two relating to selection and comparison of non-exposed patients and one question assessing presence of outcome at study start—and one question was added addressing presence of pharmaceutical industry funding. A "truly representative" exposed cohort was defined as a total group of patients who all have IMD and are receiving osimertinib. A "somewhat representative" exposed cohort was defined as a total group of patients where either 1) at least 50% had IMD but all were receiving osimertinib, or 2) all patients had IMD and at least 50% were receiving osimertinib. Adequate follow-up length was considered to be 6 months.

Ethical review of study

This study was not reviewed by any ethics review board as it did not contain live subjects, nor samples, nor individual-level patient data.

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eAppendix. List of included studies.

Devjak et al.[10]

Gadgeel et al.[11]

Goss et al.[12]

Iuchi et al.[13]

Kim et al.[14]

Mu et al.[15]

Park et al.[16]

Peled et al.[17]

Reungwetwattana et al.[4]

Sonoda et al.[18]

Wu et al.[3]

Xie et al.[19]

Xing, L et al.[20]

Xing, P et al.[21]

Zhou et al.[22]

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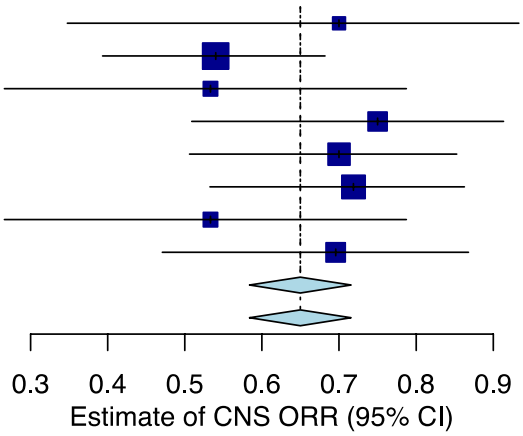
eFigure 1. Forest plot of CNS objective response rate (ORR) following outlier removal.

Two studies were removed from the forest plot in Figure 2 due to severe heterogeneity indicated by the I^2 value to produce this secondary analysis: Xie et al.[19] and Reungwetwattana et al.[4]

Study	Cases	Total	CNS ORR	95% CI
Devjak 2018	7	10	0.70	[0.35; 0.93]
Goss 2018	27	50	0.54	[0.39; 0.68]
Mu 2017	8	15	0.53	[0.27; 0.79]
Peled 2018	15	20	0.75	[0.51; 0.91]
Wu 2018	21	30	0.70	[0.51; 0.85]
Xing, L 2018	23	32	0.72	[0.53; 0.86]
Xing, P 2019	8	15	0.53	[0.27; 0.79]
Zhou 2017	16	23	0.70	[0.47; 0.87]
Total (fixed effect)		195	0.65	[0.58; 0.72]
Total (random effects)			0.65	[0.58; 0.72]

Heterogeneity: $\chi^2_7 = 6.59$ ($P = .47$), $I^2 = 0\%$



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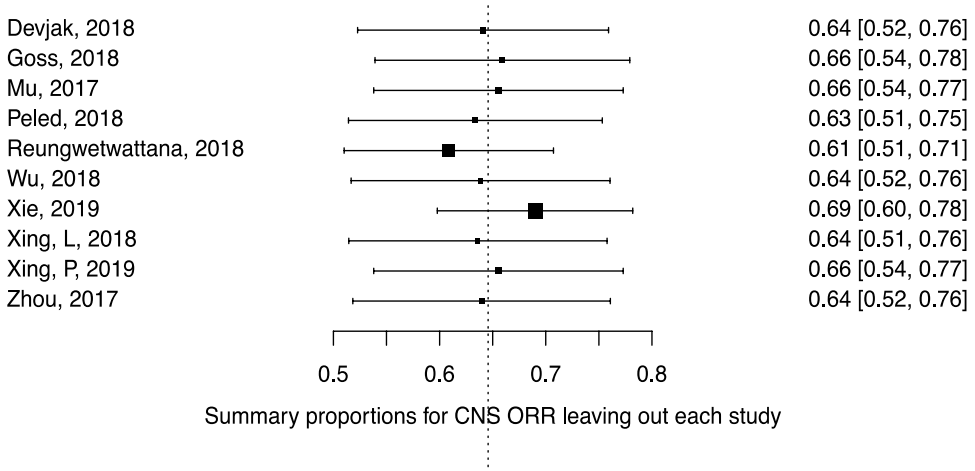
eFigure 2. Leave-out-one sensitivity analysis for identifying outlier studies for CNS objective response rate (ORR). A leave-one-out sensitivity analysis calculated summary effect sizes aggregating CNS ORR values from all studies minus one to assess the degree of heterogeneity introduced by any given study. Reungwetwattana et al.[4] and Xie et al.[19] were identified as potential outliers.



