Supplementary

Table S1 Literature search strategy in MEDLINE

Search	Query	Items found
#6	#4 Filters: Randomized Controlled Trial	25
#5	#4 Filters: Clinical Trail	68
#4	#1 AND #2 AND #3	914
#3	"Neoadjuvant Therapy"[MeSH] OR neoadjuvant[tiab] OR "neo-adjuvant"[tiab] OR perioperative[tiab] OR preoperative[tiab] OR "peri-operative"[tiab] OR "pre-operative"[tiab]	518,498
#2	Immunotherapy[MeSH] OR "Antibodies, Monoclonal, Humanized"[MeSH] OR "Programmed Cell Death 1 Receptor"[MeSH] OR "CTLA-4 Antigen"[MeSH] OR "B7-H1 Antigen"[MeSH] OR "Immune Checkpoint Inhibitors"[MeSH] OR immunotherap*[tiab] OR immuno-therap*[tiab] OR immunetherap*[tiab] OR immune-therap*[tiab] OR immune checkpoint inhibit*[tiab] OR nivolumab[tiab] OR ipilimumab[tiab] OR sintilimab[tiab] OR durvalumab[tiab] OR atezolizumab[tiab] OR pembrolizumab[tiab] OR avelumab[tiab] OR tremelimumab[tiab] OR camrelizumab[tiab] OR tislelizumab[tiab] OR toripalimab[tiab]	555,846
#1	"Carcinoma, Non-Small-Cell Lung"[MeSH] OR non-small cell lung cancer*[tiab] OR non-small cell lung carcinoma*[tiab] OR nonsmall cell lung cancer*[tiab] OR nonsmall cell lung carcinoma*[tiab] OR NSCLC[tiab]	108,679

[MeSH], Medical Subject Headings; [tiab], Title/Abstract.

Table S2 Literature search strategy in Embase

Search	Query	Items found
#17	limit #16 to randomized controlled trial	92
#16	limit #15 to clinical trial	334
#15	#3 and #11 and #14	2,450
#14	#12 or #13	761,966
#13	('neoadjuvant' or 'neo-adjuvant' or 'perioperative' or 'preoperative' or 'peri-operative' or 'pre-operative').ab,kf,ti.	750,751
#12	exp neoadjuvant therapy/	59,371
#11	#4 or #5 or #6 or #7 or #8 or #9 or #10	1,184,425
#10	('immunotherap*' or 'immuno-therap*' or 'immunetherap*' or 'immune-therap*' or 'immune checkpoint inhibit*' or 'nivolumab' or 'ipilimumab' or 'sintilimab' or 'durvalumab' or 'atezolizumab' or 'pembrolizumab' or 'avelumab' or 'tremelimumab' or 'camrelizumab' or 'tislelizumab' or 'toripalimab').ab,kf,ti.	300,102
#9	exp cytotoxic T lymphocyte antigen 4/	34,068
#8	exp programmed death 1 ligand 1/	64,240
#7	exp programmed death 1 receptor/	48,202
#6	exp immune checkpoint inhibitor/	33,229
#5	exp monoclonal antibody/	821,502
#4	exp immunotherapy/	340,314
#3	#1 or #2	231,842
#2	('non-small cell lung cancer*' or 'non-small cell lung carcinoma*' or 'nonsmall cell lung cancer*' or 'nonsmall cell lung carcinoma*' or 'NSCLC').ab,kf,ti.	165,155
#1	exp non small cell lung cancer/	170,476

Ab, abstract; Kf, keyword heading word; Ti, title.

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Table 3 Literature search strategy in Cochrane Library

