Supplementary

Appendix 1 Search strategy

PubMed

1. “Programmed Cell Death 1 Receptor”[Mesh] OR “CTLA-4 Antigen”[Mesh]
2. “anti-PD-1”[Title/Abstract] OR “PD-1”[Title/Abstract] OR “anti-PD-L1”[Title/Abstract] OR “PD-L1”[Title/Abstract] OR “anti-PD(L)-1”[Title/Abstract] OR “PD(L)-1”[Title/Abstract] OR “CTLA-4”[Title/Abstract] OR “anti-CTLA-#4”[Title/Abstract] OR ” anti-cytotoxic T-lymphocyte antigen-4”[Title/Abstract]
3. “nivolumab” [Title/Abstract] OR “Opdivo”[Title/Abstract] OR “ONO-4538”[Title/Abstract] OR “MDX-1106” [Title/Abstract] OR “BMS-936558”[Title/Abstract] OR “pembrolizumab”[Title/Abstract] OR “lambrolizumab”[Title/Abstract] OR “keytruda”[Title/Abstract] OR “MK-3475”[Title/Abstract] OR “atezolizumab”[Title/Abstract] OR “Tecentriq”[Title/Abstract] OR “RG7446”[Title/Abstract] OR “MPDL3280A”[Title/Abstract] OR “durvalumab”[Title/Abstract] OR “Imfinzi”[Title/Abstract] OR “MEDI-4736”[Title/Abstract] OR “MEDI4736”[Title/Abstract] OR “avelumab”[Title/Abstract] OR “MSB0010718C”[Title/Abstract] OR “Bavencio”[Title/Abstract] OR “cemiplimab”[Title/Abstract] OR “REGN2810”[Title/Abstract] OR “ipilimumab”[Title/Abstract] OR “Yervoy”[Title/Abstract] OR "MDX 010"[Title/Abstract] OR “MDX010”[Title/Abstract] OR “MDX-010”[Title/Abstract] OR “MDX-CTLA-4”[Title/Abstract] OR “MDX CTLA 4”[Title/Abstract] OR” tremelimumab”[Title/Abstract] OR “ticilimumab”[Title/Abstract] OR “CP 675”[Title/Abstract] OR “CP675 cpd”[Title/Abstract] OR “CP-675”[Title/Abstract] OR “CP-675206”[Title/Abstract] OR “CP675206”[Title/Abstract] OR “CP 675206”[Title/Abstract]
4. “immune checkpoint inhibitor”[Title/Abstract] OR “immune checkpoint inhibitors”[Title/Abstract] OR “ICI”[Title/Abstract] OR “immune checkpoint blockade”[Title/Abstract] OR “ICB”[Title/Abstract]
5. “immune related adverse events” [Title/Abstract] OR “toxic*.mp.” [Title/Abstract] OR “adverse event” [Title/Abstract]
6. #1 OR #2 OR #3 OR #4 and #5
7. “Lung Neoplasms” [Mesh]
8. “Lung Cancer” [All Fields] OR “Cancer, Lung” [All Fields] OR “Cancers, Lung” [All Fields] OR “Lung Cancers” [All Fields]
9. “Pulmonary Neoplasms” [All Fields] OR “Neoplasms, Lung” [All Fields] OR “Lung Neoplasm” [All Fields] OR “Neoplasm, Lung” [All Fields] OR “Neoplasms, Pulmonary” [All Fields] OR “Neoplasm, Pulmonary” [All Fields] OR “Pulmonary Neoplasm” [All Fields]
10. “Pulmonary Cancer” [All Fields] OR “Cancer, Pulmonary” [All Fields] OR “Cancers, Pulmonary” [All Fields] OR “Pulmonary Cancers” [All Fields] OR “Cancer of the Lung” [All Fields] OR “Cancer of lung” [All Fields]
11. #7 OR #8 OR #9 OR #10
12. #6 AND #11

