Supplemental Online Content

Sorin M, Prosty C, Ghaleb L, et al. Neoadjuvant chemoimmunotherapy for NSCLC: a systematic review and meta-analysis. *JAMA Oncol*. Published online March 21, 2024. doi:10.1001/jamaoncol.2024.0057

eFigure 11. Pooled Risk Ratios Across Randomized Clinical Trials Comparing Neoadjuvant Chemoimmunotherapy With Neoadjuvant Chemotherapy by Number of Patients Who Received All Cycles of Neoadjuvant Treatment

eFigure 12. Pooled Risk Ratios Across Randomized Clinical Trials Comparing Neoadjuvant Chemoimmunotherapy With Neoadjuvant Chemotherapy by Number of Patients Who Received a Pneumonectomy

eFigure 13. Pooled Risk Ratios Across Randomized Clinical Trials Comparing Neoadjuvant Chemoimmunotherapy With Neoadjuvant Chemotherapy by Number of Patients Who Received a Bilobectomy

eFigure 14. Pooled Risk Ratios Across Randomized Clinical Trials Comparing Neoadjuvant Chemoimmunotherapy With Neoadjuvant Chemotherapy by Number of Patients Who Had Surgical Delay

eFigure 15. Pooled Risk Ratios Across Randomized Clinical Trials Comparing Neoadjuvant Chemoimmunotherapy With Neoadjuvant Chemotherapy by Number of Patients Who Had Open Surgery

eFigure 16. Pooled Risk Ratios Across Randomized Clinical Trials Comparing Neoadjuvant Chemoimmunotherapy With Neoadjuvant Chemotherapy by Number of Patients Who Had Grade 3-4 Treatment-Related Adverse Events

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eFigure 19. Pooled Risk Ratios Across Randomized Clinical Trials Comparing Neoadjuvant Chemoimmunotherapy With Neoadjuvant Chemotherapy by Number of Patients Who Had Grade 3-4 Surgery-Related Adverse Events

eFigure 20. Pooled Risk Ratios Across Randomized Clinical Trials Comparing Neoadjuvant Chemoimmunotherapy With Neoadjuvant Chemotherapy by Number of Patients Who Had Grade 5 Surgery-Related Adverse Events

eFigure 21. Pooled Risk Ratios Across Randomized Clinical Trials Comparing Neoadjuvant Chemoimmunotherapy With Neoadjuvant Chemotherapy by Number of Patients Who Had Surgery-Related Adverse Events

eFigure 22. Pooled Risk Ratios Across Randomized Clinical Trials Comparing Neoadjuvant Chemoimmunotherapy With Neoadjuvant Chemotherapy by Number of Patients Who Did Not Receive Surgery

eFigure 23. Pooled Risk Ratios Across Randomized Clinical Trials Comparing Neoadjuvant Chemoimmunotherapy With Neoadjuvant Chemotherapy by Number of Patients Who Had Progression Precluding Surgery

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

eMethods. Methodology

Study Protocol

The study was pre-registered with PROSPERO with the registration number CRD42023392998, and the full protocol has been made available.

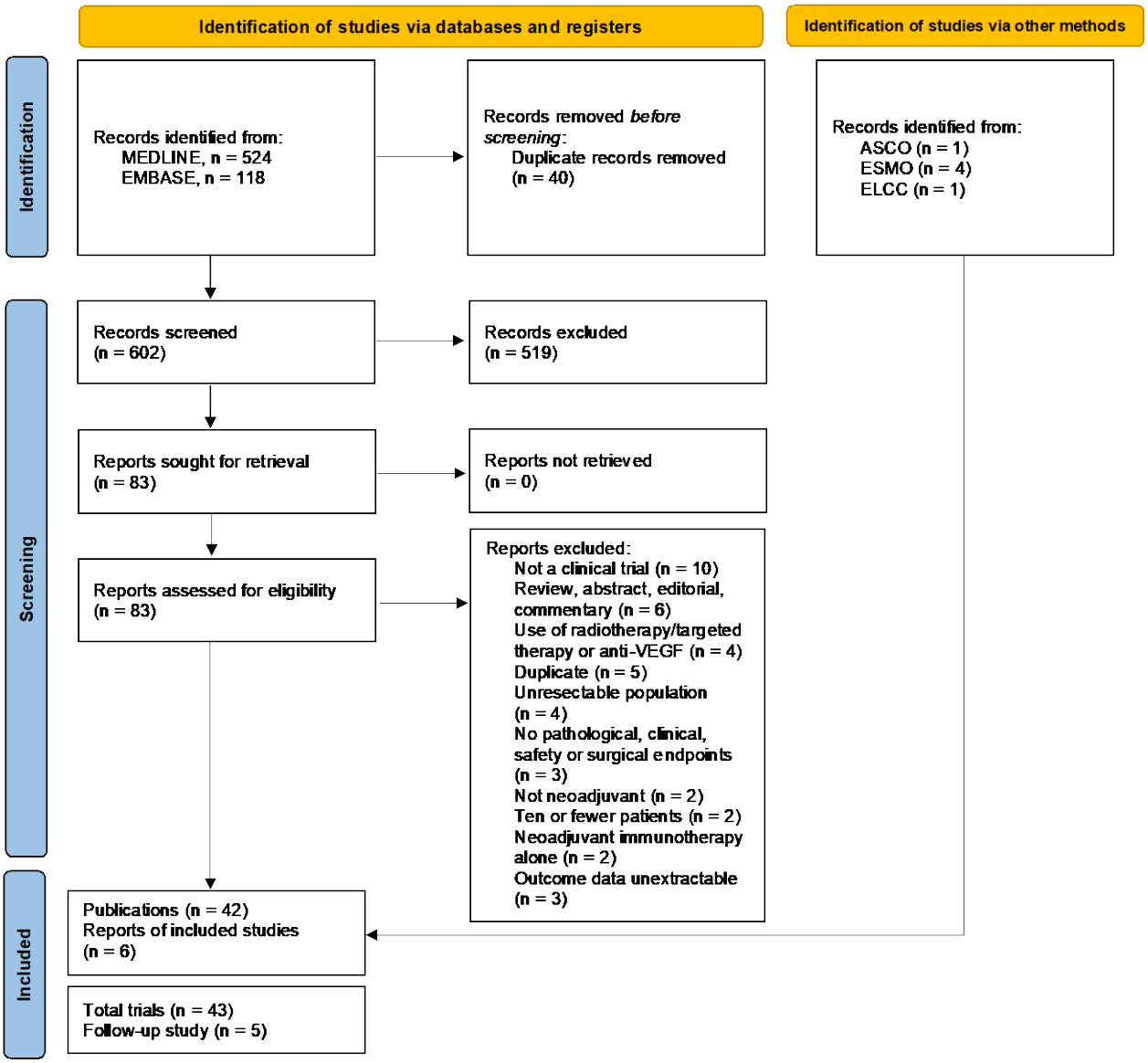
Extracted Data

Extracted data were as follows: (I) study information, including the title, first author, year of publication, country of origin (or international), clinical trial phase, study design, inclusion and exclusion criteria for patients, definition of endpoints reported, neoadjuvant treatment regimens, and the intention-to-treat sample size; (II) baseline characteristics of the included patients, including sex, age, stage, lung cancer histology, ethnicity, smoking status, and tumor PD-L1 expression; (III) data on treatment-related outcomes, including the number of patients who achieved MPR, pCR, and clinical response measures (complete, partial, stable disease, and progressive disease). The total incidence of grade 3-4 and grade 5 TRAEs adverse events were also extracted. Relevant data related to OS, EFS, PFS, RFS, and DFS were extracted if available; (IV) surgical outcome measures were also extracted, including the incidence of grade 3-4, grade 5, and any grade SRAEs, the number of patients who received surgery, the type of operation performed, the incidence of R0, R1, R2 and Rx resection margins, and the total number of patients who received any subsequent adjuvant treatment.

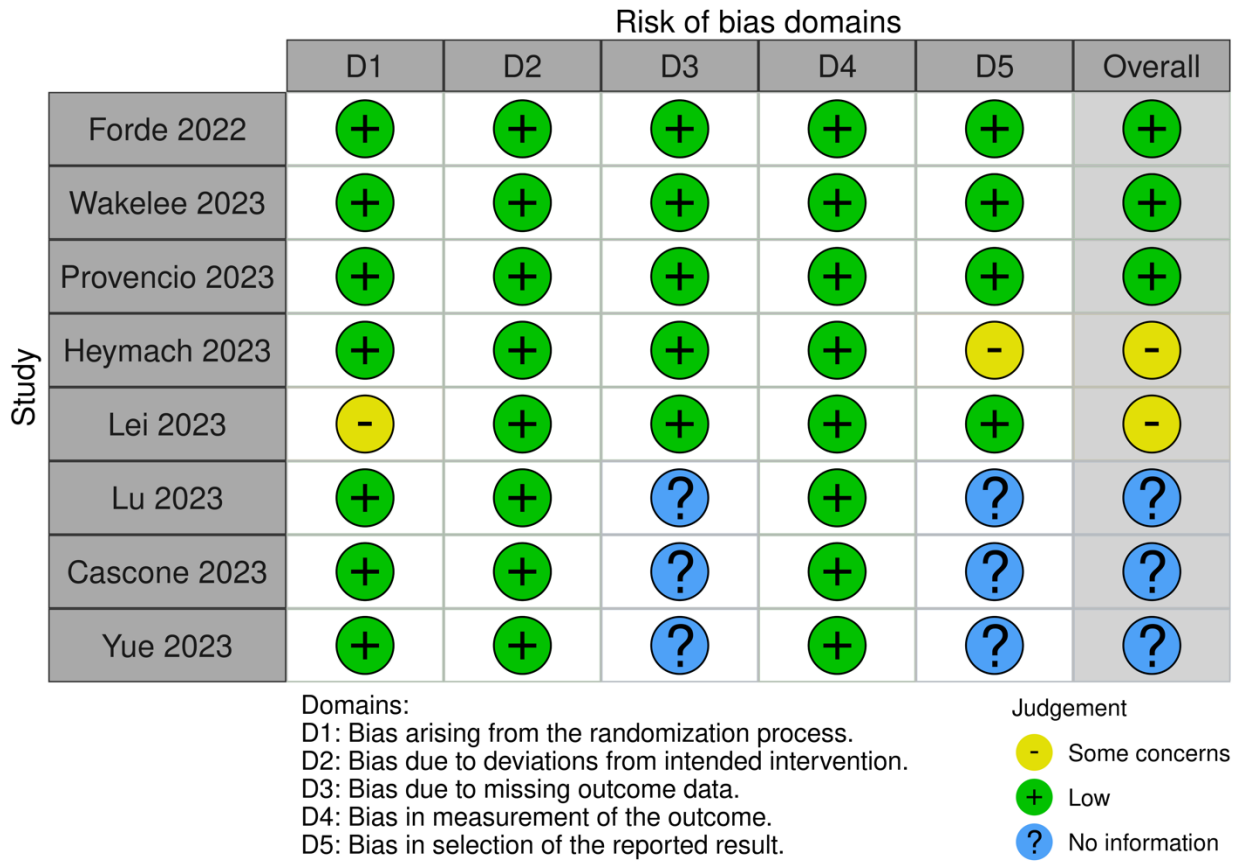
Criteria and Definitions of Endpoints for RCTs

Among RCTs, major pathological response was defined as 10% or less viable tumor cells in the primary tumor and sampled lymph nodes while complete pathological response was defined as the absence of residual tumor in the primary tumor and sampled lymph nodes. Overall survival was defined as the time from randomization to death. Definitions of disease-free survival and progression-free survival can be found in Supplemental Table 5. Adverse events were graded using the Common Terminology Crieteria for Adevrse Events (version 4.0 for CheckMate 816, version 5.0 for NADIM II and version 4.03 for Keynote 671). For staging purposes, the AJCC was used (7th edition for CheckMate 816, 8th edition for NADIM II and Keynote 671).

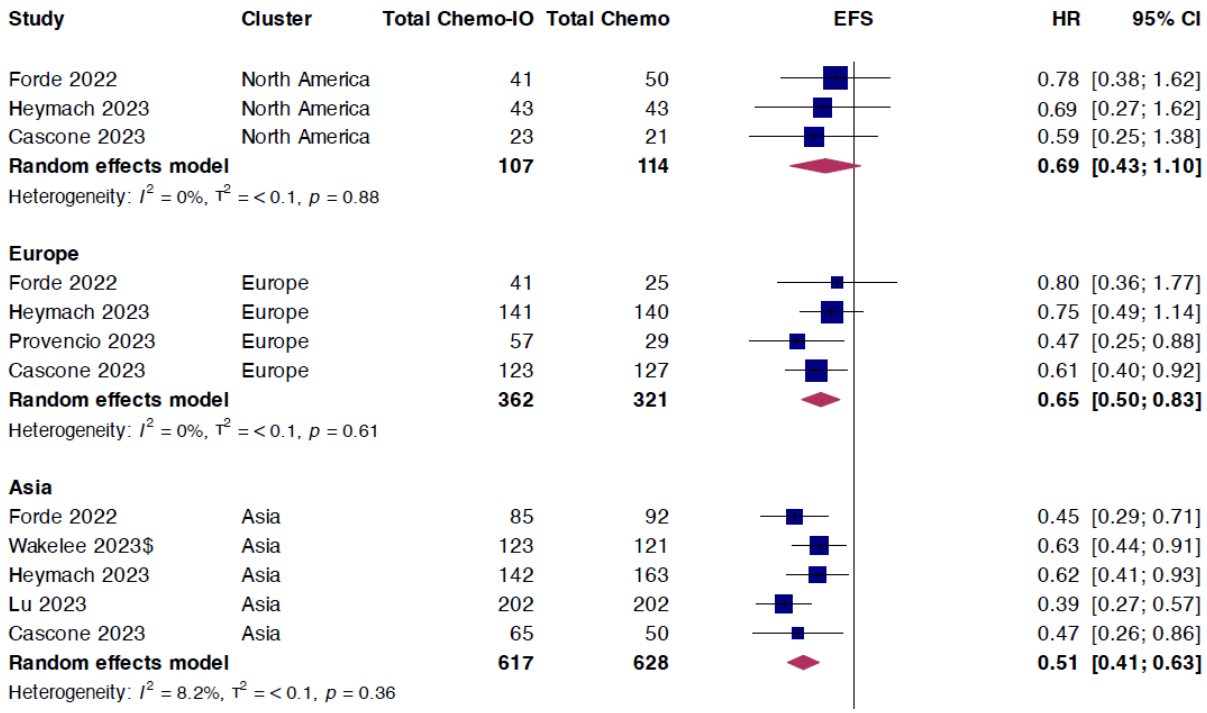
eFigure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram.