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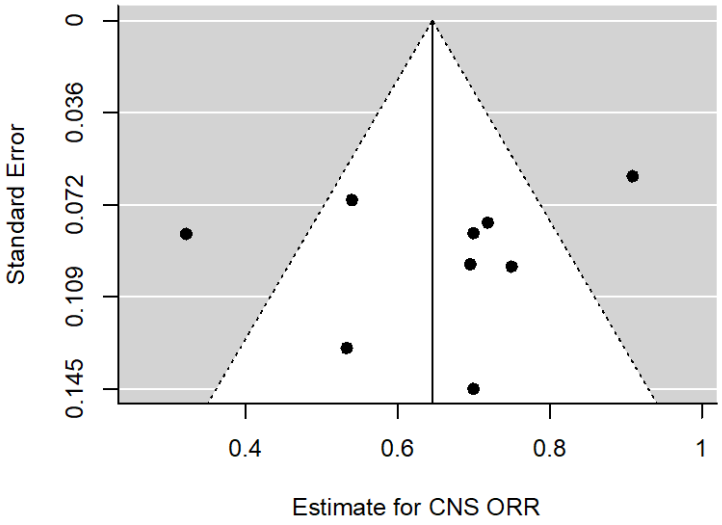
eFigure 3. Funnel plot for publication bias in CNS objective response rate (ORR).

Publication bias was not detected on visual inspection of the funnel plot, nor on unweighted Egger's regression test (z = -0.68, p = 0.49).



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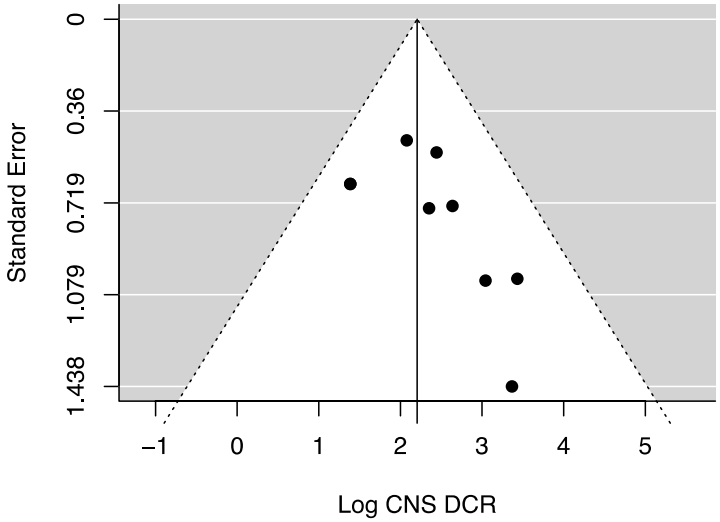
eFigure 4. Funnel plot for publication bias in CNS disease control rate (DCR). Publication bias was not detected on visual inspection of the funnel plot, nor on unweighted Egger's regression test (and z = 1.43, p = 0.15).



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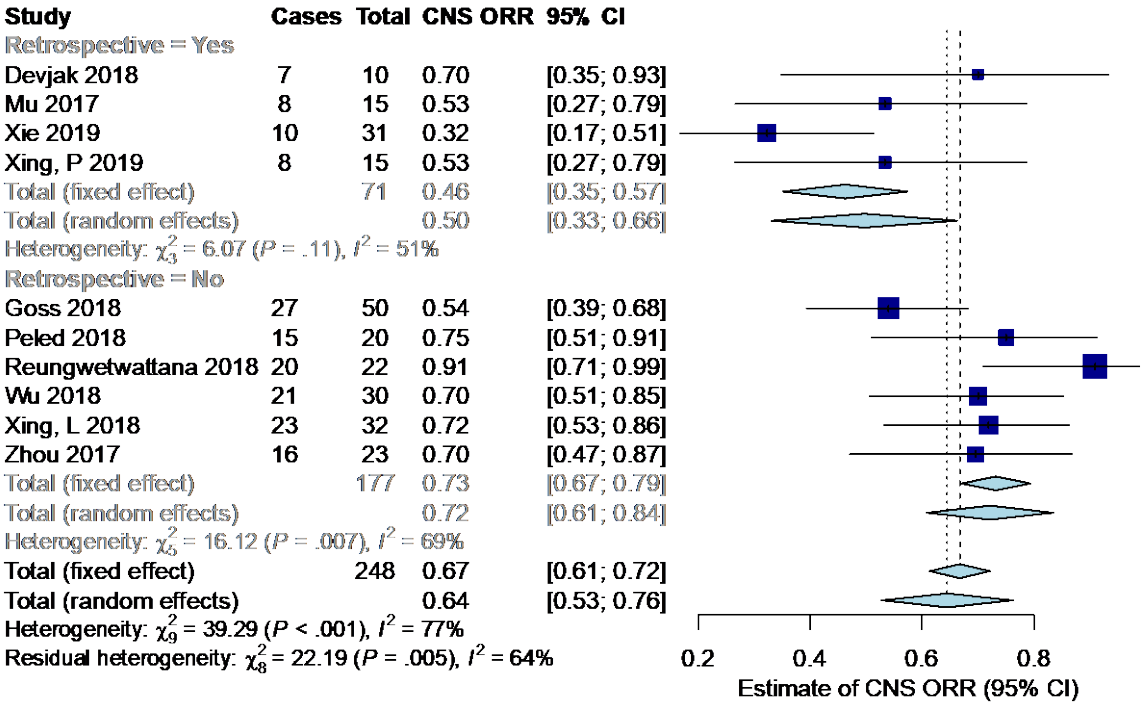
eFigure 5. Forest plot of reported CNS ORR, stratified by retrospective versus prospective studies.