Search	Query	Items found
#15	#3 AND #11 AND #14 in Trials	317
#14	#12 OR #13	80,228
#13	(neoadjuvant):ab,ti,kw OR (neo-adjuvant):ab,ti,kw OR (perioperative):ab,ti,kw OR (preoperative):ab,ti,kw OR (peri-operative):ab,ti,kw OR (pre-operative):ab,ti,kw	80,228
#12	MeSH descriptor: [Neoadjuvant Therapy] explode all trees	2,641
#11	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	49,991
#10	(immunotherap*):ab,ti,kw OR (immuno-therap*):ab,ti,kw OR (immunetherap*):ab,ti,kw OR (immune-therap*):ab,ti,kw OR (immune checkpoint inhibit*):ab,ti,kw OR (nivolumab):ab,ti,kw OR (ipilimumab):ab,ti,kw OR (sintilimab):ab,ti,kw OR (durvalumab):ab,ti,kw OR (atezolizumab):ab,ti,kw OR (pembrolizumab):ab,ti,kw OR (avelumab):ab,ti,kw OR (tremelimumab):ab,ti,kw OR (camrelizumab):ab,ti,kw OR (tislelizumab):ab,ti,kw OR (toripalimab):ab,ti,kw	22,734
#9	MeSH descriptor: [B7-H1 Antigen] explode all trees	394
#8	MeSH descriptor: [CTLA-4 Antigen] explode all trees	88
#7	MeSH descriptor: [Programmed Cell Death 1 Receptor] explode all trees	223
#6	MeSH descriptor: [Antibodies, Monoclonal] explode all trees	21,809
#5	MeSH descriptor: [Immune Checkpoint Inhibitors] explode all trees	275
#4	MeSH descriptor: [Immunotherapy] explode all trees	12,175
#3	#1 OR #2	17,659
#2	(non-small cell lung cancer*): ab, ti kw OR (non-small cell lung carcinoma*): ab,ti,kw OR (nonsmall cell lung cancer*):ab,ti,kw OR (nonsmall cell lung carcinoma*):ab,ti,kw OR (NSCLC):ab,ti,kw	17,659
#1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees	6,655

ab: Abstract, ti: Title, kw: keyword

Table S4 Absolute risk difference of pre-operative treatment interruption in paired meta-analyses

Outcome	Event rate in neoadjuvant chemotherapy alone (No. of studies)*,†	Absolute risk difference for neoadjuvant chemotherapy plus ICIs (95% CI)
Neoadjuvant therapy discontinuation		
Total	148.6 (8)	6.4 (–33.2 to 59.7)
AE	84 (7)	26.7 (0.4 to 61.2)
PD	13.2 (7)	–6.2 (–9.3 to –0.6)
AE plus PD	94 (7)	6.4 (–14.8 to 33.2)
Surgery cancellation		
Total	187 (8)	–38.5 (–56.7 to –17.8)
AE	46.5 (8)	37.5 (8.3 to 82.1)
PD	55.1 (8)	–28.4 (–37.5 to –14.6)
AE plus PD	91 (8)	–26.6 (–38.2 to –12.5)
Surgery delay		
Total	151.8 (6)	15.8 (–15.4 to 54.1)
AE	44.3 (6)	9.8 (–8.1 to 36.5)

The ARD calculation formula is as follows: Control Event Rate = Σ (Weighted of each study × Event numbers of each study ÷ Total patients of each study). *, per 1,000 patients. †, the baseline risk in the control group is obtained by calculating a weighted average of the event rates across studies involved in this study. ARD, absolute risk difference; ICIs, immune checkpoint inhibitors; CI, confidence interval; AE, adverse event; PD, progression of disease.

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Table S5 Results of paired meta-analysis assessing potential confounding factors

Outcome	Age	Male proportion	Squamous cell carcinoma proportion	Never smoker proportion	Study population
Neoadjuvant therapy discontinuation					
Total	–0.02 (–0.29 to 0.25)	0.07 (–3.77 to 3.91)	0.02 (–2.55 to 2.59)	1.97 (–11.03 to 14.97)	0.07 (–0.63 to 0.76)
AE	0.14 (–0.22 to 0.5)	4.59 (–2.91 to 12.1)	3.42 (–0.91 to 7.76)	2.21 (–13.79 to 18.21)	–0.08 (–0.84 to 0.69)
PD	0.17 (–0.5 to 0.84)	–0.47 (–9.68 to 8.75)	0.06 (–5.38 to 5.5)	–10.31 (–41.01 to 20.4)	–0.48 (–2.51 to 1.56)
AE plus PD	0.2 (–0.1 to 0.5)	2.92 (–2.4 to 8.24)	1.95 (–1.09 to 5)	4.83 (–10 to 19.65)	0.37 (–0.44 to 1.17)
Surgery cancellation					
Total	0.1 (–0.01 to 0.21)	–0.82 (–2.32 to 0.69)	–0.58 (–1.55 to 0.4)	1.96 (–4.33 to 8.25)	0.35 (0.03 to 0.66)
AE	–0.11 (–0.58 to 0.35)	5.51 (–1.48 to 12.5)	3.23 (–1.06 to 7.52)	4.16 (–16.95 to 25.27)	–0.06 (–1.09 to 0.97)
PD	0.34 (0.1 to 0.58)	–3.76 (–7.88 to 0.36)	–2.29 (–5.19 to 0.61)	3.8 (–13.12 to 20.72)	0.59 (–0.28 to 1.47)
AE plus PD	0.19 (0.02 to 0.37)	–1.88 (–4.55 to 0.79)	–1.13 (–2.83 to 0.57)	3.79 (–6.97 to 14.55)	0.48 (–0.07 to 1.04)
Surgery delay					
Total	–0.12 (–0.31 to 0.07)	1.9 (–1.19 to 4.98)	1.44 (–0.52 to 3.4)	2.4 (–5.95 to 10.75)	–0.46 (–0.9 to –0.01)
AE	–0.28 (–0.65 to 0.08)	4.29 (–1.19 to 9.77)	2.85 (–0.86 to 6.56)	10.15 (–4.78 to 25.09)	–0.48 (–1.51 to 0.54)