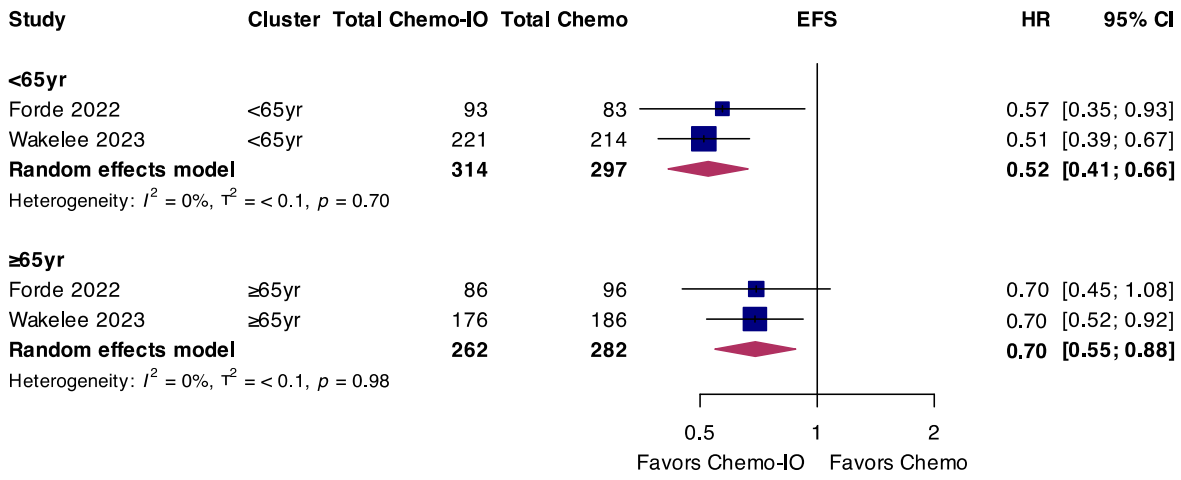
eFigure 2. RCT risk of bias (ROB2) assessment.



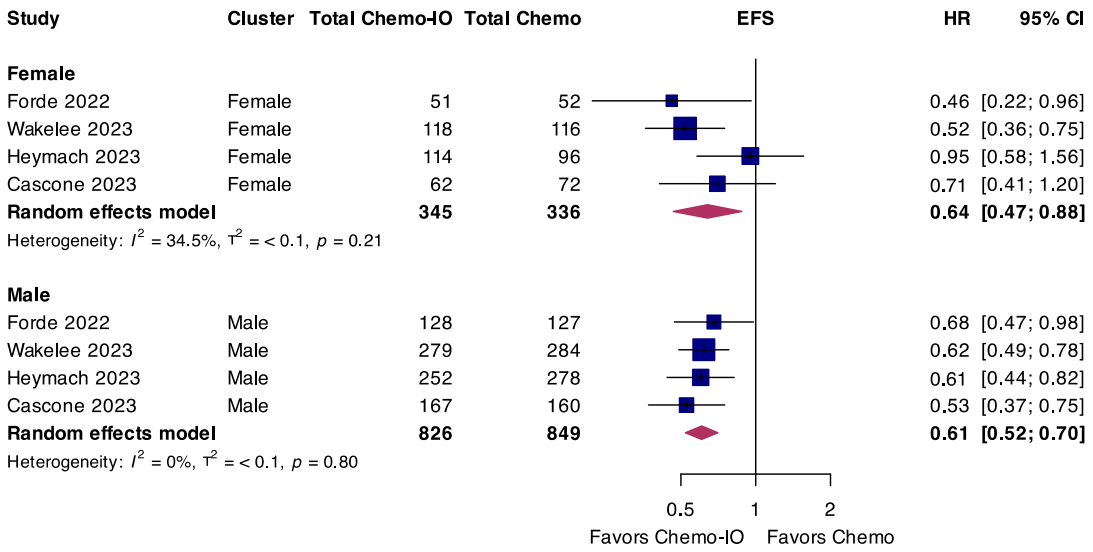
eFigure 3. Pooled hazard ratios of EFS across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by geographic region. [$]For Wakelee 2023, the geographic region was East Asia.



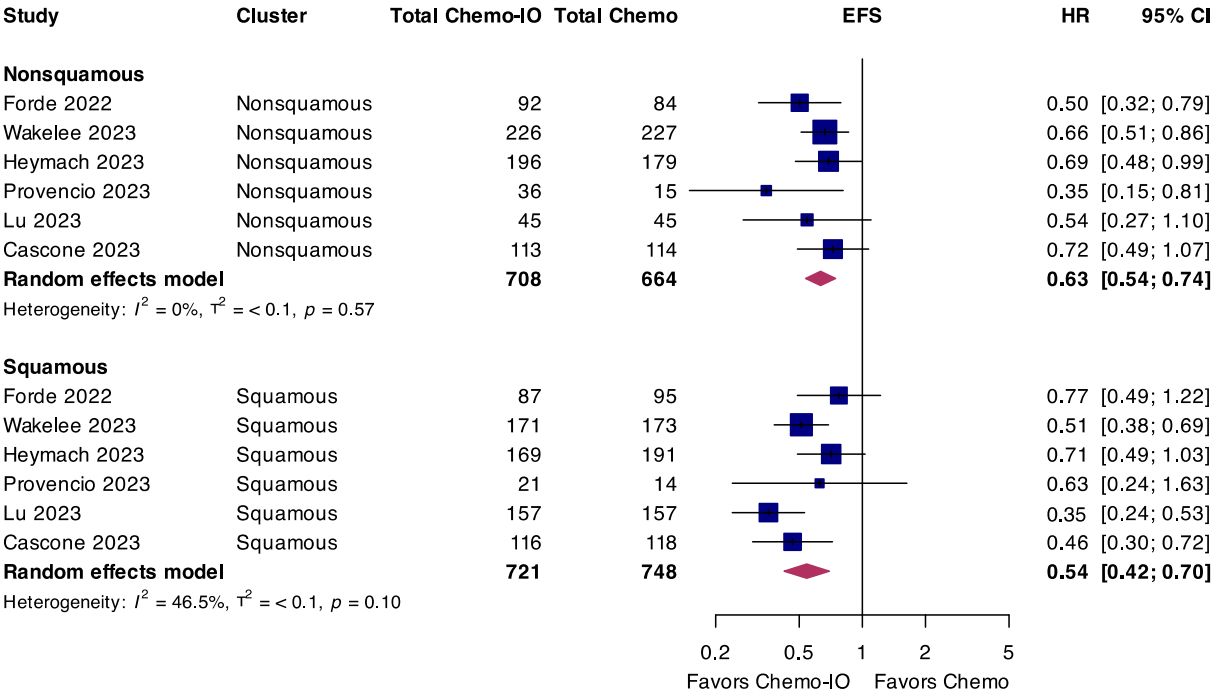
eFigure 4. Pooled hazard ratios of EFS across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by age.



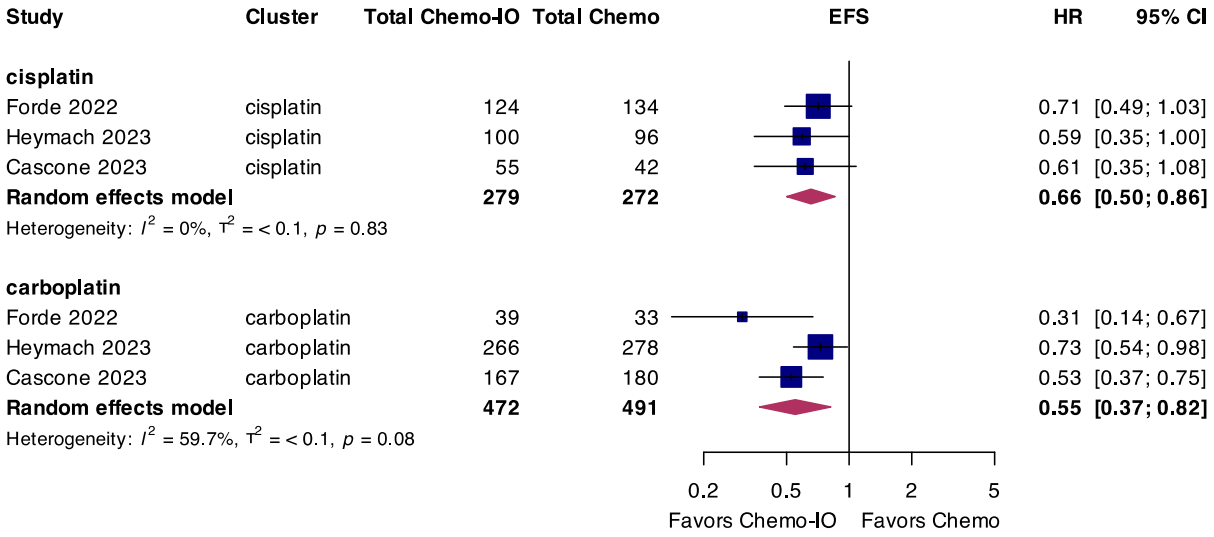
eFigure 5. Pooled hazard ratios of EFS across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by sex.



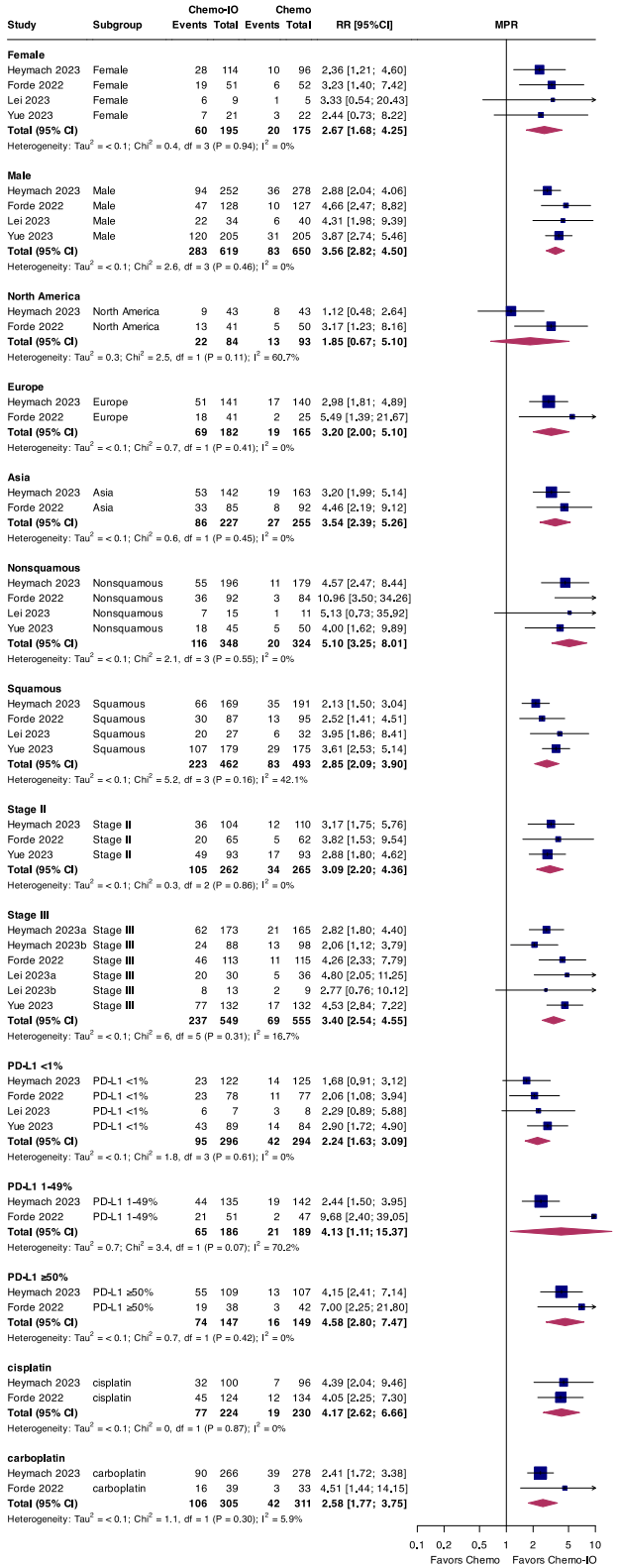
eFigure 6. Pooled hazard ratios of EFS across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by histology.



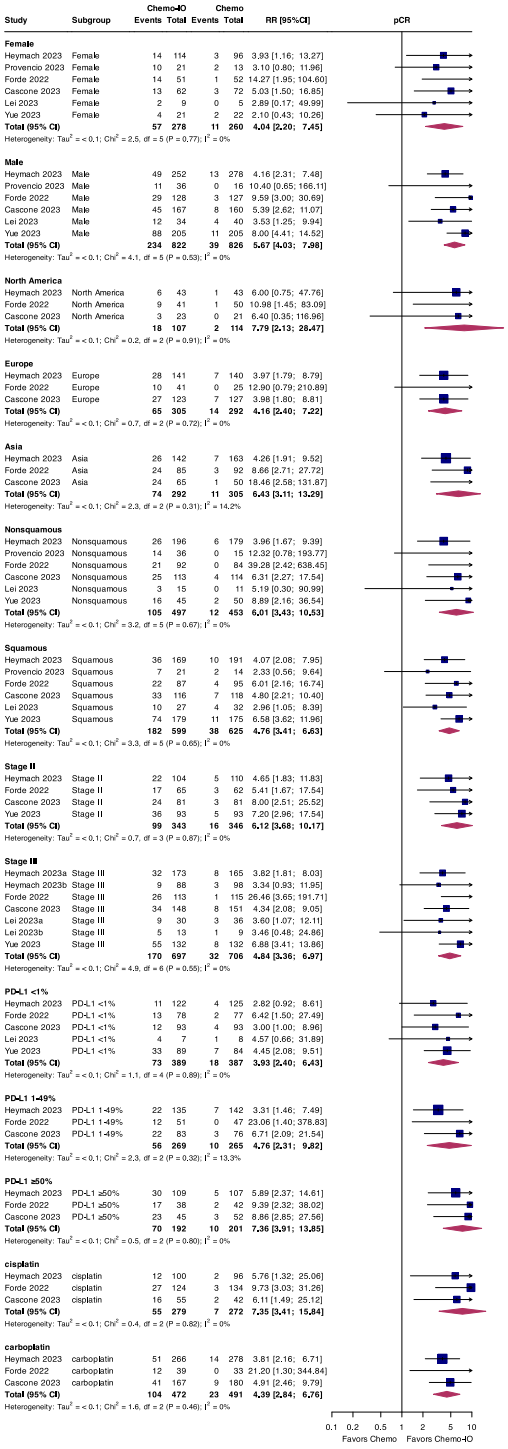
eFigure 7. Pooled hazard ratios of EFS across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by chemotherapy type.