Embase

1. 'anti ctla 4':ab,ti OR 'cytotoxic t-lymphocyte associated antigen-4':ab,ti OR 'anti pd 1':ab,ti OR 'programmed cell death protein':ab,ti OR 'anti pd l1':ab,ti OR 'programmed cell death protein-1':ab,ti OR 'programmed cell death-ligand 1':ab,ti
2. nivolumab:ab,ti OR pembrolizumab:ab,ti OR lambrolizumab:ab,ti OR atezolizumab:ab,ti OR durvalumab:ab,ti OR avelumab:ab,ti OR cemiplimab:ab,ti OR ipilimumab:ab,ti OR tremelimumab:ab,ti OR ticilimumab:ab,ti
3. 'immune checkpoint inhibitor':ab,ti OR 'immune checkpoint blockade':ab,ti OR ici:ab,ti OR icb:ab,ti
4. 'immune related adverse events':ab,ti OR toxicity:ab,ti
5. 'cancer of lung' OR 'cancer of the lung' OR 'pulmonary cancers' OR 'pulmonary cancer' OR 'lung cancer' OR 'lung cancers' OR 'pulmonary neoplasm' OR 'lung neoplasm' OR 'pulmonary neoplasms' OR 'iung cancer'
6. #1 OR #2 OR #3
7. #4 AND #5 AND #6

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Cochrane

1. (anti-CTLA-4):ti,ab,kw OR (cytotoxic T-lymphocyte associated antigen-4):ti,ab,kw OR (anti-PD-1):ti,ab,kw OR (programmed cell death protein):ti,ab,kw OR (anti-PD-L1):ti,ab,kw
2. (programmed cell death protein-1):ti,ab,kw OR (programmed cell death-Ligand 1):ti,ab,kw OR (nivolumab):ti,ab,kw OR (pembrolizumab):ti,ab,kw OR (lambrolizumab):ti,ab,kw
3. (atezolizumab):ti,ab,kw OR (durvalumab):ti,ab,kw OR (avelumab):ti,ab,kw OR (cemiplimab):ti,ab,kw OR (ipilimumab):ti,ab,kw
4. (tremelimumab):ti,ab,kw OR (ticilimumab):ti,ab,kw OR (immune checkpoint blockade):ti,ab,kw OR (ICI):ti,ab,kw OR (ICB):ti,ab,kw
5. MeSH descriptor: [Immune Checkpoint Inhibitors] explode all trees
6. (immune related adverse events):ti,ab,kw OR (toxicity):ti,ab,kw
7. (Lung of pulimon) OR (cancer of lung) OR (cancer of the lung) AND (pulmonary cancer) AND (lung cancer)
8. MeSH descriptor: [Lung Neoplasms] explode all trees
9. (pulmonary neoplasm) OR (lung neoplasm)
10. (#1 OR #2 OR #3 OR #4 OR #5) AND #6 AND (#7 OR #8 OR #9)

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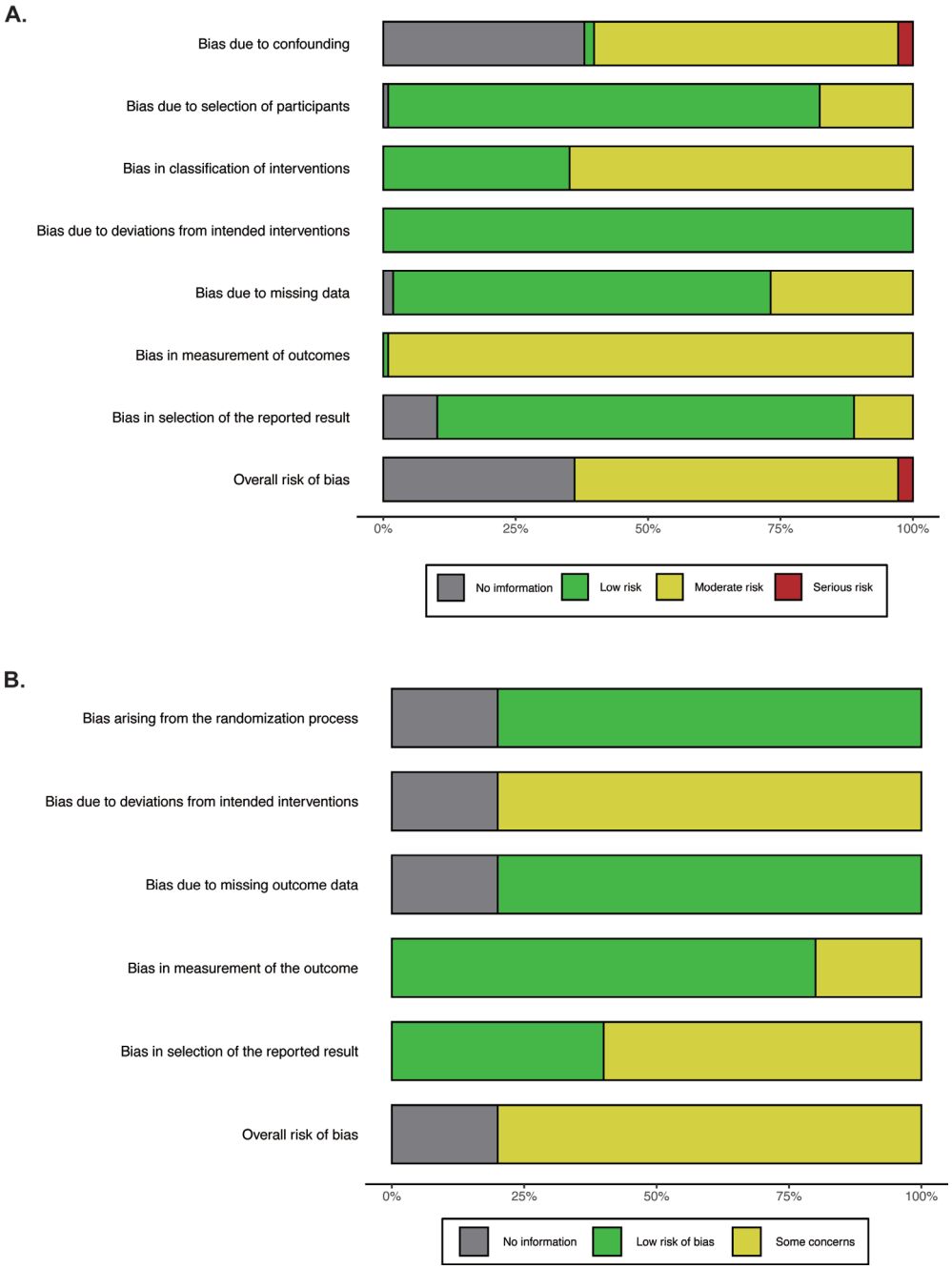