The results were reported as β coefficients with their corresponding 95% credible intervals. The 95% credible intervals including 0 indicate nonsignificant effects. AE, adverse event; PD, progression of disease.

Table S6 Comparison of model fit between random effects and fixed effects models using DIC

Model	Neoadjuvant therapy discontinuation				Surgery cancellation			
	Total	AE	PD	AE plus PD	Total	AE	PD	AE plus PD
Fixed effect model	38.91	26.06	12.90	28.40	37.08	28.38	45.49	37.78
Random effect model	36.50	27.06	14.09	29.24	37.98	29.66	38.40	37.58

DIC is a Bayesian model evaluation criterion that measures the goodness-of-fit of a model. It varies with changes in model complexity, and the smaller the DIC value, the better the model fit. DIC, deviance information criterion; AE, adverse event; PD, progression of disease.

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Table S7 Results of NMA assessing potential confounding factors

Outcome	Age	Male proportion	Squamous cell carcinoma proportion	Never smoker proportion	Study population
Neoadjuvant therapy discontinuation					
Total	−0.19 (−2.28, 1.58)	0.02 (−1.46, 1.52)	0.03 (−1.14, 1.29)	0.23 (−1.38, 1.86)	0.07 (−1.44, 1.23)
AE	−0.01 (−2.77, 2.28)	0.94 (−1.09, 3.24)	0.83 (−0.69, 2.42)	0.22 (−1.55, 2.03)	−0.12 (−1.57, 1.36)
PD	0.21 (−1.01, 1.57)	−0.07 (−1.45, 1.19)	−0.02 (−1.3, 1.19)	−0.27 (−1.73, 0.97)	−0.16 (−1.43, 1.01)
AE + PD	0.65 (−1.61, 2.97)	0.81 (−0.92, 2.85)	0.57 (−0.74, 1.98)	0.62 (−0.97, 2.59)	0.35 (−1.04, 2.08)
Surgery cancellation					
Total	0.57 (−0.49, 1.55)	−0.17 (−0.98, 0.96)	−0.21 (−0.81, 0.57)	0.31 (−0.6, 1.32)	0.56 (−0.05, 1.21)
AE	−1.38 (−5.11, 1.45)	1.96 (−0.5, 4.84)	1.48 (−0.28, 3.59)	0.4 (−1.94, 3)	−0.47 (−2.32, 1.76)
PD	1.93 (−0.28, 4.05)	−0.6 (−2.54, 2.23)	−0.6 (−2.13, 1.38)	0.57 (−1.98, 3.1)	1.34 (−0.33, 3.79)
AE + PD	1.09 (−0.5, 2.75)	−0.3 (−1.55, 1.43)	−0.35 (−1.34, 0.89)	0.5 (−1.02, 2.06)	0.86 (−0.16, 2.21)

The results were reported as β coefficients with their corresponding 95% credible intervals. The 95% credible intervals including 0 indicate nonsignificant effects. NMA, network meta-analysis; AE, adverse event; PD, progression of disease.