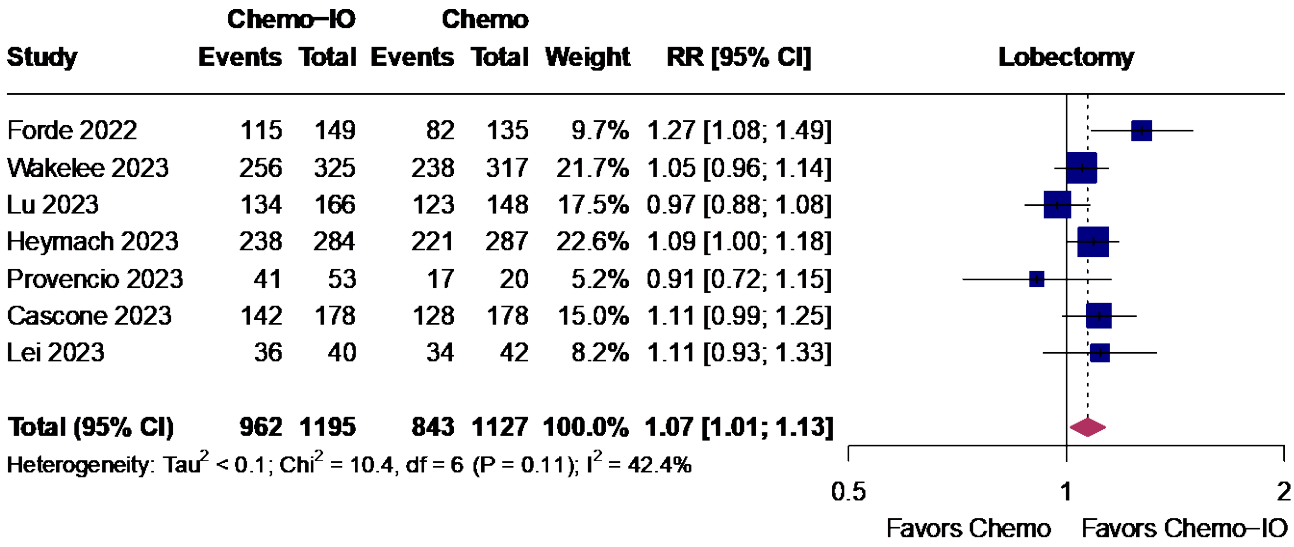
eFigure 8. Pooled risk ratios of MPR across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by sex, geographic region, histology, stage, PD-L1 status and chemotherapy type.



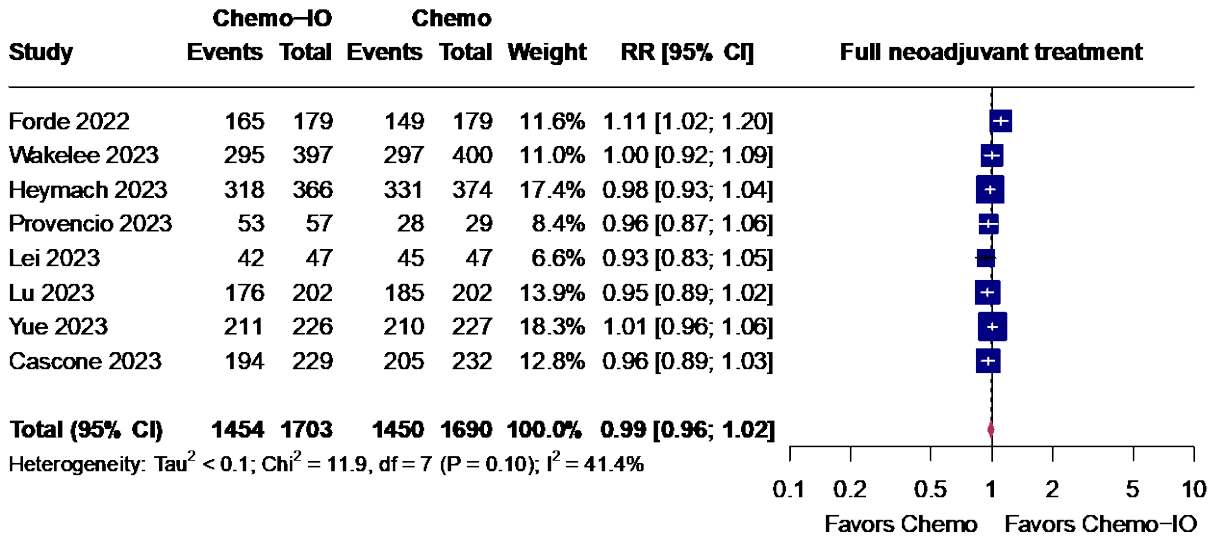
eFigure 9. Pooled risk ratios of pCR across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by sex, geographic region, histology, stage, PD-L1 status and chemotherapy type.



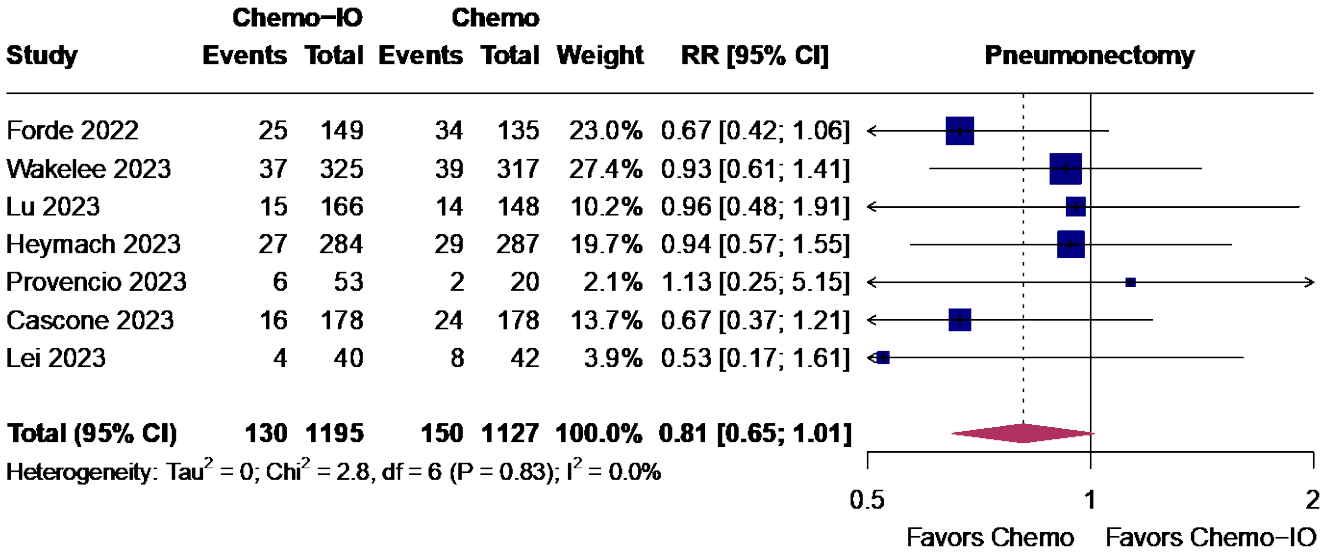
eFigure 10. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who received a lobectomy.



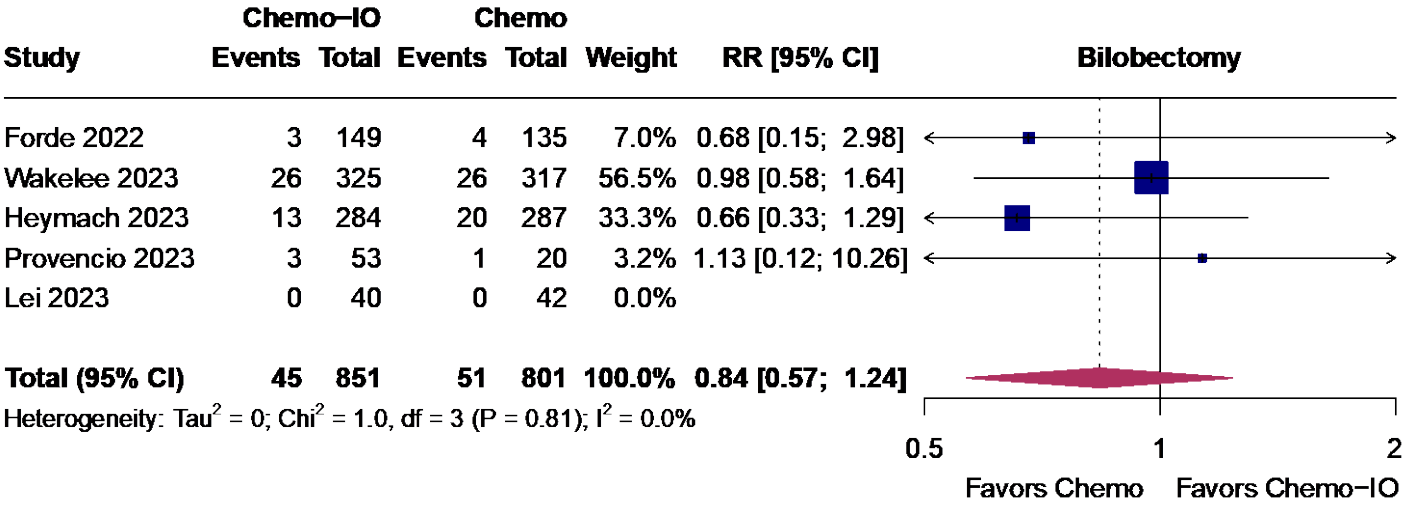
eFigure 11. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who received all cycles of neoadjuvant treatment.



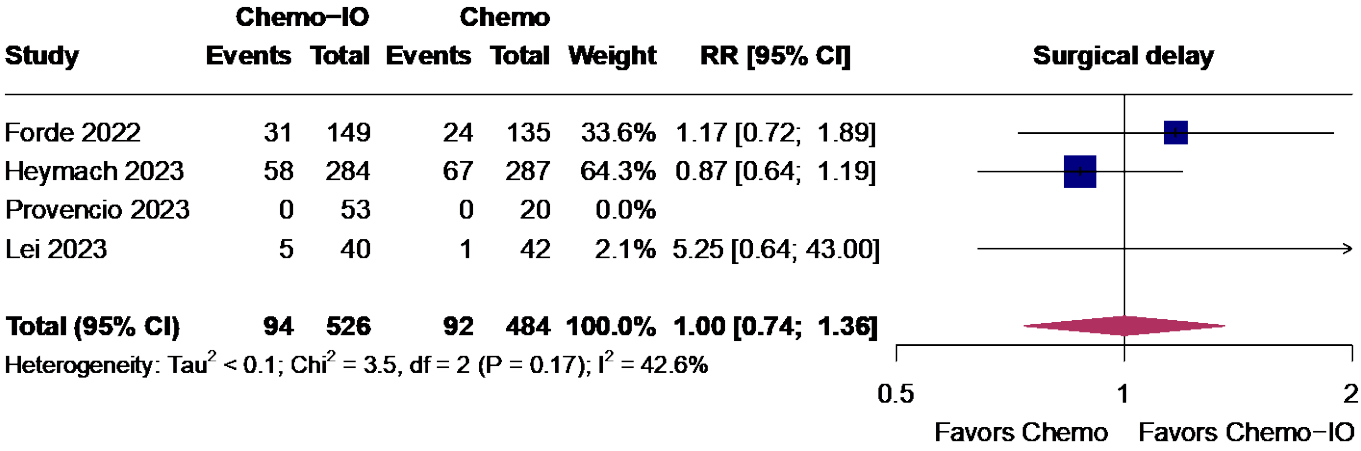
eFigure 12. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who received a pneumonectomy.



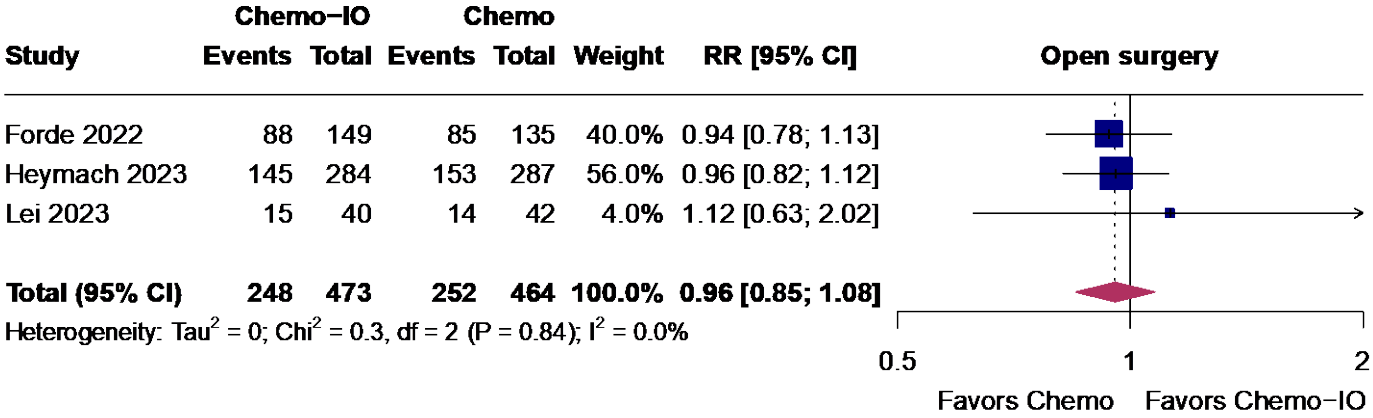
eFigure 13. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who received a bilobectomy.