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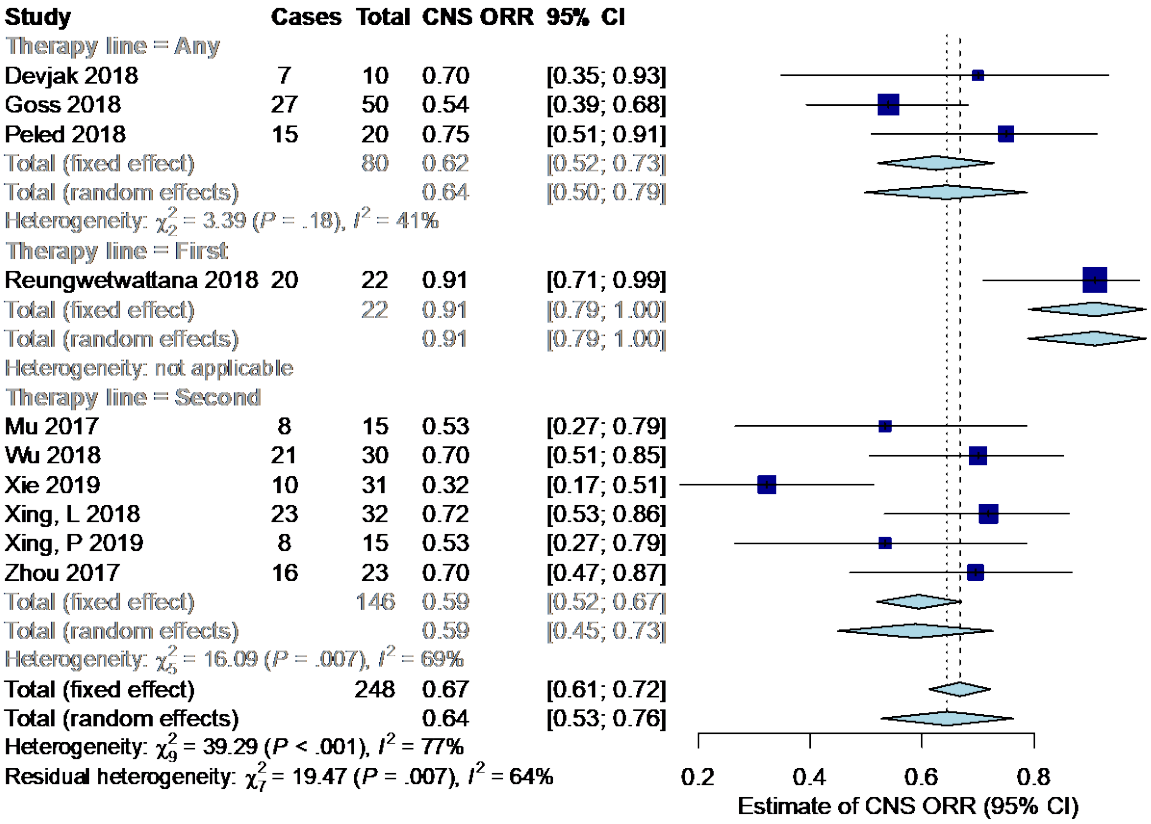
eFigure 6. Forest plot of reported CNS ORR, stratified by line of therapy.



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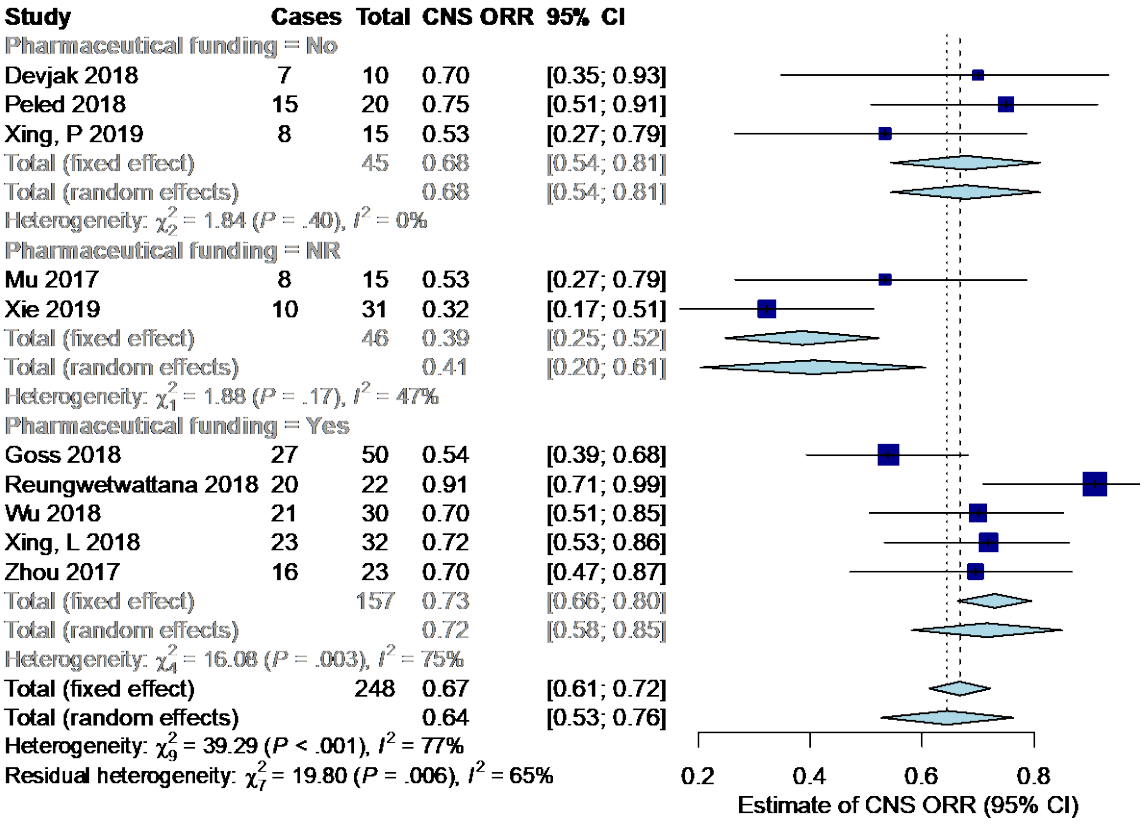
eFigure 7. Forest plot of reported CNS ORR, stratified by pharmaceutical industry funding.