Table S8 Detail reasons for pre-operative treatment interruption

Detail reasons	ICI plus CT	CT alone	ICI alone	ICI + RT
Total neoadjuvant treatment discontinuation (9)	233	219	3	3
Adverse events	114 (48.9%)	84 (38.4%)	3 (100%)	3 (100%)
Disease progression	63 (27%)	66 (30.1%)	–	–
Patient decision	10 (4.3%)	18 (8.2%)	–	–
Physician decision	11 (4.7%)	14 (6.4%)	–	–
COVID-19	2 (0.9%)	–	–	–
Other reasons*	33 (14.2%)	37 (16.9%)	–	–
Reasons for surgery cancellation (10)	237	290	9	4
Adverse events	52 (21.9%)	36 (12.4%)	3 (33%)	1 (25%)
Disease progression	59 (24.9%)	120 (41.4%)	4 (44%)	3 (75%)
Patient decision	64 (27.0%)	73 (25.2%)	2 (22%)	–
Physician decision	27 (11.4%)	34 (11.7%)	–	–
COVID-19	1 (0.4%)	–	–	–
Other reasons	34 (14.4%)	27 (9.3%)	–	–
Reasons for surgery delay (6)	119	113	2	–
Adverse events	50 (42.0%)	38 (33.6%)	1 (50%)	–
Disease progression	–	–	1 (50%)	–
COVID-19	5 (4.2%)	5 (4.4%)	–	–
Other reasons	64 (53.8%)	67 (59.3%)	–	–

*, other reasons included unknown dead, unfit for surgery and other reasons not related to the study. The study by Lu et al. reported treatment interruptions caused by both neoadjuvant and adjuvant therapies combined, therefore, this study was not included in the table. ICI, immune checkpoint inhibitor; CT, chemotherapy; SBRT, stereotactic body radiotherapy.

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Table S9 Detailed reasons for adverse events leading to pre-operative treatment interruption

Reasons	ICB plus CT	CT alone	ICB alone	ICB + RT
Adverse events leading to neoadjuvant treatment discontinuation (7)	114	84	3	3
Digestive system	1 (1%)	–	1 (33%)	2 (67%)
Colitis	1	–	1	–
Hepatitis	–	–	–	1
Pancreatitis	–	–	–	1
Hematological system	–	–	–	1 (33%)
Decreased platelet count + fatigue	–	–	–	1
Respiratory system	–	–	2 (67%)	–
Hypoxia + nonmalignant pleural effusion	–	–	1	–
Pneumonitis	–	–	1	–
Not report	113 (99%)	84 (100%)	–	–
Adverse events leading to surgical cancellation (9)	52	36	3	1
Cardiovascular system	4 (8%)	3 (8%)	1 (33%)	–
Left ventricular dysfunction	–	1	–	–
Atrial fibrillation	–	1	–	–
Cerebrovascular accident	1	–	–	–
Coronary artery disease	1	1	–	–
Myocarditis	1	–	–	–
Stroke	1	–	1	–
Digestive system	3 (6%)	–	–	–
Colitis	1	–	–	–
Immune-mediated hepatitis	1	–	–	–
Aggravation of cirrhosis	1	–	–	–
Immune system	1 (2%)	–	–	–
Hypophysitis	1	–	–	–
Nervous system	1 (22%)	–	–	–
Cerebral infarction	1	–	–	–
Respiratory system	6 (12%)	3 (8%)	2 (67%)	–
Chronic respiratory failure	–	1	–	–
Poor lung function	1	2	–	–
Inadequate lung perfusion	–	–	1	–
Hemoptysis	1	–	–	–
Hypoxia + nonmalignant pleural effusion	–	–	1	–
Pneumonitis	4	–	–	–
Urinary system	–	1 (3%)	–	–
Increased blood creatinine	–	1	–	–
Not report	37 (71 %)	29 (81%)	–	–
Adverse events leading to surgical delay (6)	50	38	1	–
General symptoms	1 (2%)	2 (5%)	–	–
Asthenia	1	1	–	–
Fatigue	–	1	–	–
Cardiovascular system	2 (4%)	4 (11%)	–	–
Myocardial infarction	–	1	–	–
Deep vein thrombosis	–	1	–	–
Embolism	2	-	–	–
Stress cardiomyopathy	–	1	–	–
Ventricular thrombosis	–	1	–	–
Digestive system	1 (2%)	2 (5%)	1 (100%)	–
Colitis	–	1	1	–
Increased lipase	1	–	–	–
Intestinal ischemia	–	1	–	–
Endocrine system	1 (2%)	–	–	–
Hyperthyroidism	1	–	–	–
Hematological system	4 (8%)	2 (5%)	–	–
Anemia	4	–	–	–
Decreased neutrophil count	–	1	–	–
Decreased white blood cell count	–	1	–	–
Nervous system	1 (2%)	1 (3%)	–	–
Ataxia	–	1	–	–
Guillain-Barré syndrome	1	–	–	–
Respiratory system	6 (12%)	3 (8%)	–	–
Acute respiratory failure	1	–	–	–
Bronchitis	1	–	–	–
Bronchospasm	1	–	–	–
Pneumonitis	3	–	–	–
Pulmonary embolism	–	3	–	–
Skin system	1 (2%)	1 (3%)	–	–
Herpes zoster	–	1	–	–
Maculopapular rash	1	–	–	–
Not report	33 (66%)	23 (61%)	–	–