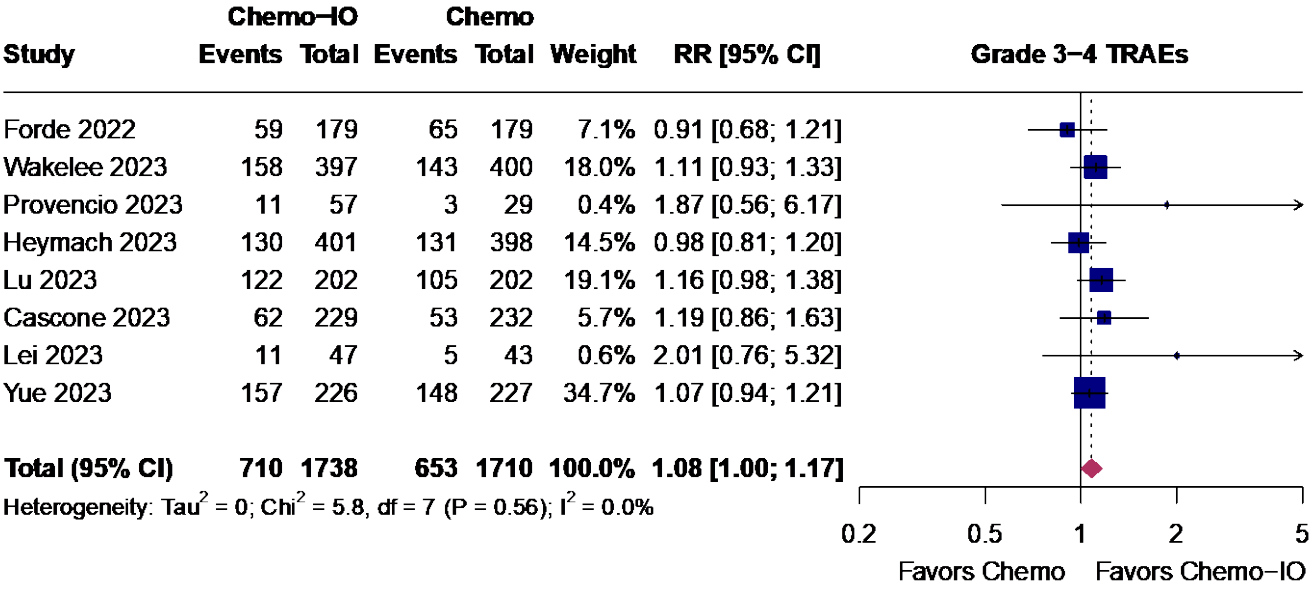
eFigure 14. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who had surgical delay.



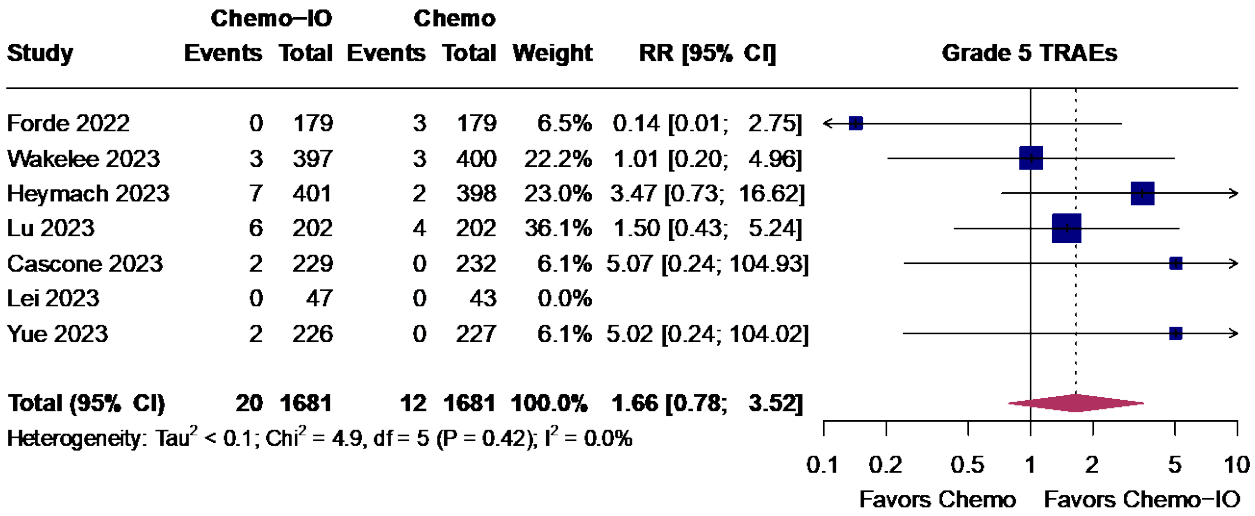
eFigure 15. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who had open surgery.



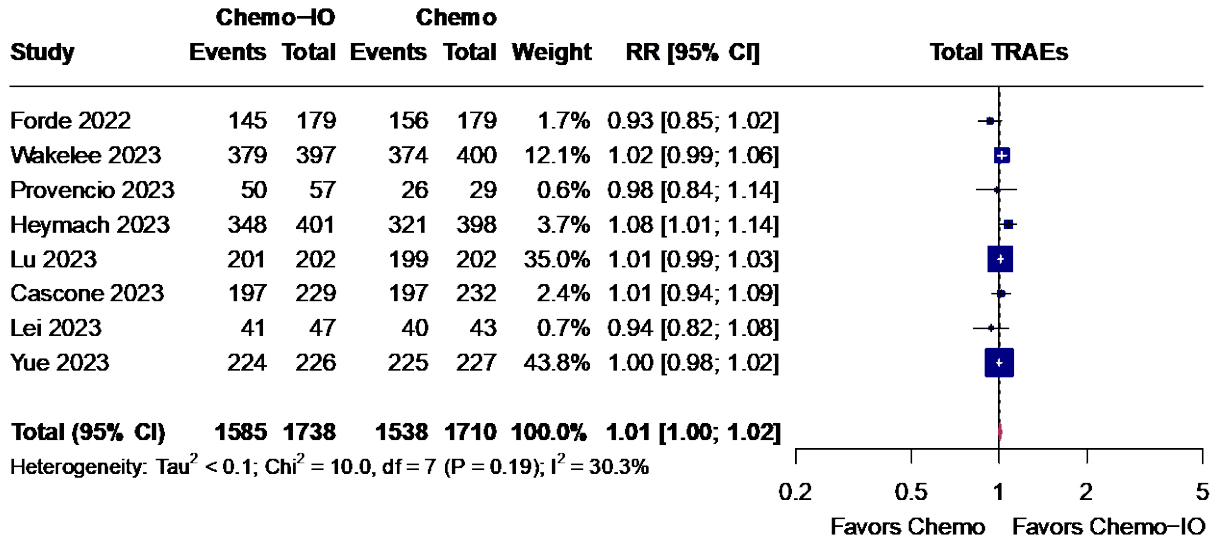
eFigure 16. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who had grade 3-4 treatment-related adverse events.



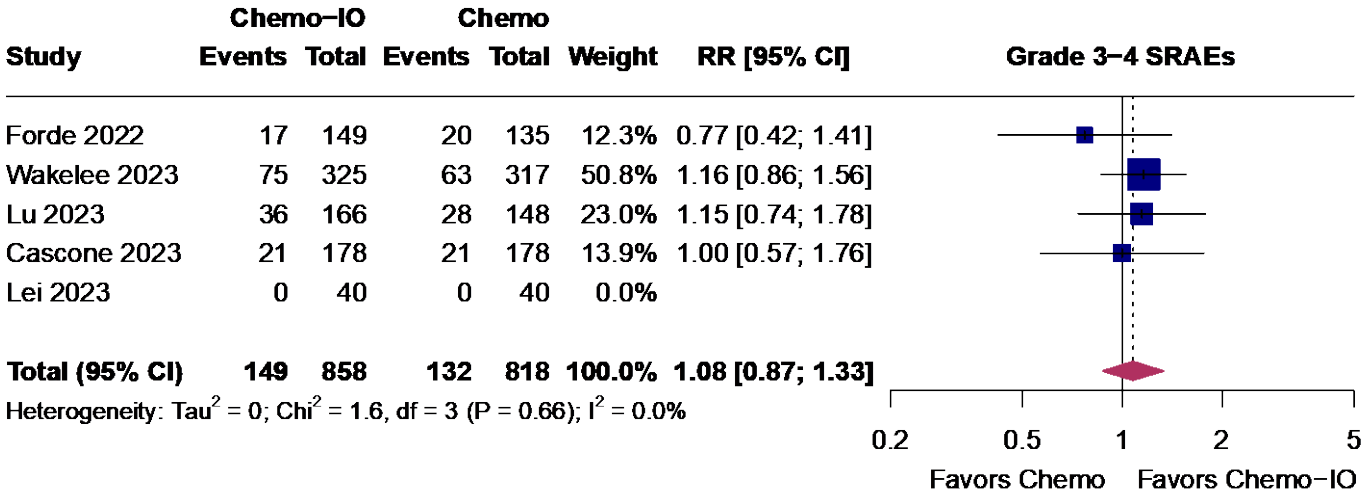
eFigure 17. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who had grade 5 treatment-related adverse events.



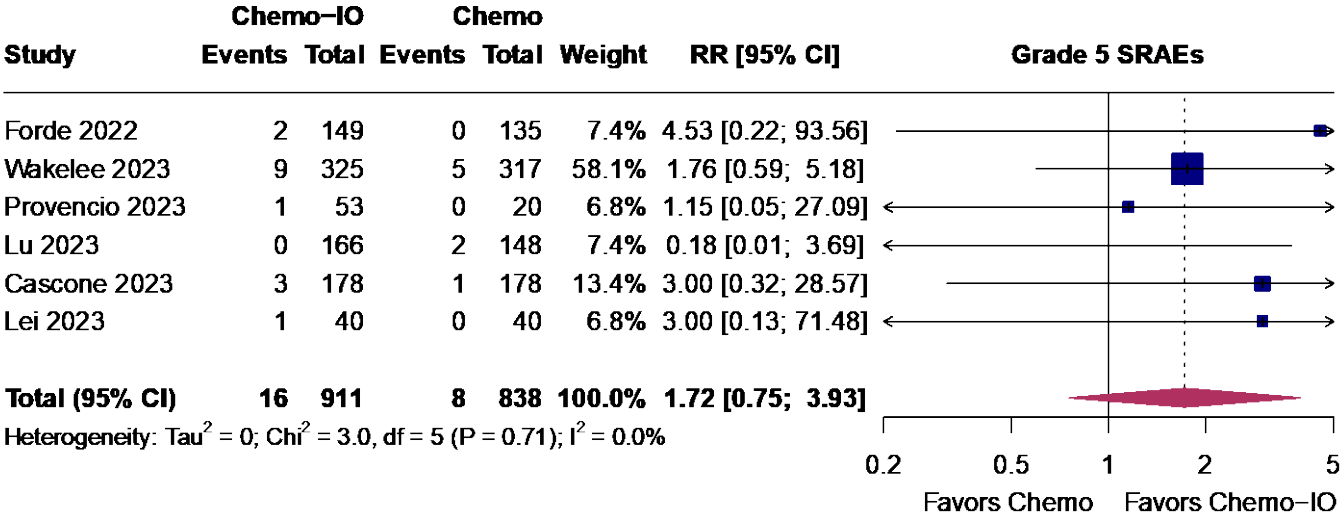
eFigure 18. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who had treatment-related adverse events.



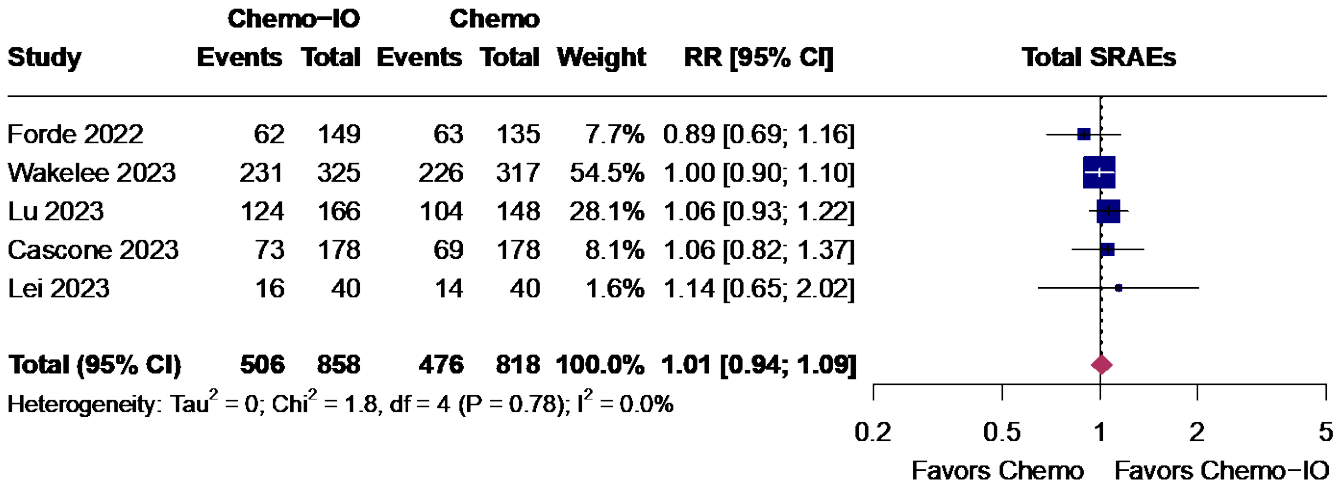
eFigure 19. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who had grade 3-4 surgery-related adverse events.