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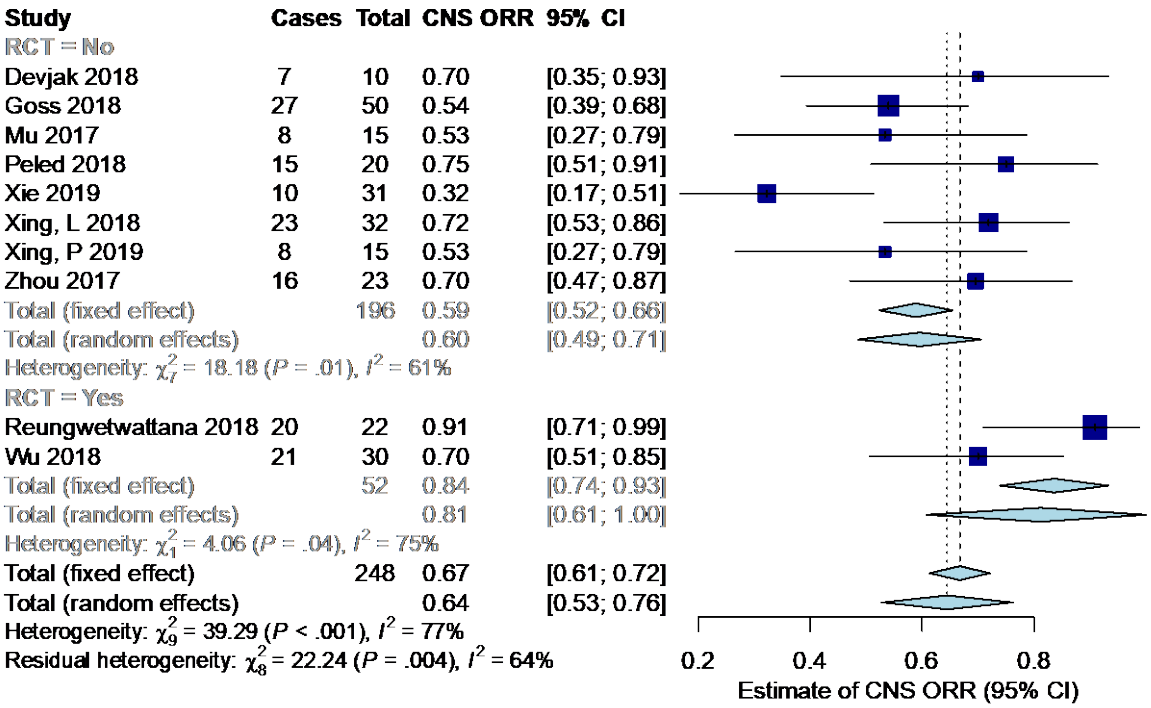
eFigure 8. Forest plot of reported CNS ORR, stratified by randomized controlled trials versus other study types.



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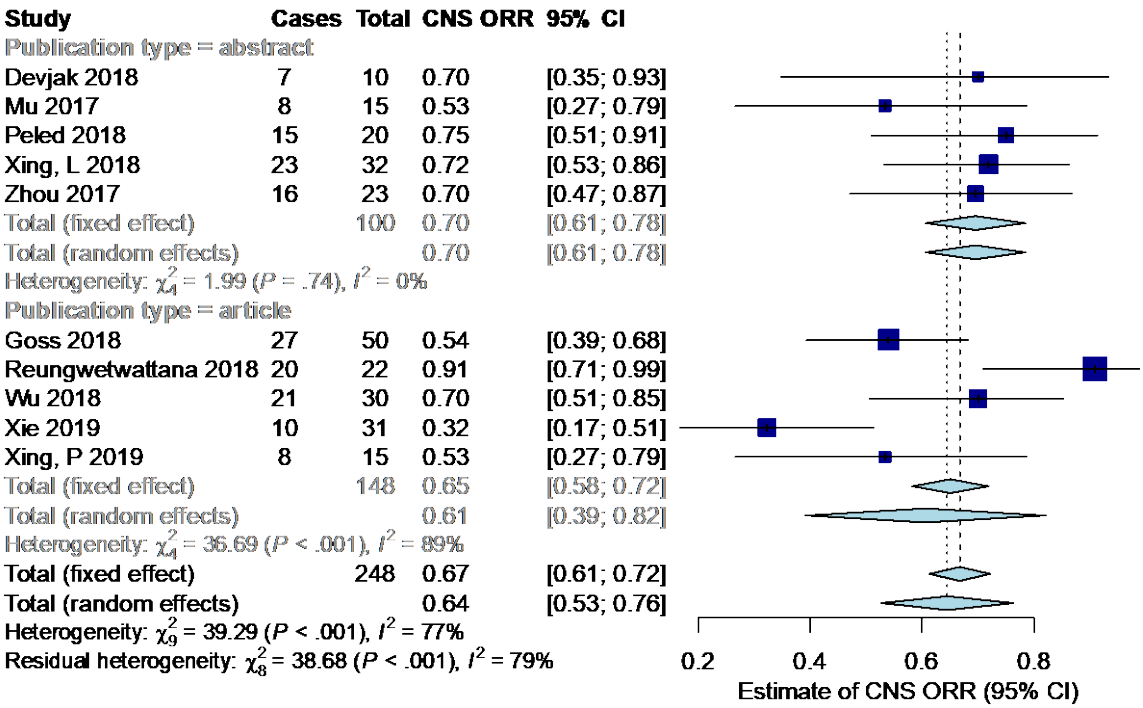
eFigure 9. Forest plot of reported CNS ORR, stratified by abstract versus article.