Figure S1 Summary graph presenting the quality assessment results of eligible studies. (A) Distribution of the risk of bias for each criterion according to ROBINS-I, for nonrandomized studies. (B) Distribution of the risk of bias for each criterion according to RoB2, for randomized trials.

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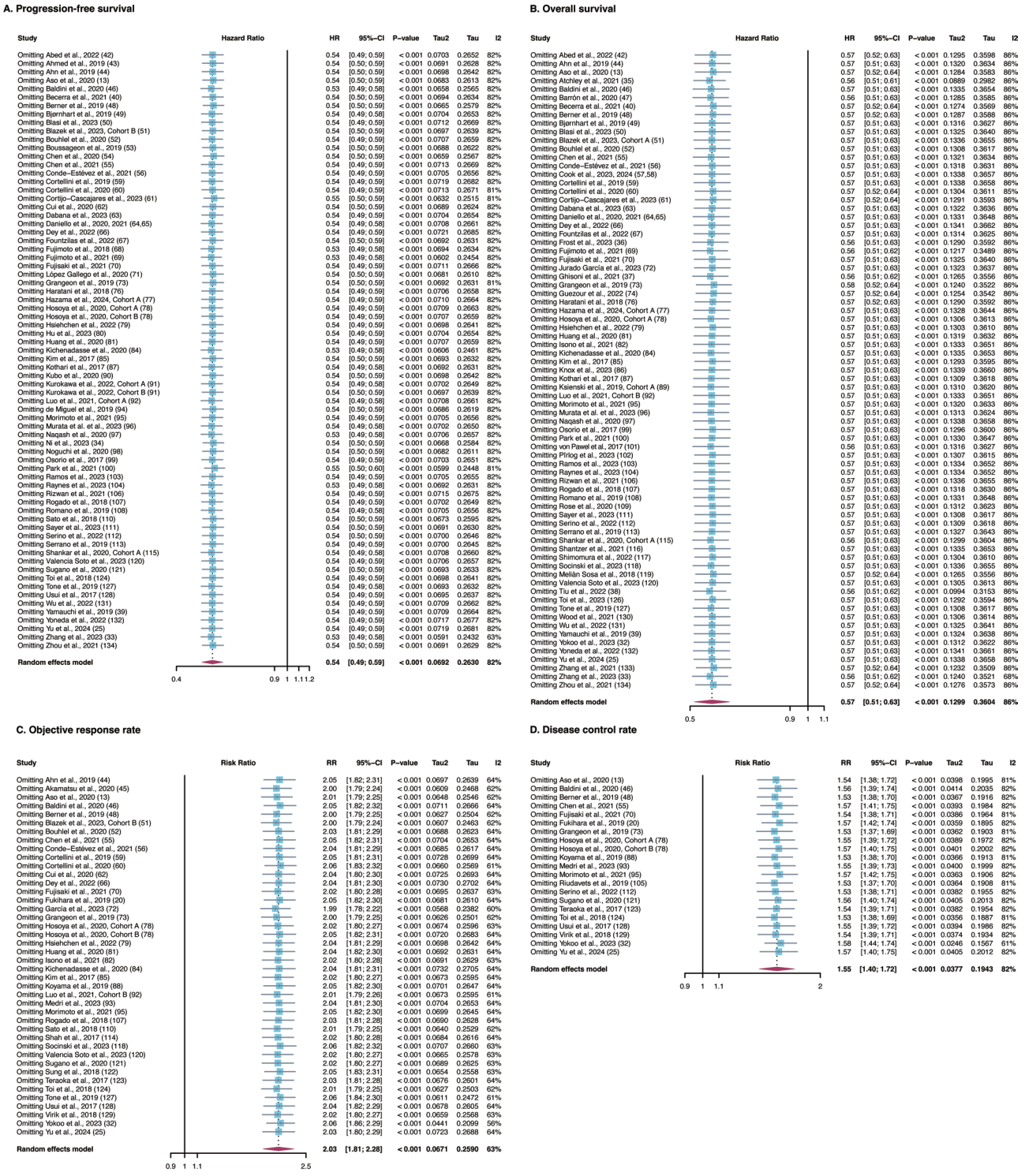