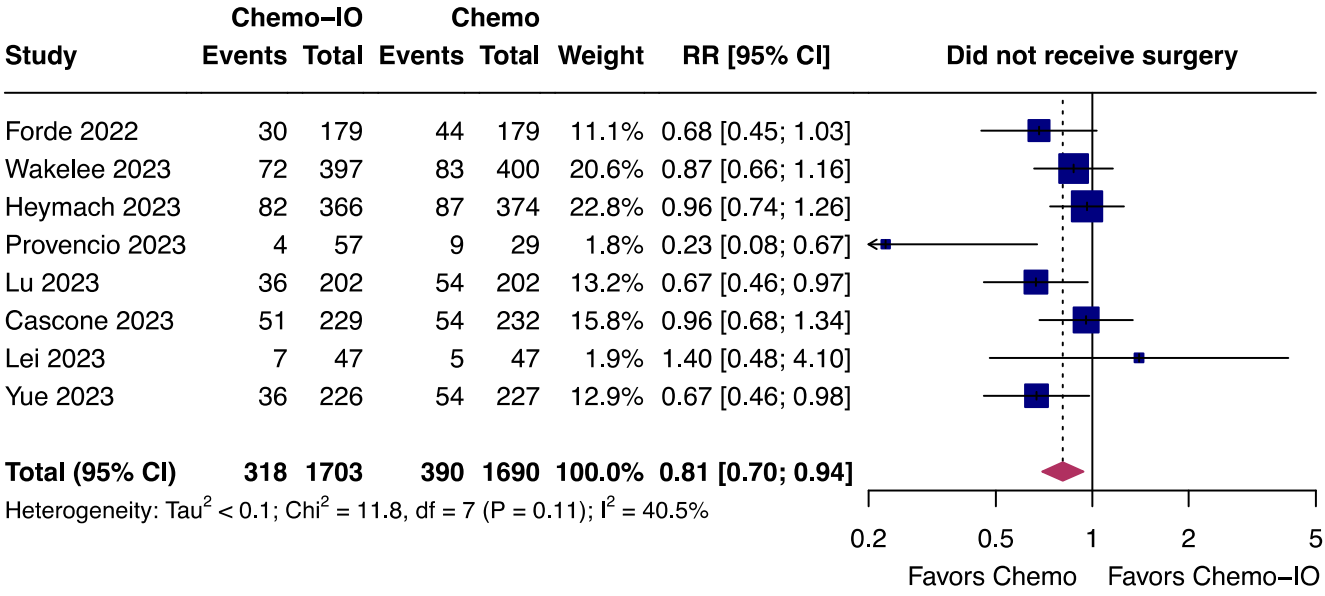
eFigure 20. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who had grade 5 surgery-related adverse events.



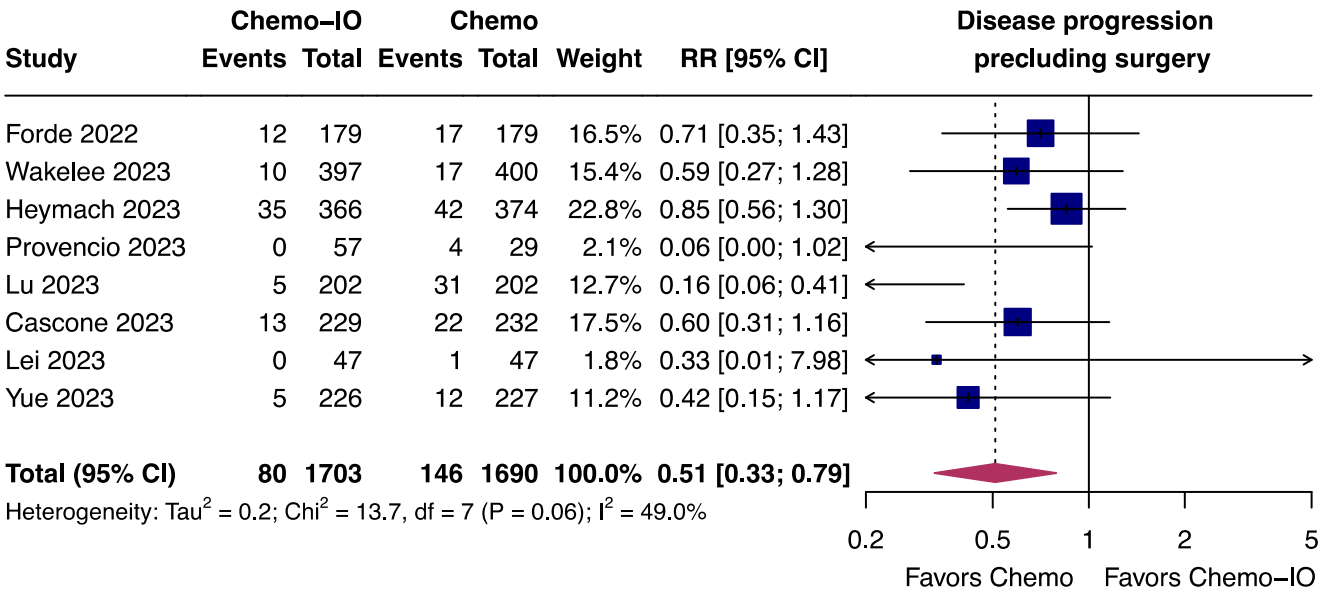
eFigure 21. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who had surgery-related adverse events.



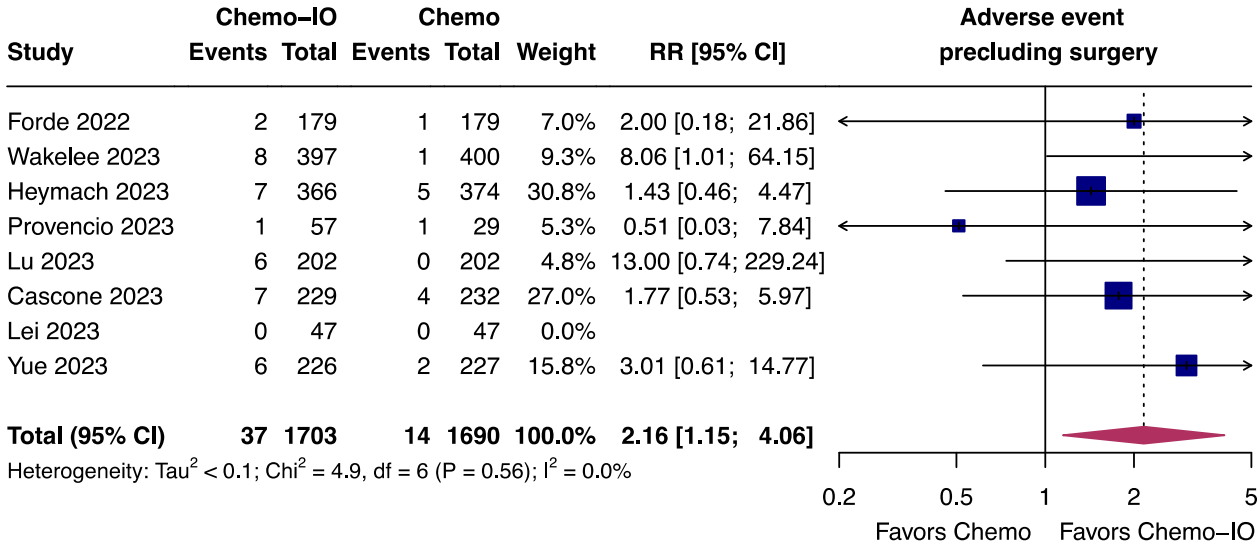
eFigure 22. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who did not receive surgery.



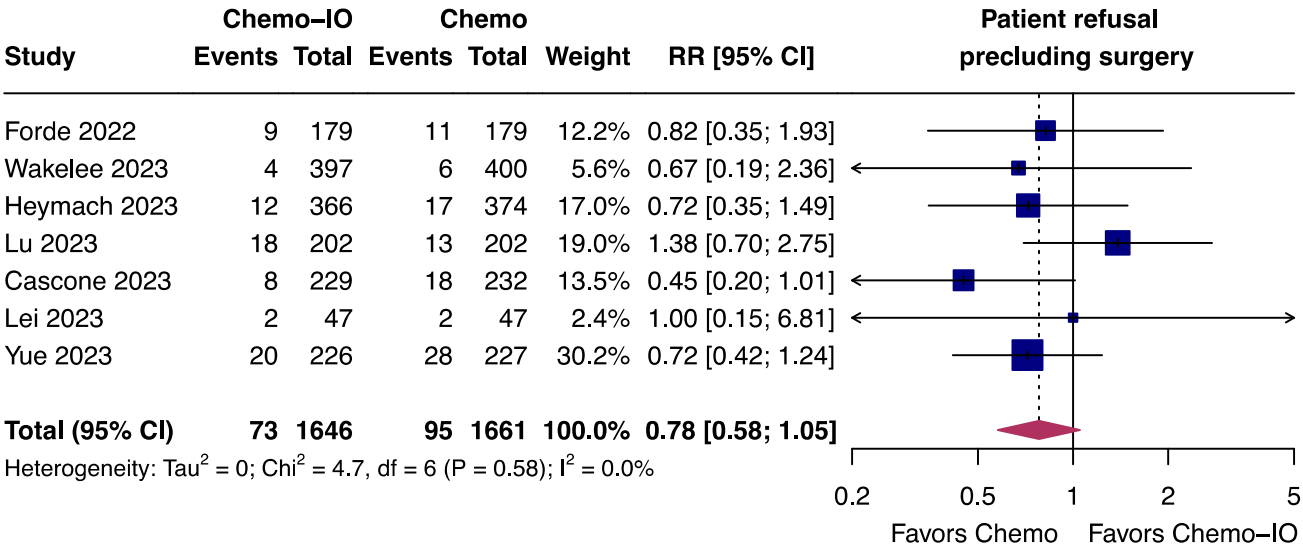
eFigure 23. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who had progression precluding surgery.



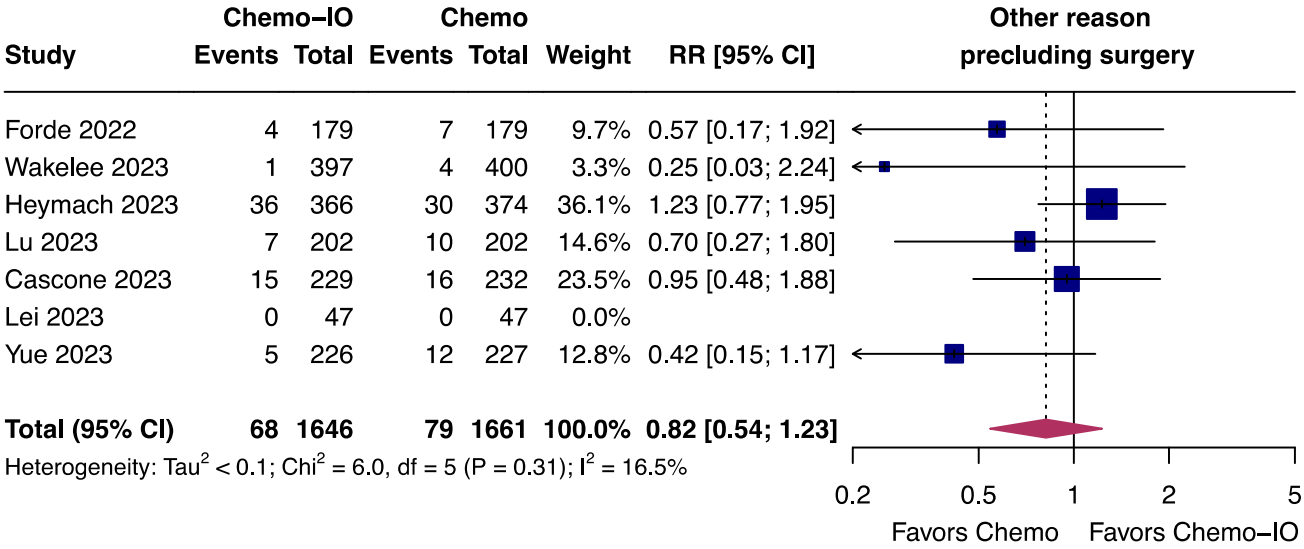
eFigure 24. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who had adverse events precluding surgery.



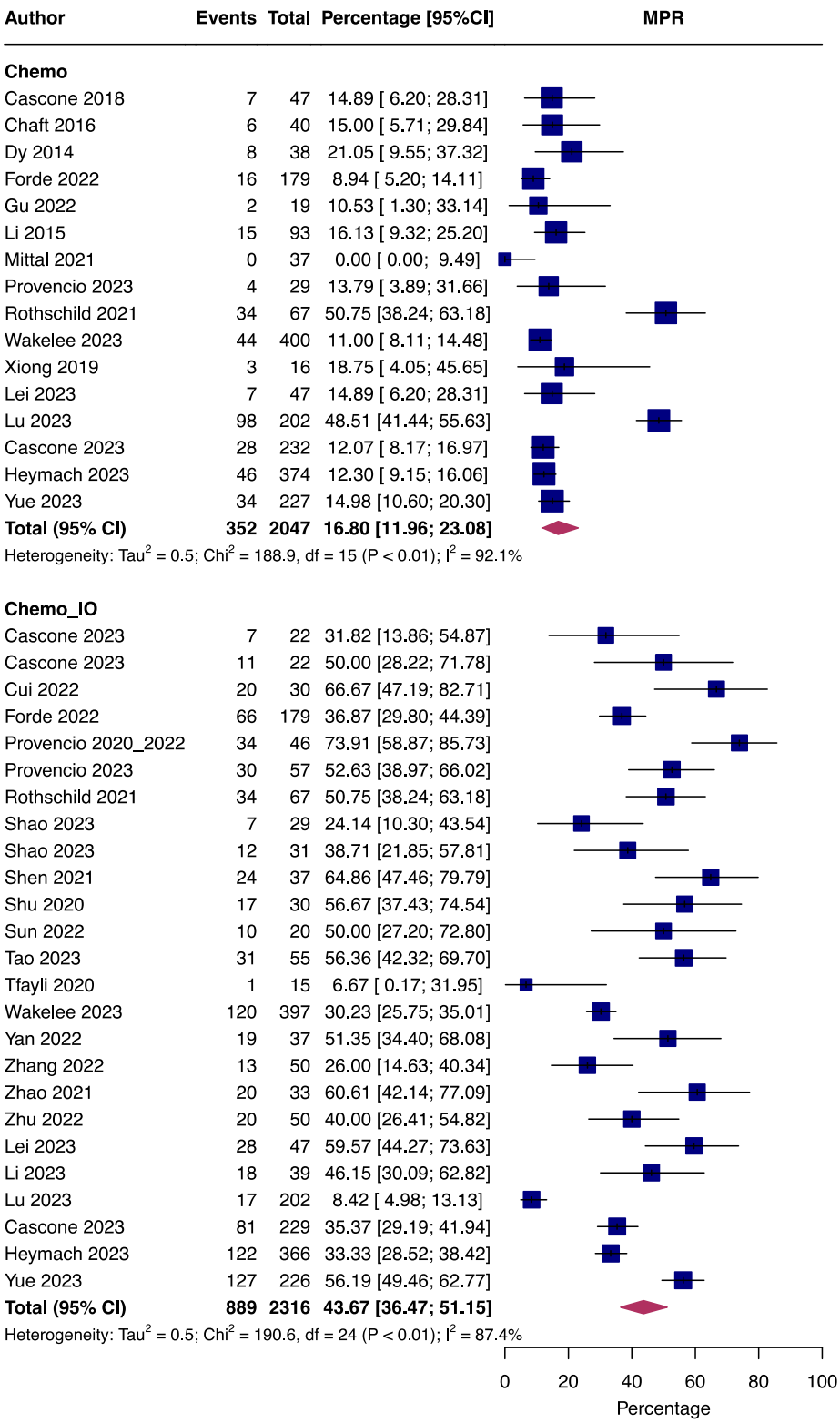
eFigure 25. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patient refusals precluding surgery.