The number of patients not listed in the detailed system-based table has already been included in the total adverse events count. ICB, immune checkpoint blockade; CT, chemotherapy; RT, radiotherapy; PD, progression of disease.

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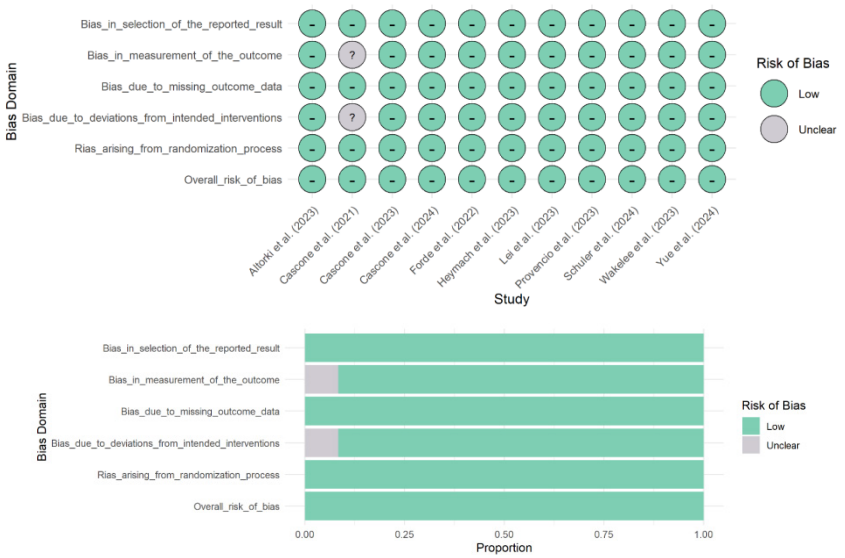

Figure S1 Summary of results from assessment of studies using the Cochrane risk of bias tool.

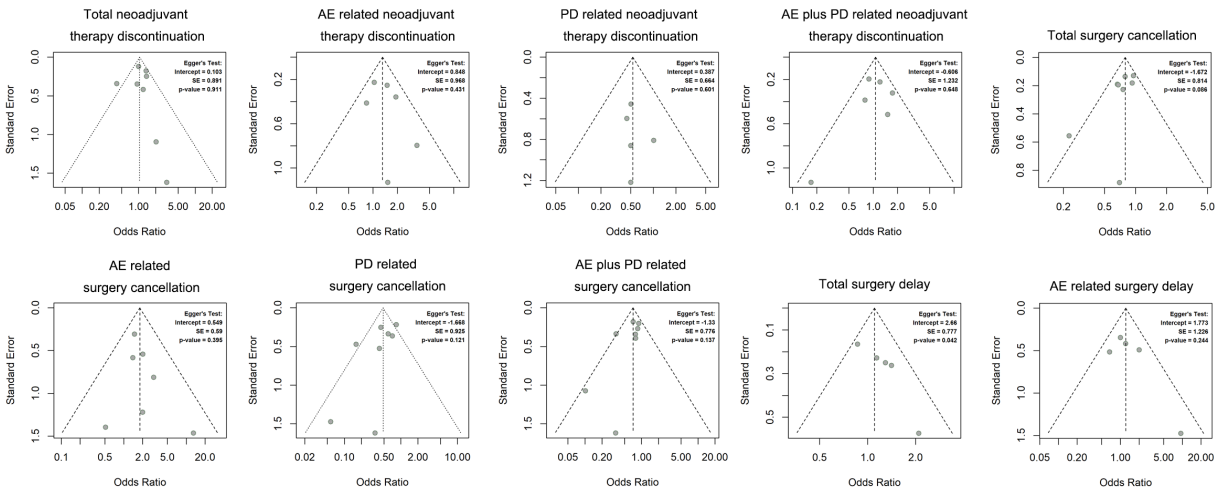

Figure S2 Publication bias results for paired meta-analyses: Egger's test and Funnel plot. Egger's test was used to explore the publication bias of all included studies on 10 outcome measures and was visualized using funnel plot. AE, adverse event; PD, progression of disease.