Figure S2 Sensitivity analyses performed by leave-one out method. (A) Progression-free survival. (B) Overall survival. (C) Objective response rate. (D) Disease control rate. CI, confidence interval.

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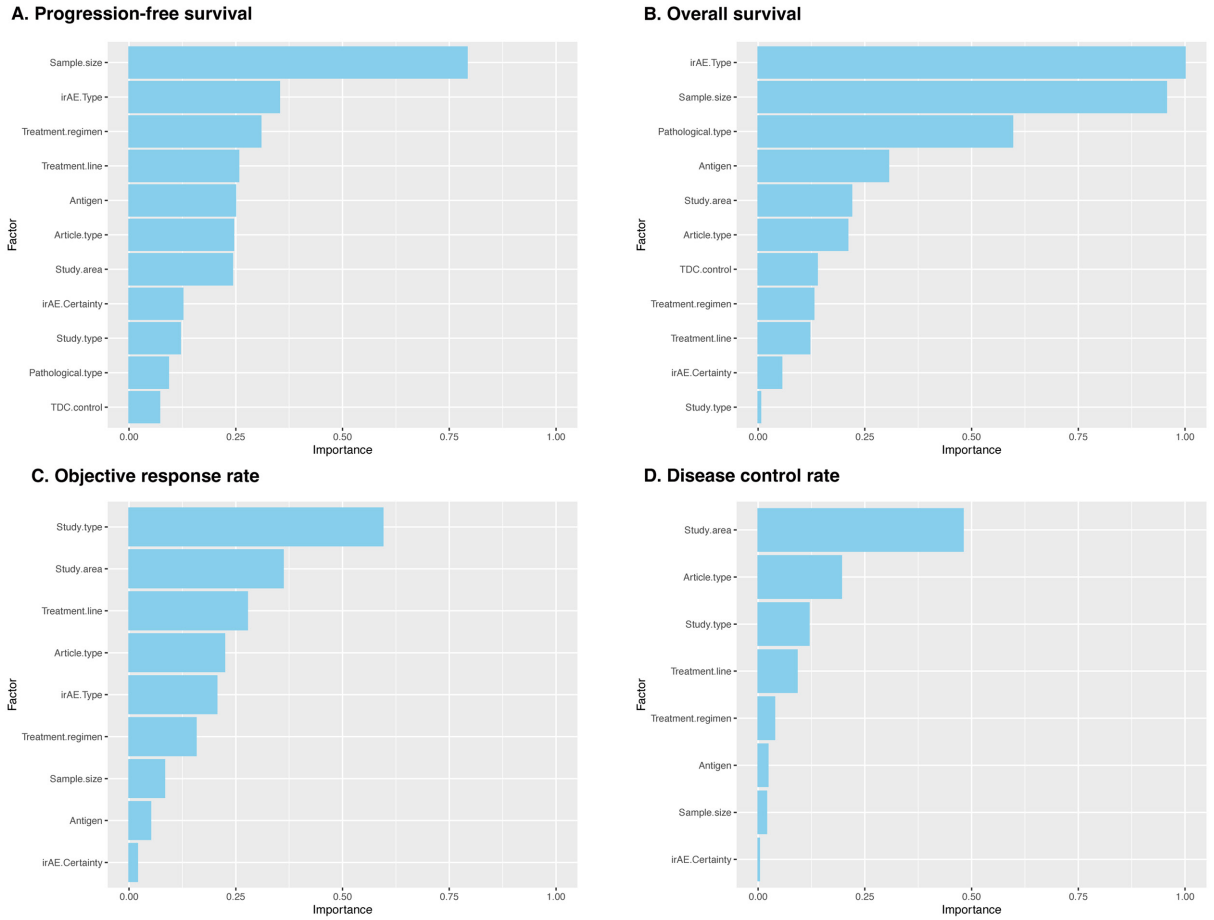