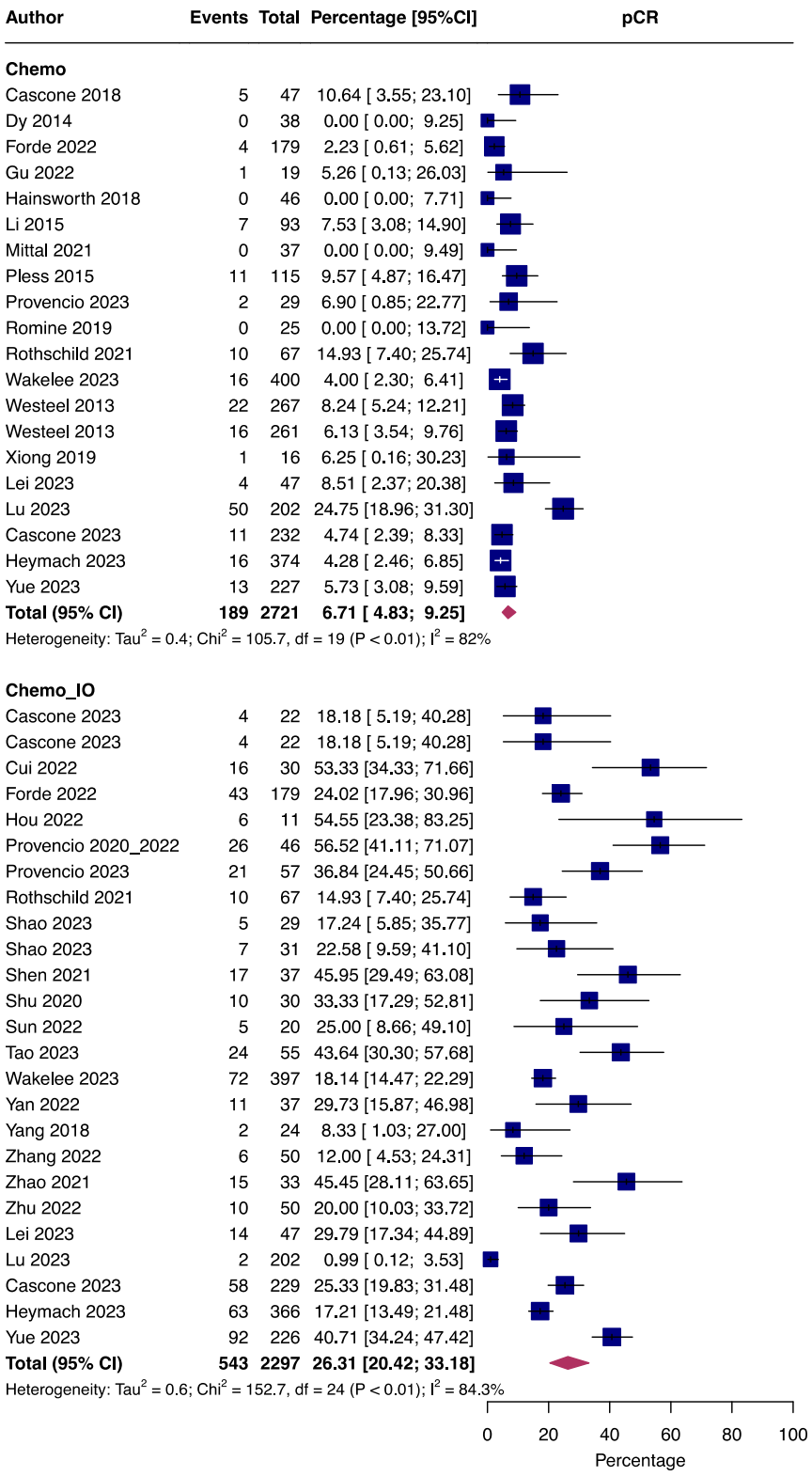
eFigure 26. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients with other reasons precluding surgery.



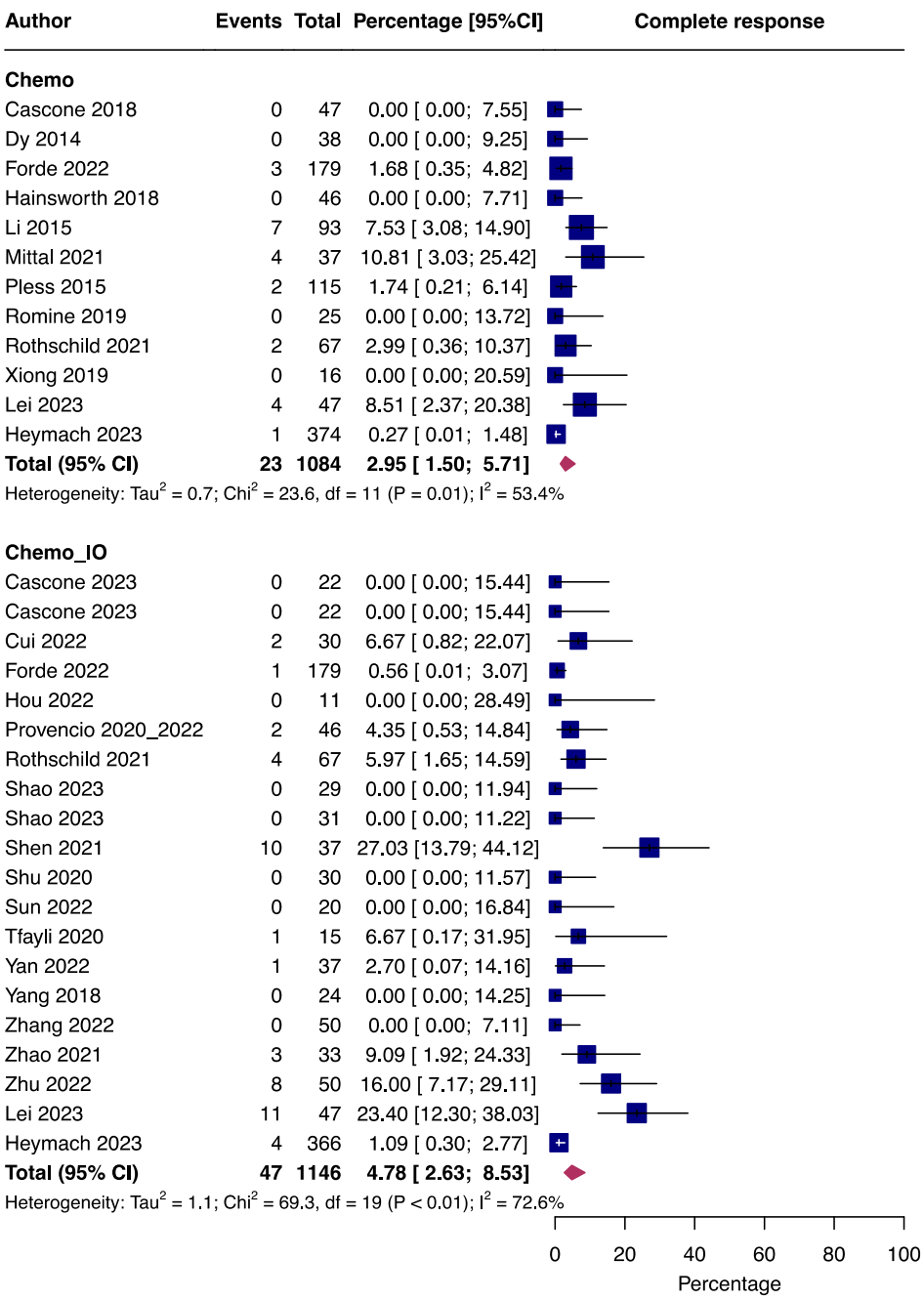
eFigure 27. Pooled proportions across all studies comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by MPR.



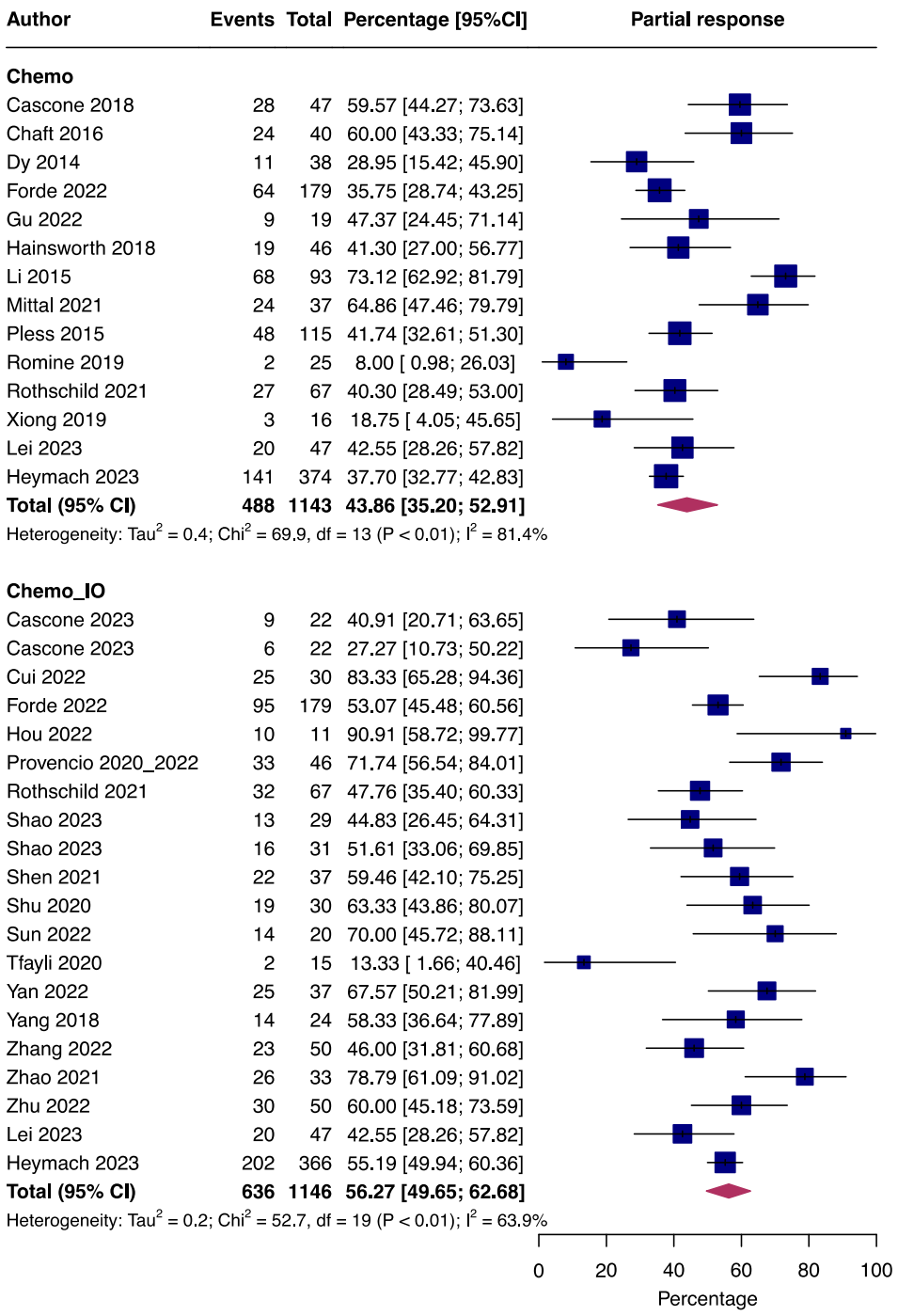
eFigure 28. Pooled proportions across all studies comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by pCR.