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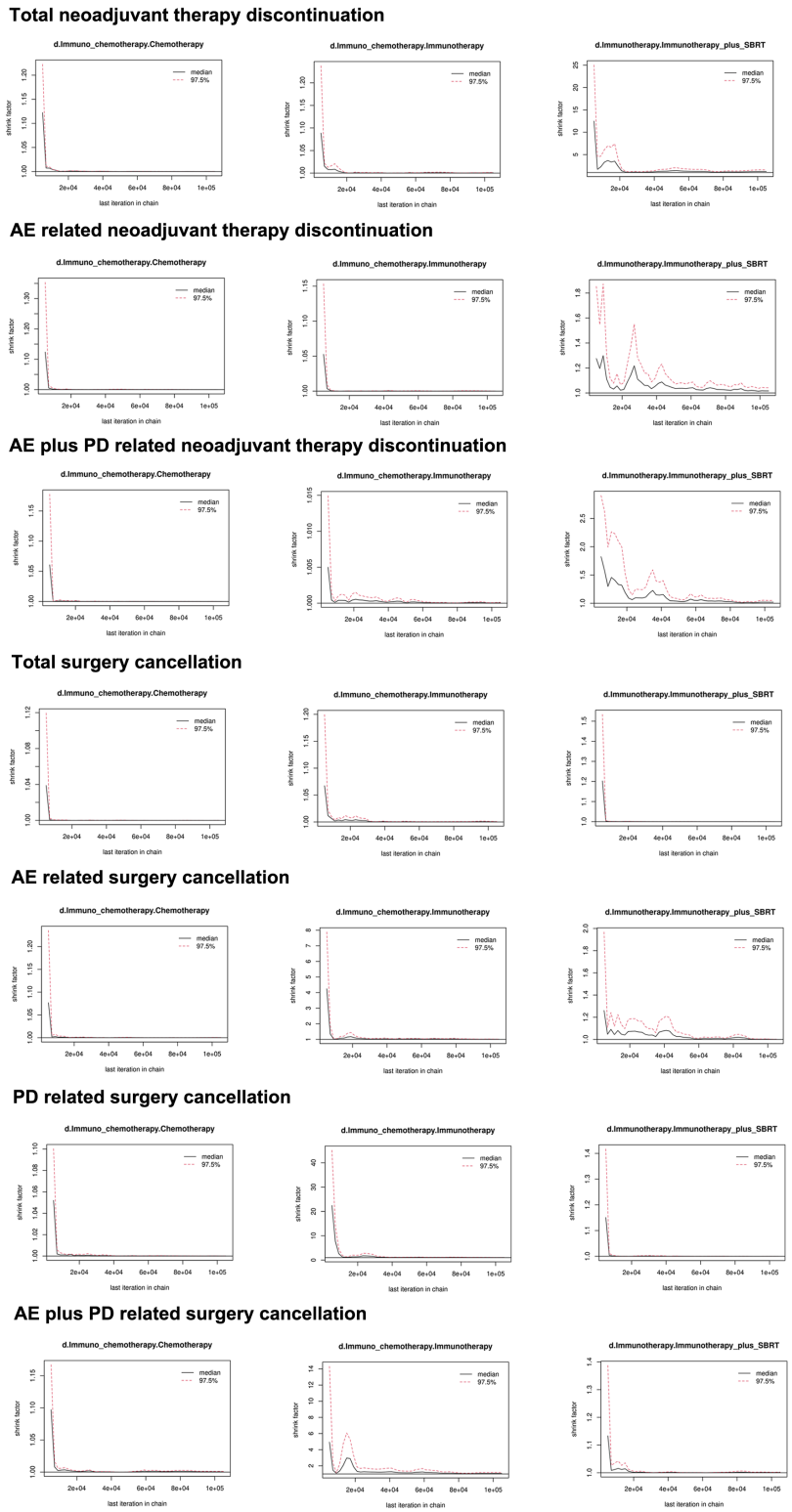

Figure S3 Brooks-Gelman-Rubin diagnostic plot for assessing model convergence. The Brooks-Gelman-Rubin diagnostic plot assessed the convergence of seven Bayesian-based models. A PSRF value approaching 1 indicates satisfactory model convergence. SBRT, stereotactic body radiotherapy; PSRF, potential scale reduction factor; AE, adverse event; PD, progression of disease.