Figure S3 Model-averaged predictor importance plots visualizing the identified factors account for between-study heterogeneity from a multiple meta-regression process called multi-model inference. (A) Progression-free survival. (B) Overall survival. (C) Objective response rate. (D) Disease control rate. IrAE, immune-related adverse event; TDC, time-dependent confounding.

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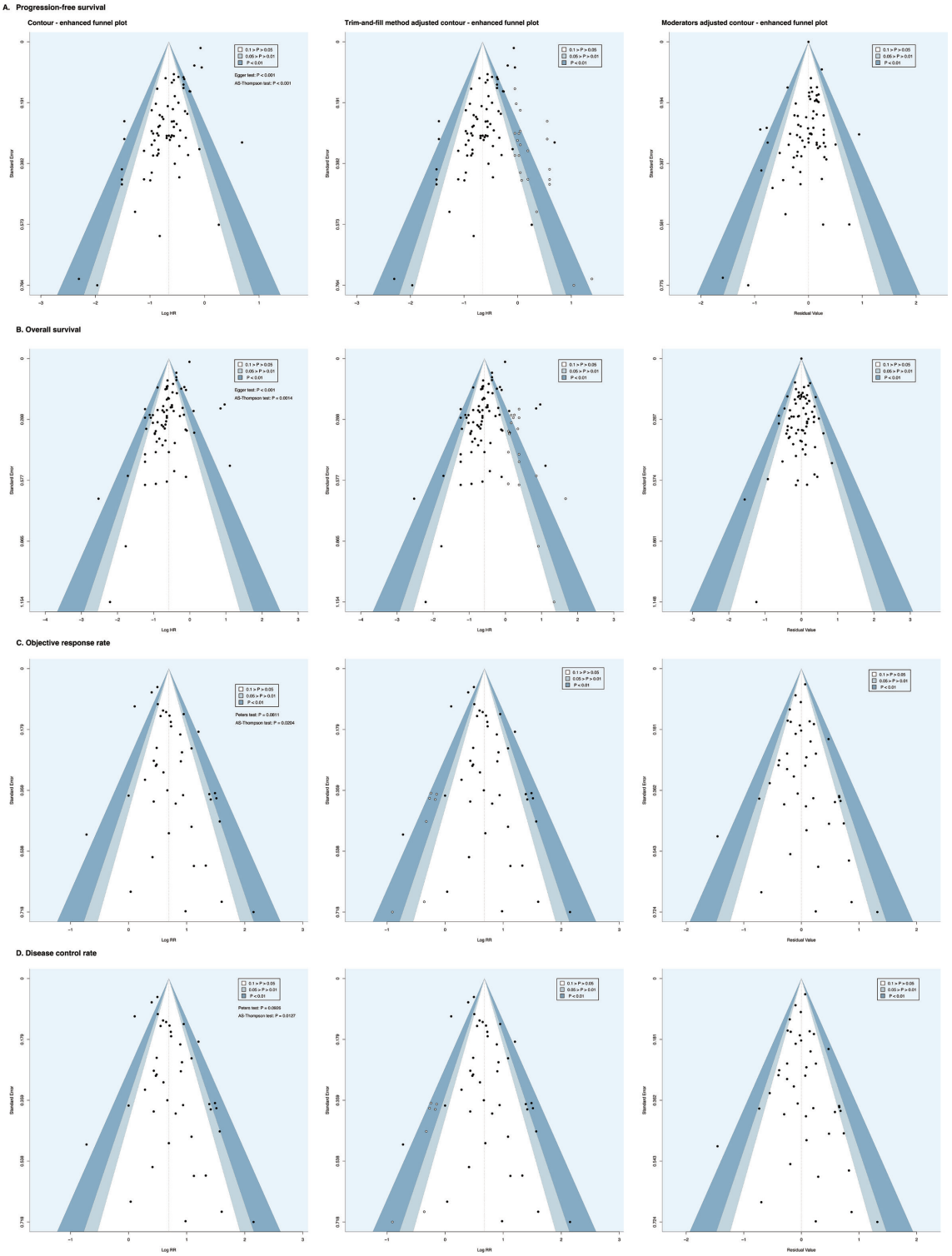