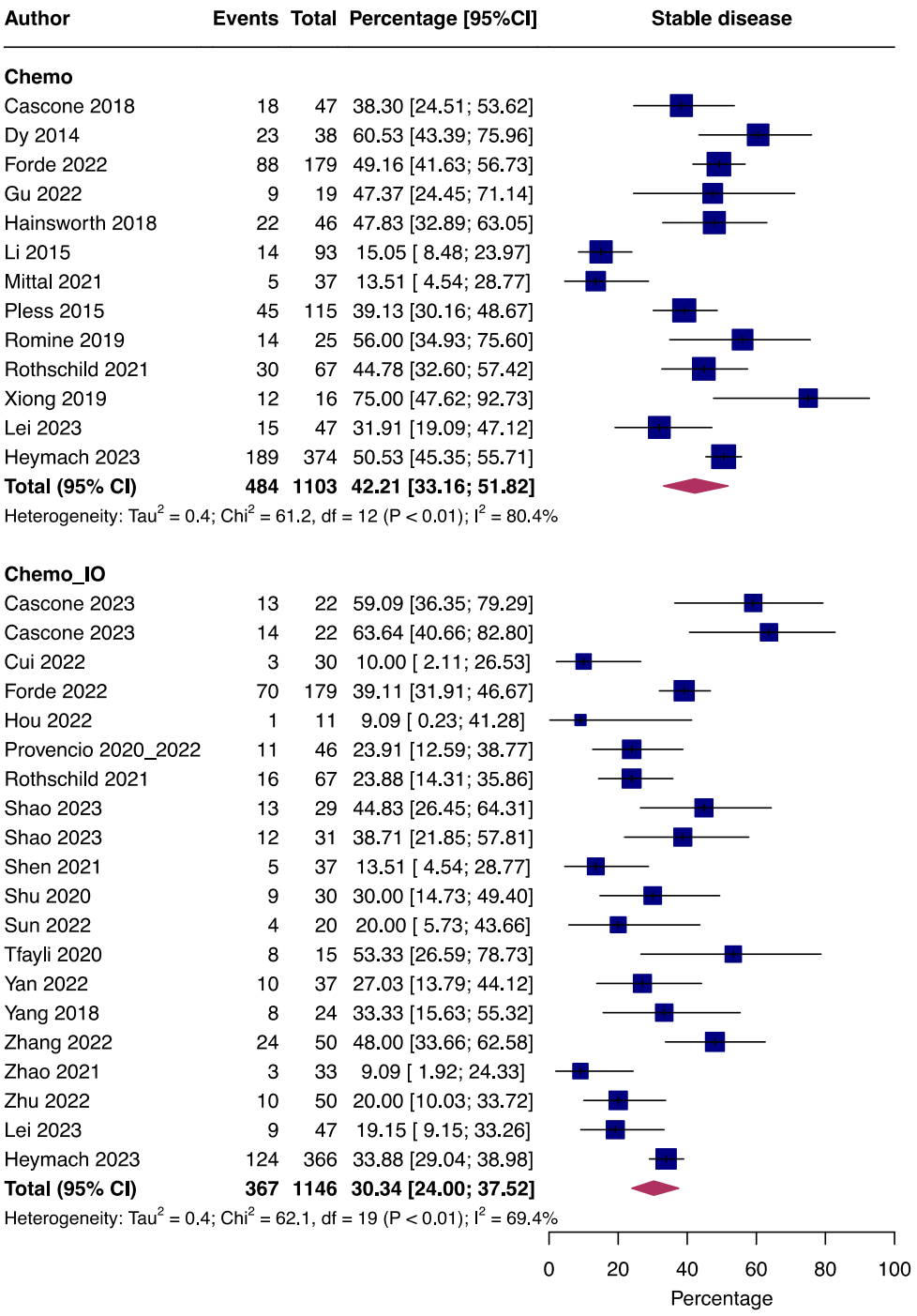
eFigure 29. Pooled proportions across all studies comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by complete response per RECIST.



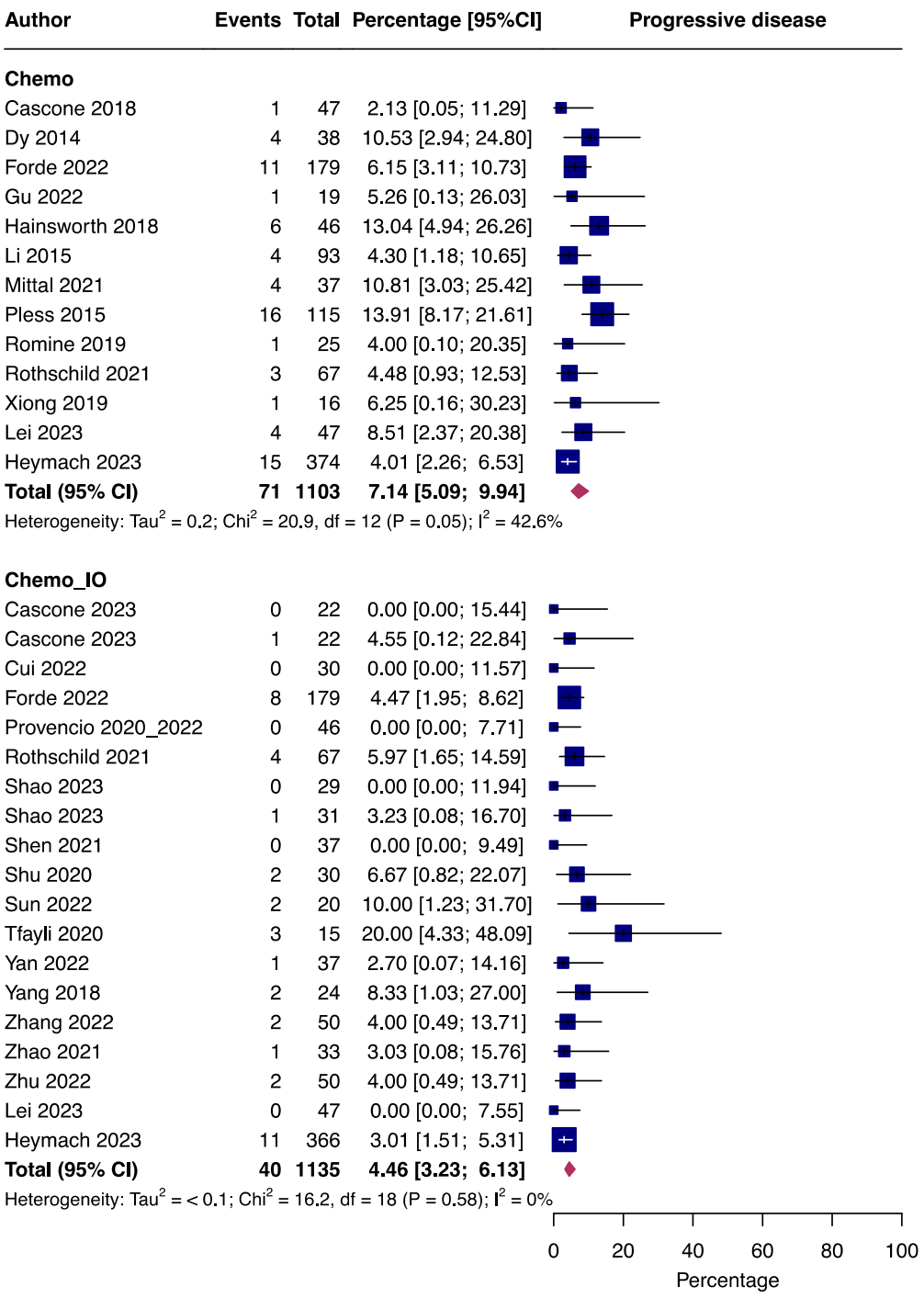
eFigure 30. Pooled proportions across all studies comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by partial response per RECIST.



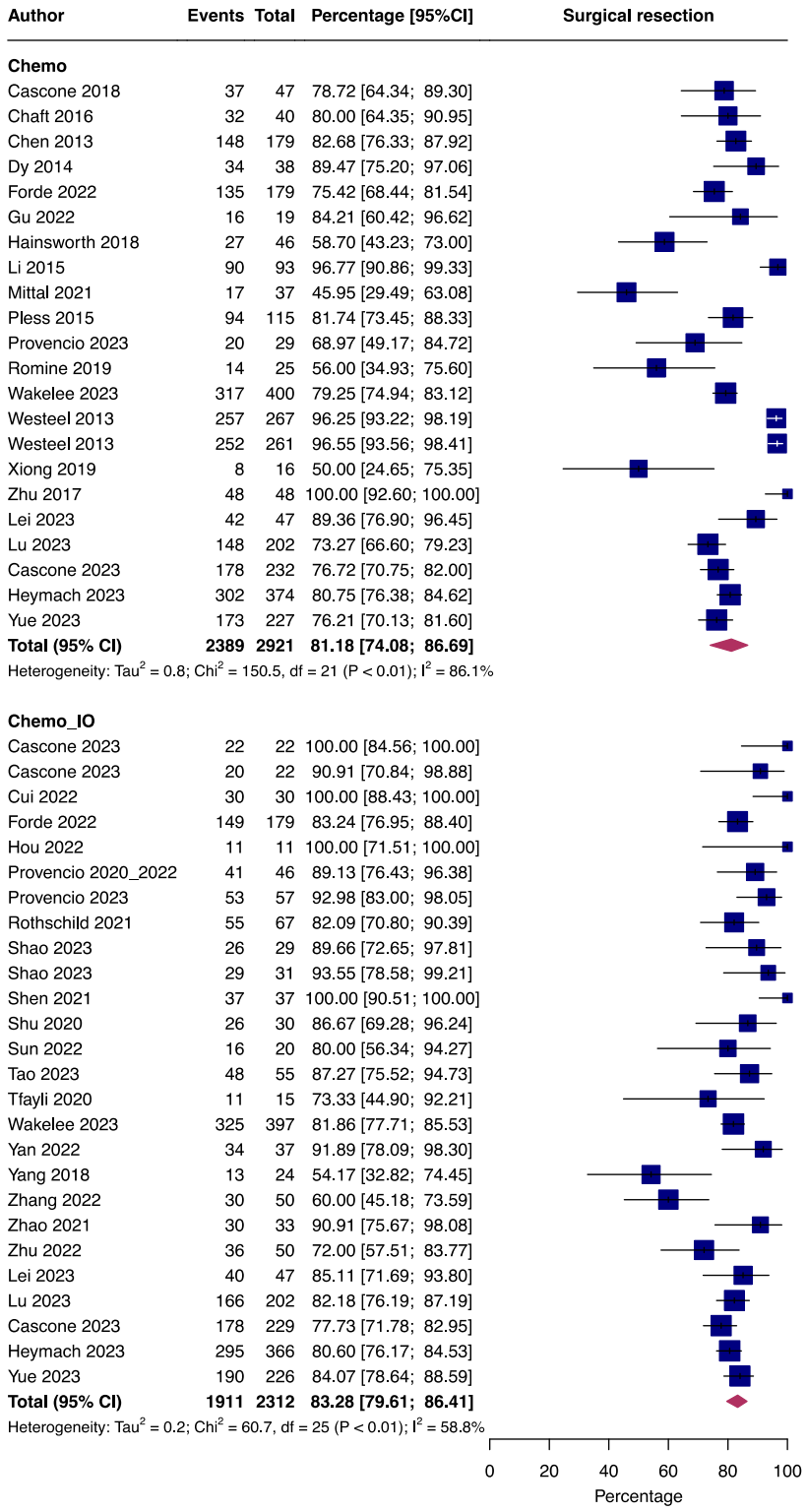
eFigure 31. Pooled proportions across all studies comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by stable disease per RECIST.



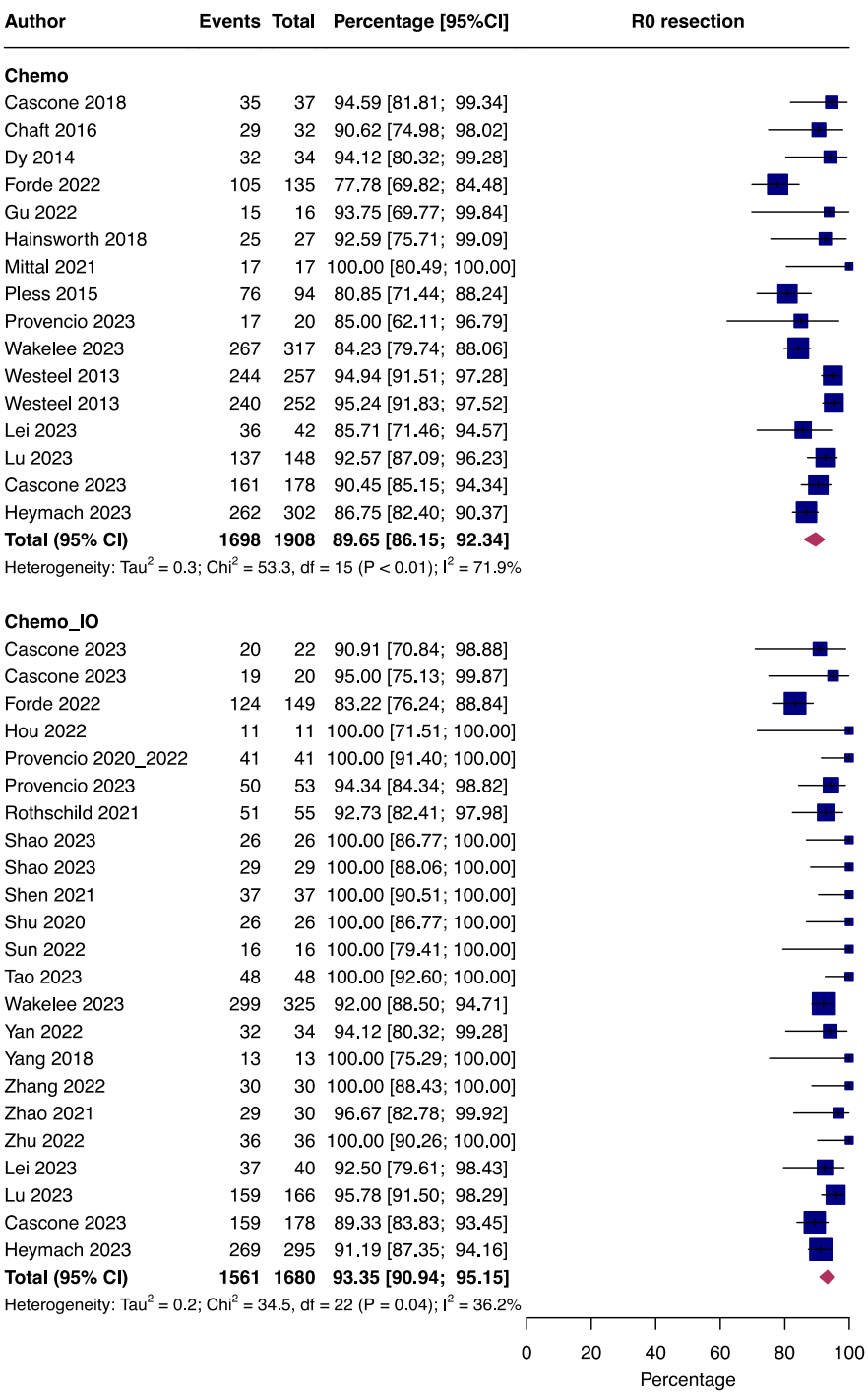
eFigure 32. Pooled proportions across all studies comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by progressive disease per RECIST.