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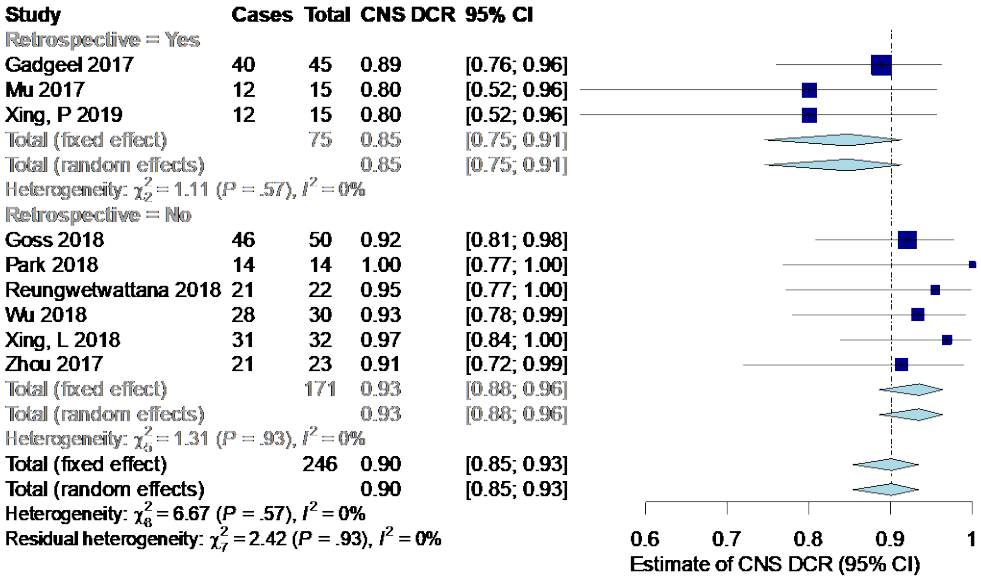
eFigure 10. Forest plot of reported CNS DCR, stratified by retrospective versus prospective.



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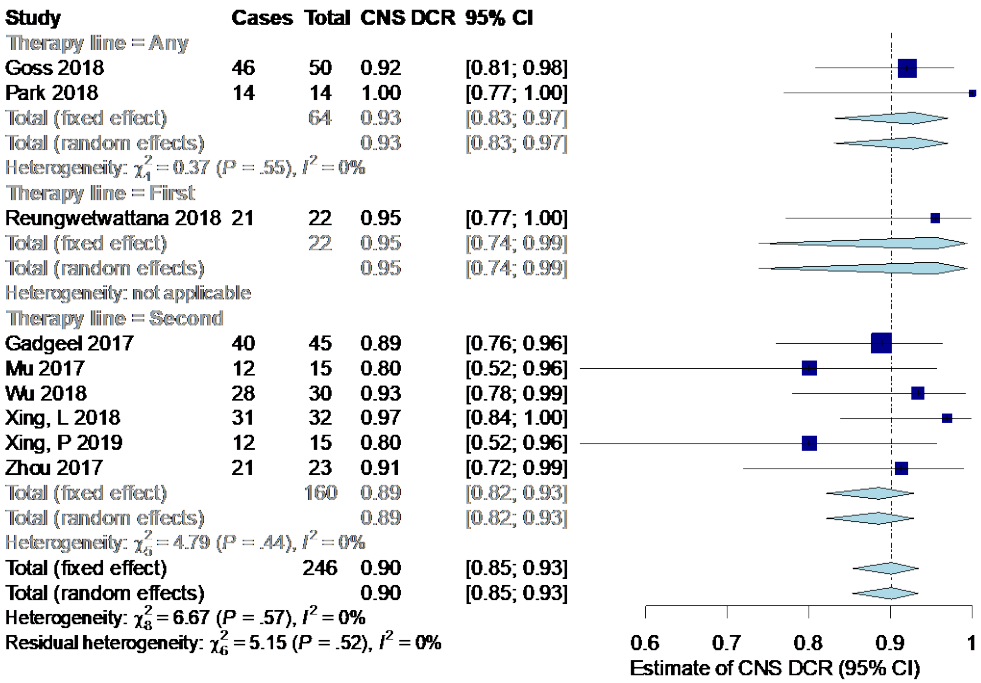
eFigure 11. Forest plot of reported CNS DCR, stratified by line of therapy.