Figure S4 Contour-enhanced funnel plots plus symmetry test results presenting the possibility of publication bias. Trim-and-fill method adjusted contour-enhanced funnel plots demonstrating only few studies were missing in the white area (statistically non-significant area, 0.1>P>0.05). Enhanced symmetry was observed after moderating the contour-enhanced funnel plots with heterogeneity factors. (A) Progression-free survival. (B) Overall survival. (C) Objective response rate. (D) Disease control rate.

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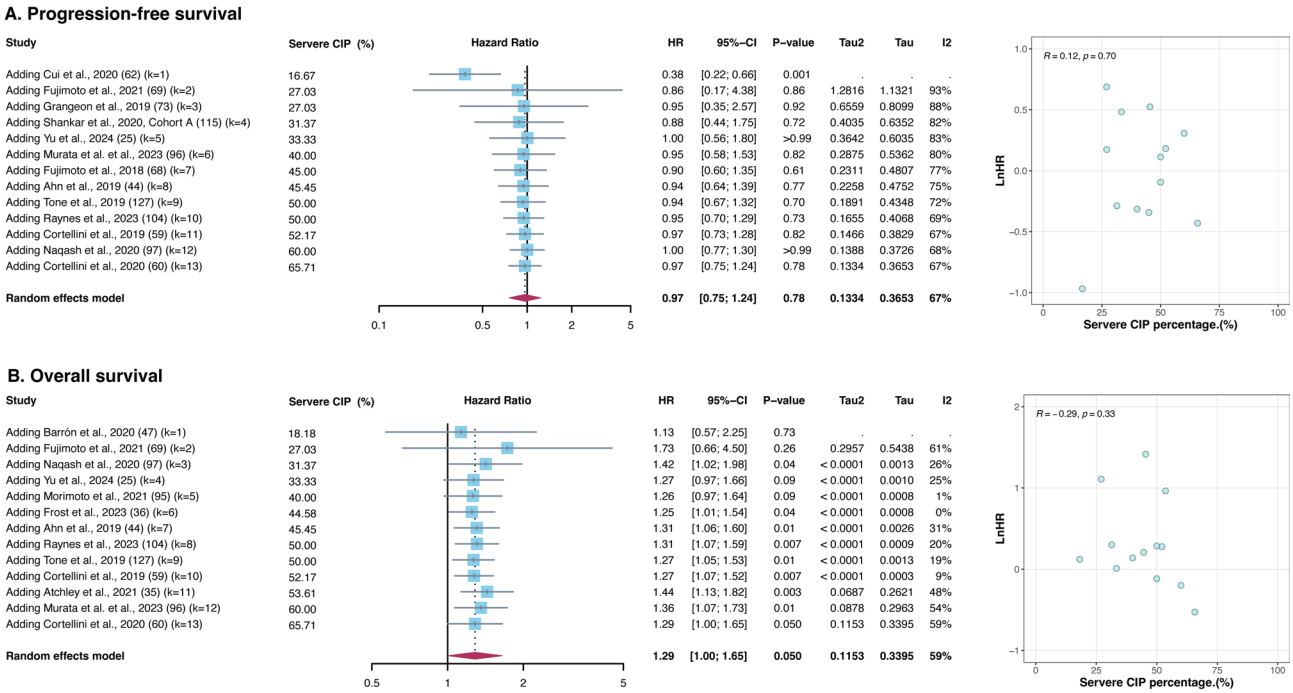

Figure S5 Cumulative meta-analyses performed by sequentially adding studies according to the proportion of patients with severe (grade ≥3) pulmonary irAEs plus dot plots demonstrating the correlation between severe pulmonary irAEs proportion and effect size (lnHR) based on pulmonary irAEs status. (A) Progression-free survival. (B) Overall survival. CIP, checkpoint inhibitor pneumonitis; HR, hazard ratio; CI, confidence interval; irAE, immune-related adverse event.

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