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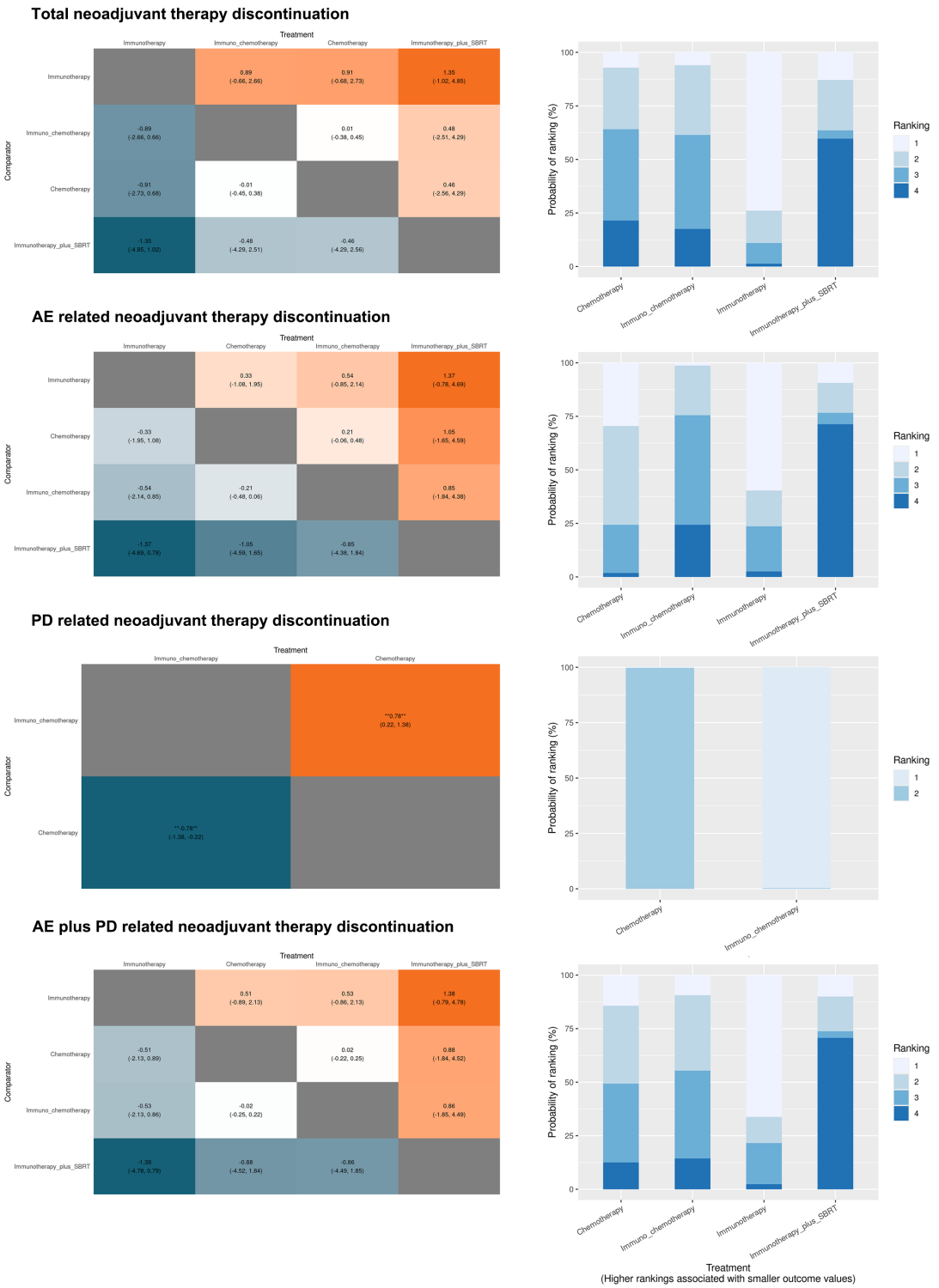

Figure S4 Detailed results of network meta-analysis for neoadjuvant therapy discontinuation. Detailed results of the Bayesian network meta-analysis (left) and rankogram plot (right). The detailed results present the pairwise comparisons among all neoadjuvant treatment strategies. The rankogram plot illustrates the ranking probabilities of different treatment strategies for various outcome measures, with higher rankings indicating better priority.