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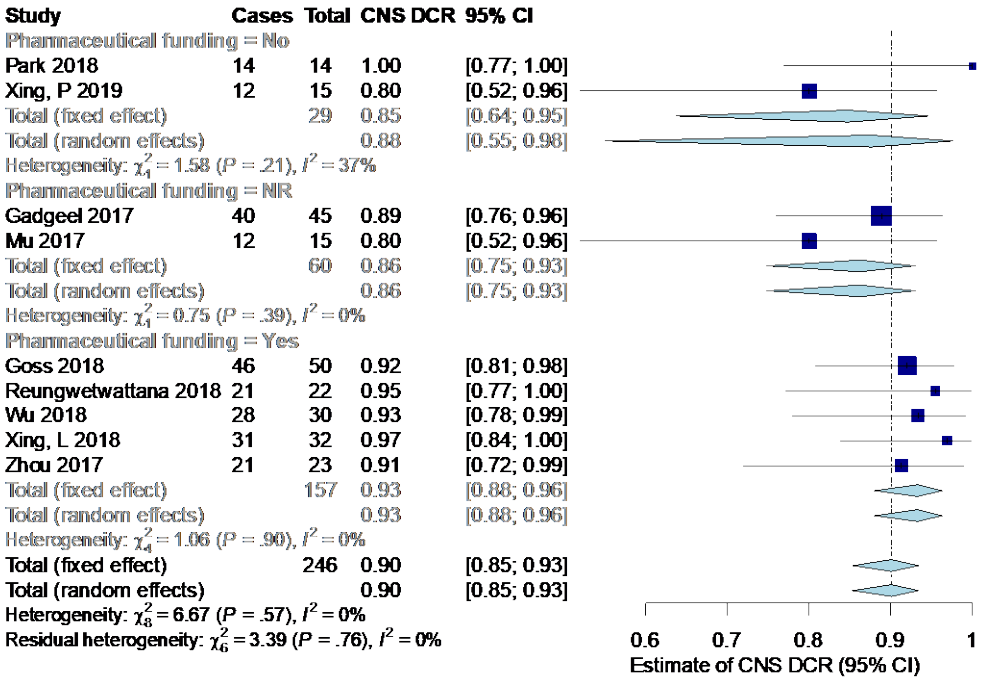
eFigure 12. Forest plot of reported CNS DCR, stratified by pharmaceutical industry funding.



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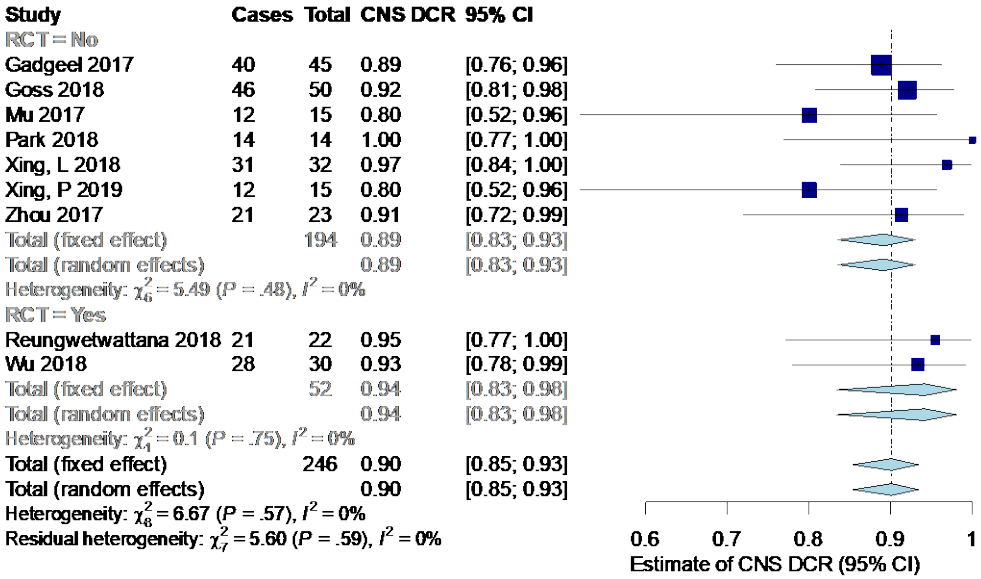
eFigure 13. Forest plot of reported CNS DCR, stratified by randomized controlled trials versus other study types.