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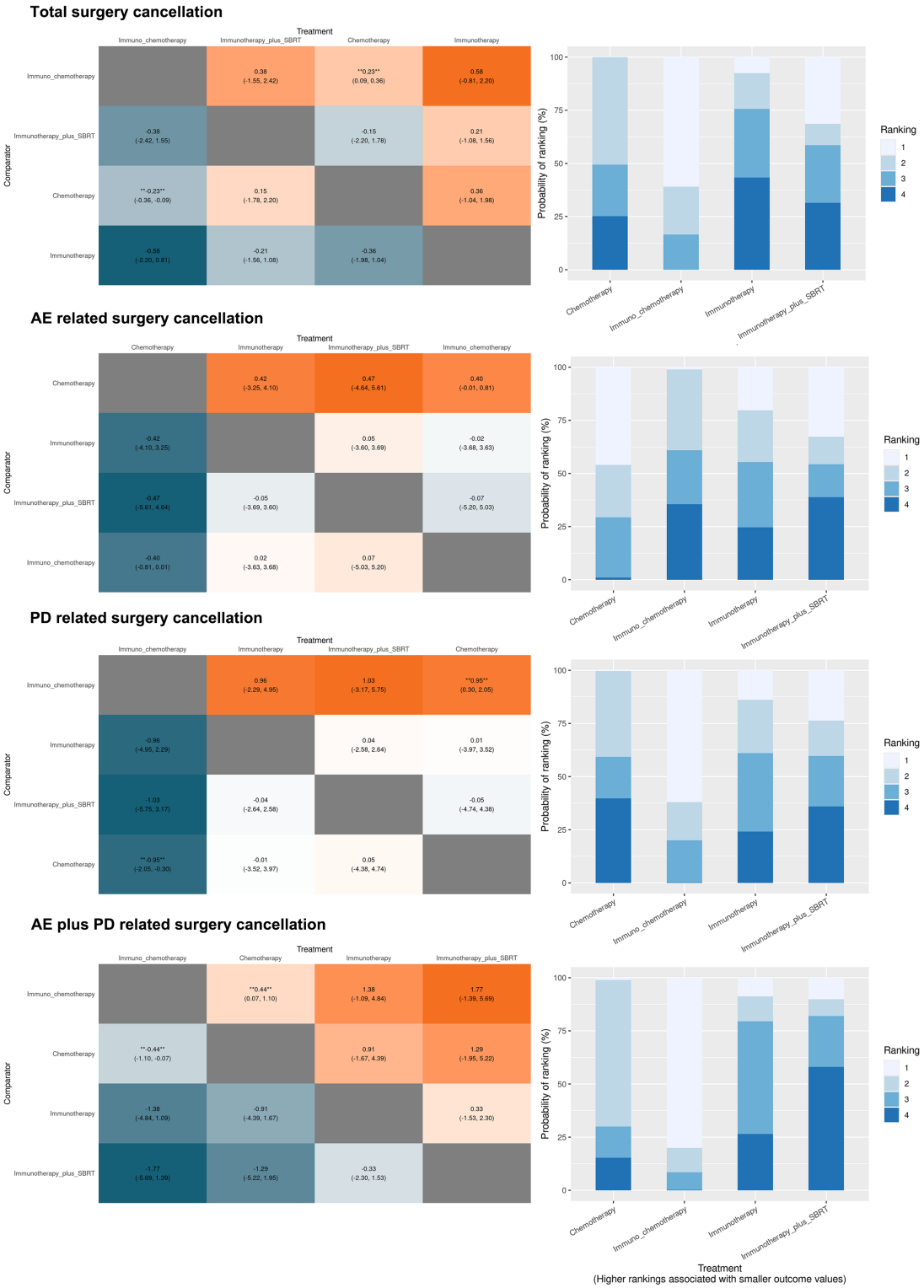

Figure S5 Detailed results of network meta-analysis for surgery cancellation. Detailed results of the Bayesian network meta-analysis (left) and rankogram plot (right). The detailed results present the pairwise comparisons among all neoadjuvant treatment strategies. The rankogram plot illustrates the ranking probabilities of different treatment strategies for various outcome measures, with higher rankings indicating better priority.

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