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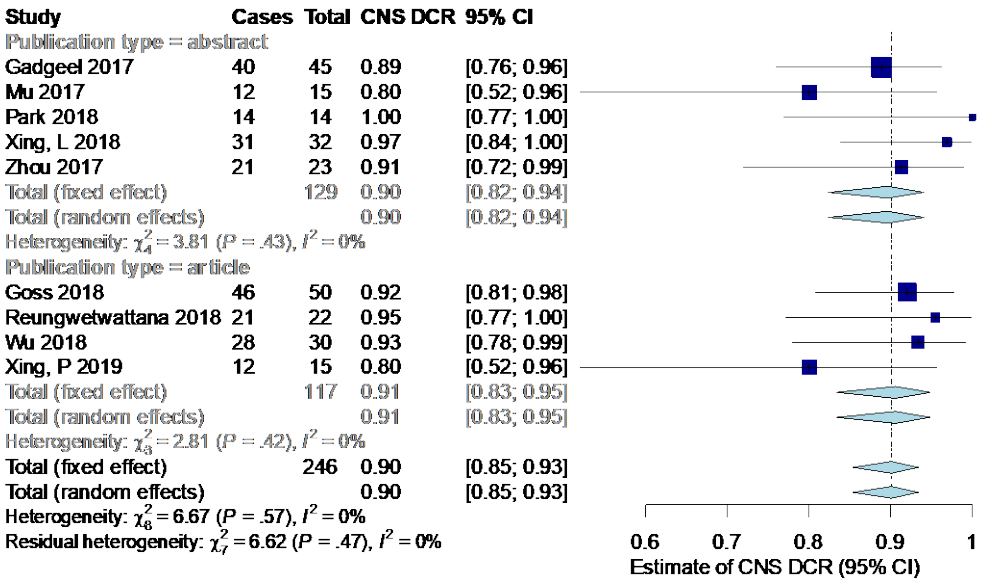
eFigure 14. Forest plot of reported CNS DCR, stratified by abstract versus article.



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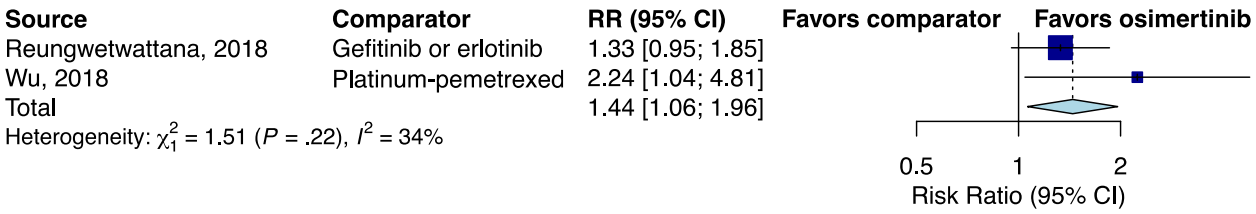
eFigure 15. Forest plot of risk ratio for CNS ORR among included randomized controlled trials.



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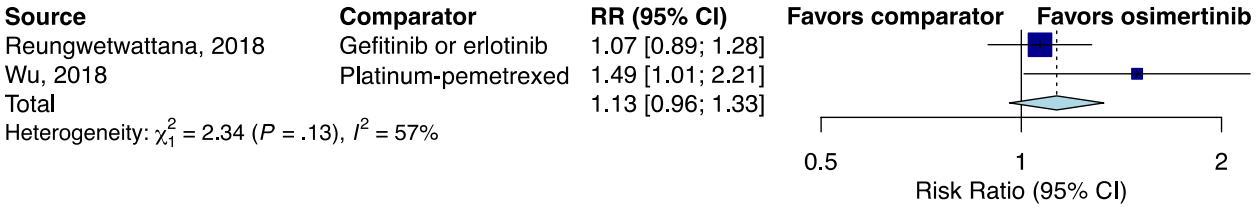
eFigure 16. Forest plot of risk ratio for CNS DCR among included randomized controlled trials.



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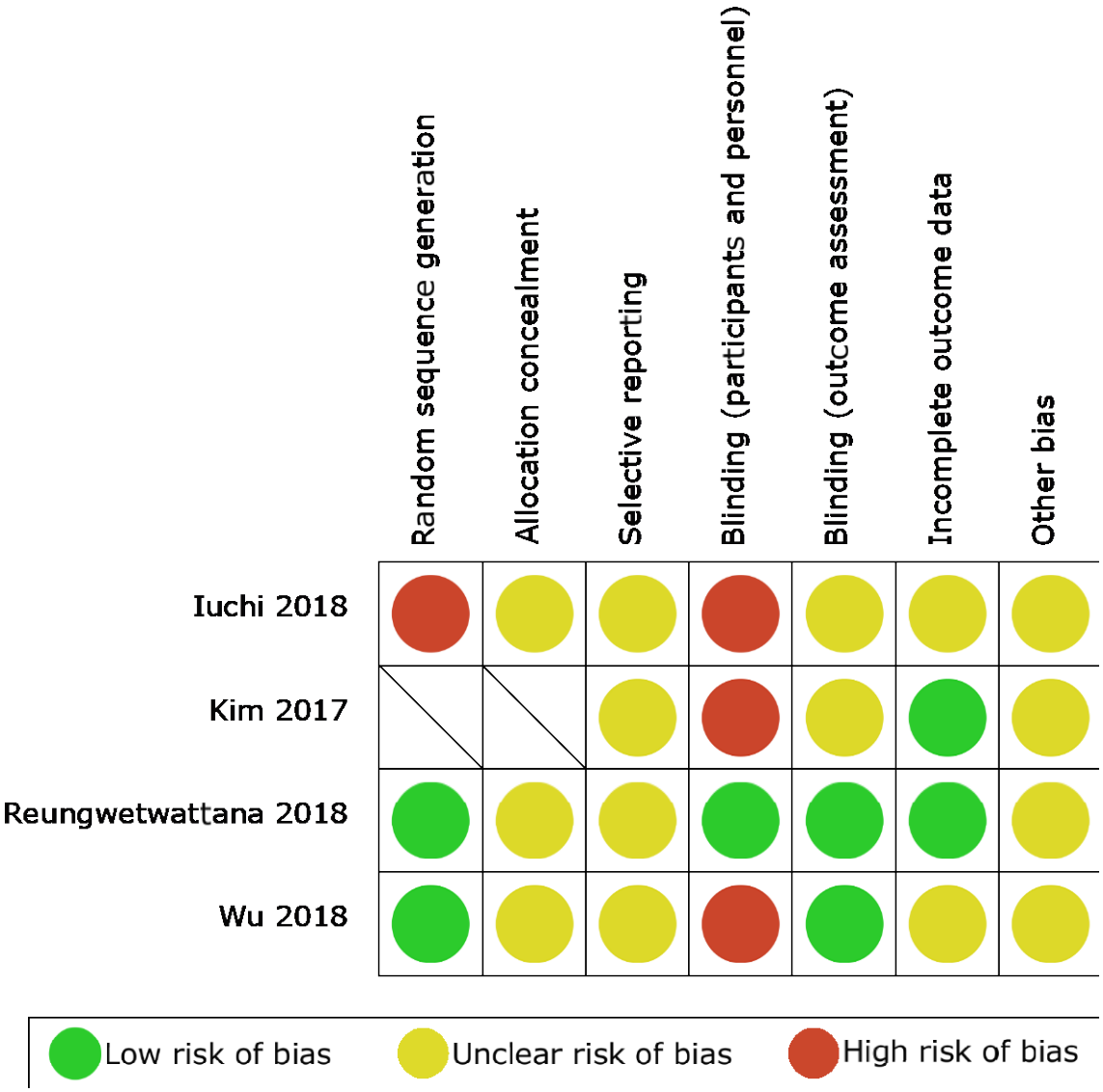
eFigure 17. Cochrane risk of bias tool assessment of phase III studies. All four studies identified as phase III were assessed using the Cochrane RoB 2 tool. Two phase III studies did not include comparator groups and were not eligible for assessment of bias in randomization or allocation concealment.



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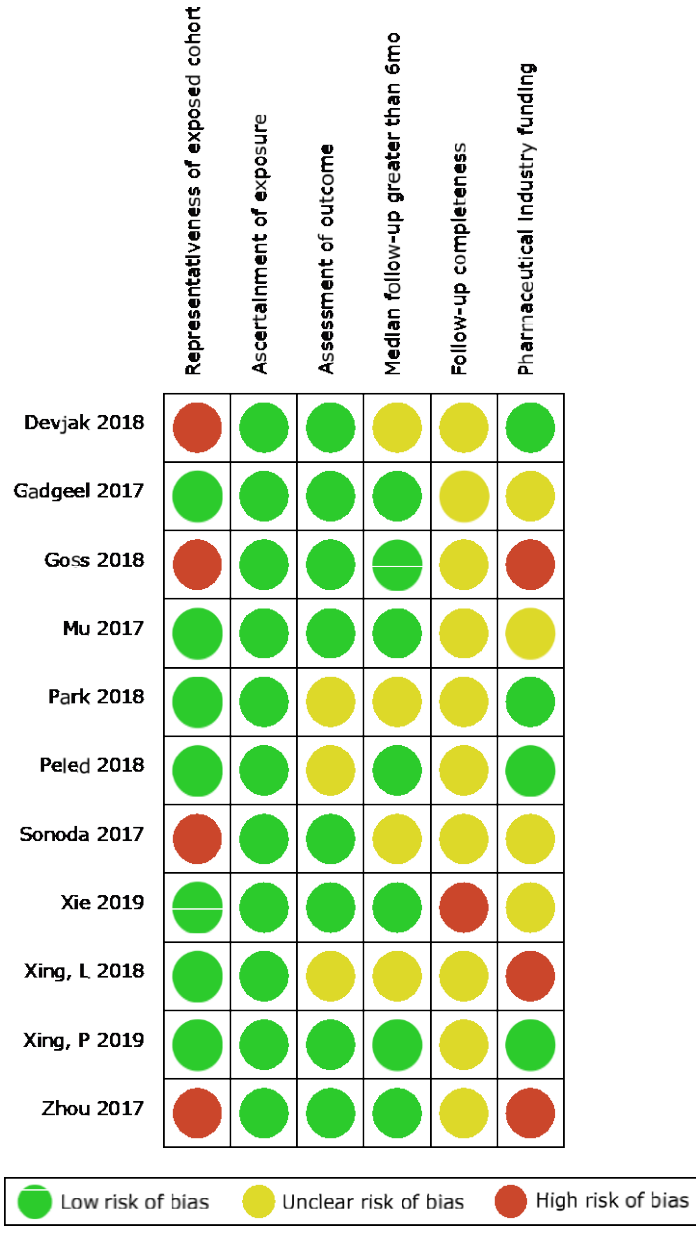
eFigure 18. Modified Newcastle-Ottawa scale assessment of phase II and retrospective studies. The Newcastle-Ottawa scale for cohort studies was modified with the subtraction of three questions—two relating to selection and comparison of non-exposed patients and one assessing presence of outcome at study start—and the addition of one question addressing presence of pharmaceutical industry funding.



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