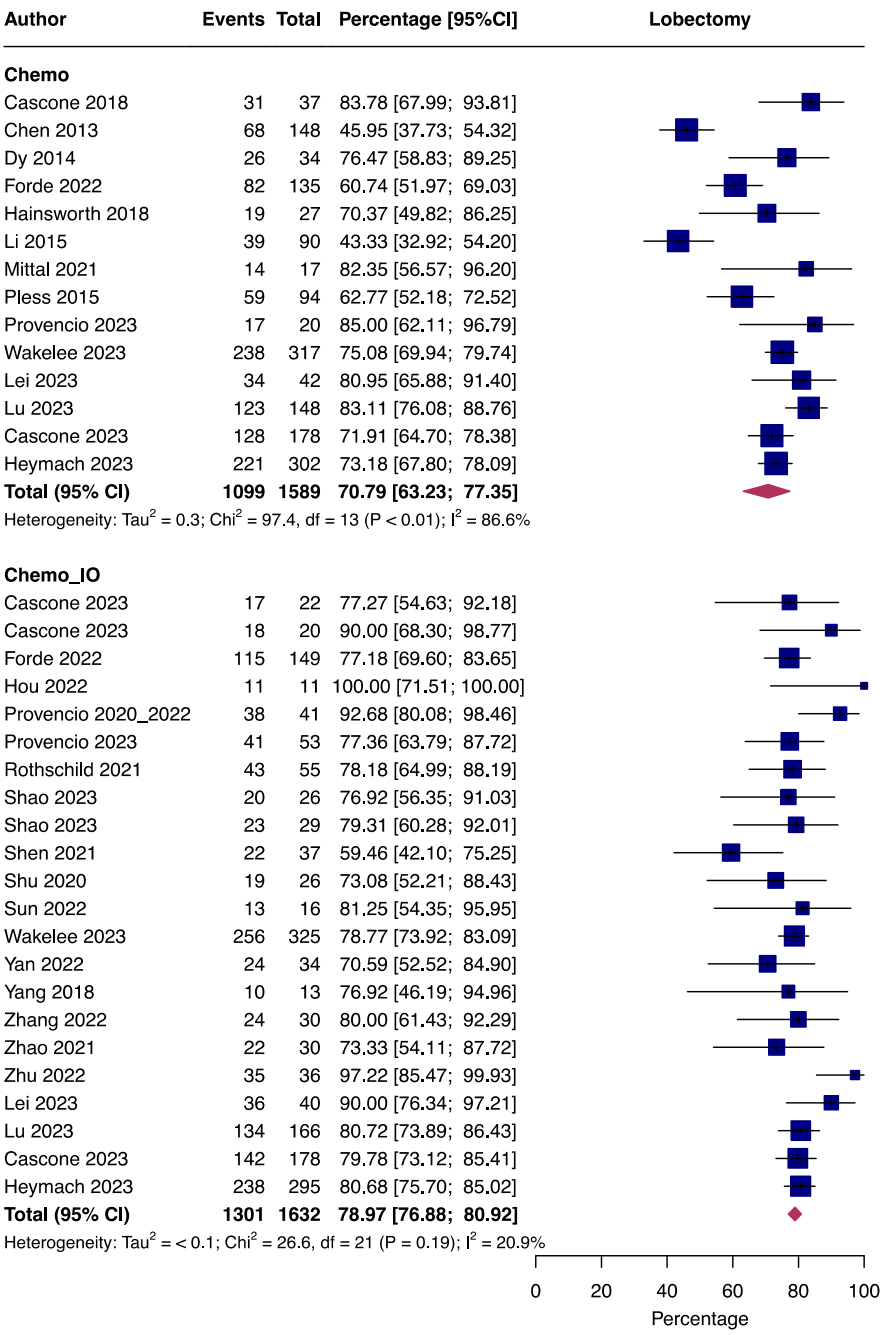
eFigure 33. Pooled proportions across all studies comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by surgical resection.



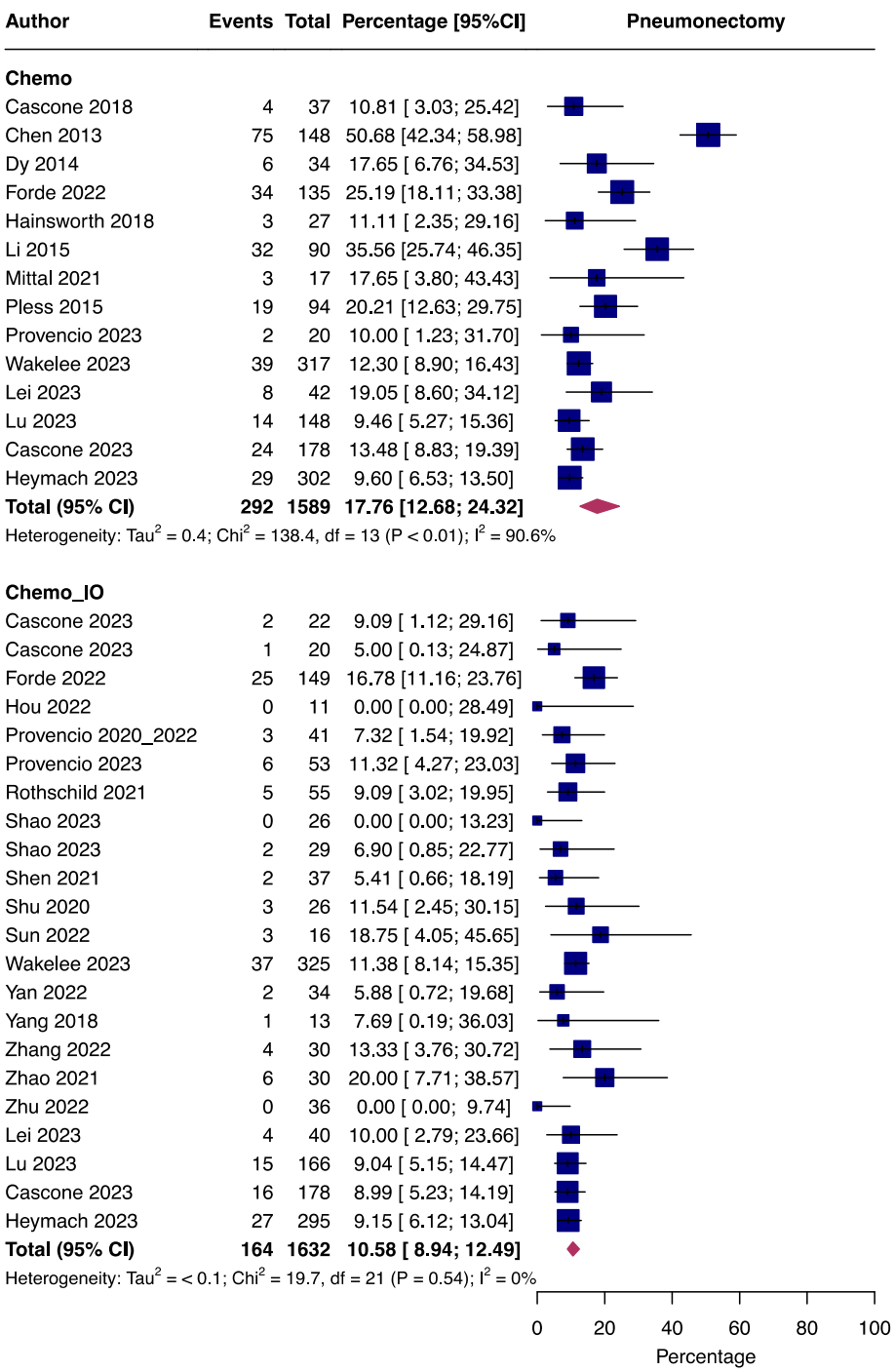
eFigure 34. Pooled proportions across all studies comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who had R0 resection.



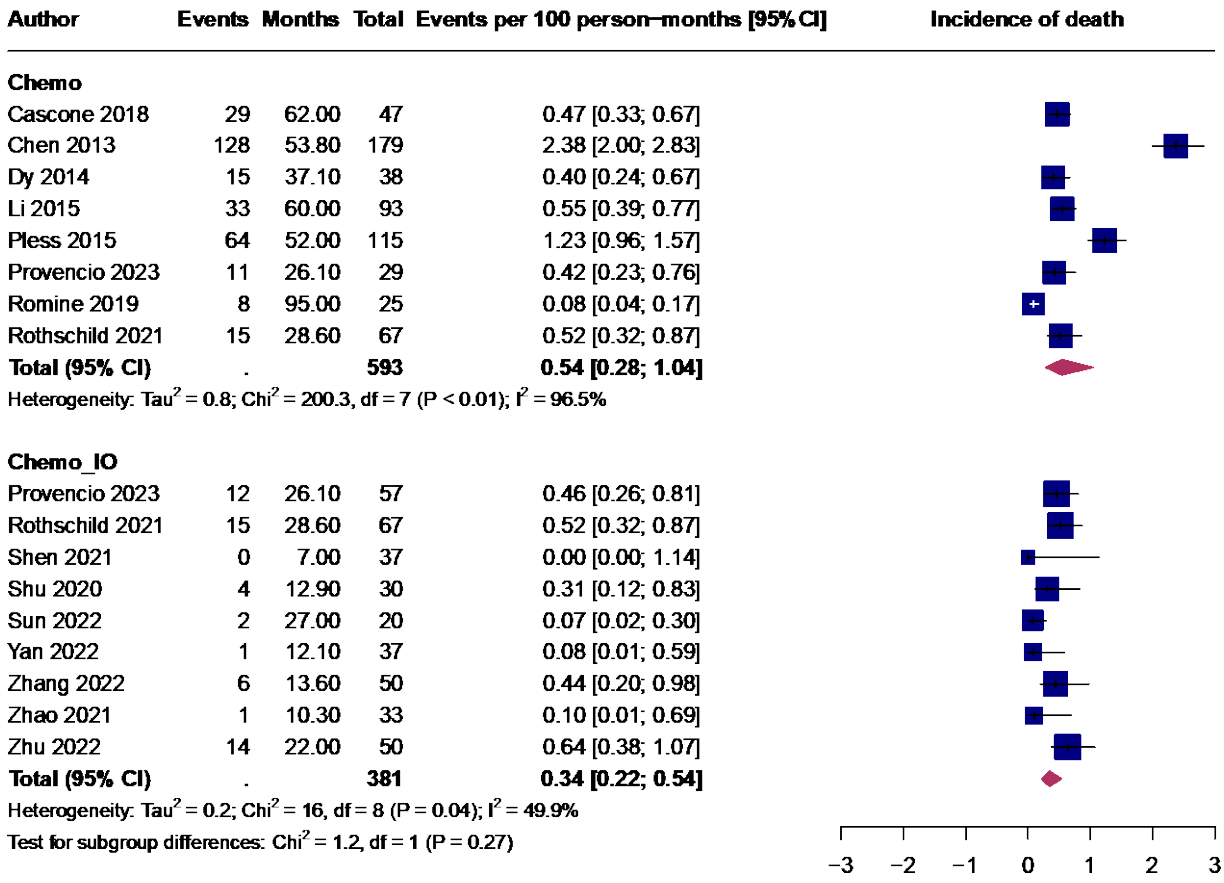
eFigure 35. Pooled proportions across all studies comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who had a lobectomy.



eFigure 36. Pooled proportions across all studies comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who had a pneumonectomy.



eFigure 37. Pooled proportions across all studies comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the incidence of death events.



eTable 1. Search strategy for Embase.

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2	(cross adj over*).tw.	38625
3	(trial* and (control* or comparative)).tw.	842069
4	((blind* or mask*) and (single or double or triple or treble)).tw.	329610
5	(treatment adj arm*).tw.	26745
6	(control* adj group*).tw.	852318
7	((phase adj (III or three)) or (phase adj (II or two))).tw.	175257
8	(versus or vs).tw.	2788454
9	rct.tw.	54724
10	Crossover Procedure/	75990
11	double blind procedure/	214267
12	single blind procedure/	52165
13	randomization/	99085
14	placebo/	414590
15	exp clinical trial/	1869347
16	parallel design/	18809
17	latin square design/	491
18	randomized controlled trial/	791270
19	"randomized controlled trial (topic)"/	264085
20	controlled clinical trial/	471606
21	"controlled clinical trial (topic)"/	13456
22	or/1-21	6567900
23	exp animal/ or exp nonhuman/ or exp animal experiment/ or exp animal model/	35123223
24	exp human/	27044216
25	23 not 24	8079007
26	22 not 25	5777199
27	(NSCLC or ((cancer or carcinoma or tumo?r* or neoplasm*) adj2 (non-small cell or nonsmall cell or).tw,kf. or lung tumor/	415333
28	lung non small cell cancer/ or non small cell lung cancer/	163890
29	27 or 28	439985
30	(neoadjuvant or neo-adjuvant or preoperative or pre-operative or induction).tw,kf.	1335880
31	exp neoadjuvant therapy/	52738
32	exp induction chemotherapy/	18384
33	30 or 31 or 32	1350877
34	(immunotherap* or chemoimmunotherap* or chemo-immunotherap*).tw,kf.	229384
35	immune checkpoint inhibitor*.tw,kf.	38043
36	exp immunological antineoplastic agent/ or immunological antineoplastic agent.tw,kf. or immune checkpoint or/	387482
37	(nivolumab or Opdivo).tw,kf,dy. or nivolumab/	39743
38	(bms 936558 or bms936558 or cmab 819 or cmab819 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or).tw,kf,dy.	1673
39	(pembrolizumab or Keytruda).tw,kf,dy. or pembrolizumab/	39062
40	(mk 3475 or mk4375 or sch 900475 or sch900475).tw,kf,dy.	733
41	cemiplimab.tw,kf,dy. or cemiplimab/	1959
42	(Libtayo or regn 2810 or regn2810 or sar 439684 or sar439684).tw,kf,dy.	225

43	durvalumab.tw,kf,dy. or durvalumab/	10884
44	(Imfinzi or medi 4736 or medi4736).tw,kf,du.	967
45	atezolizumab.tw,kf,du. or atezolizumab/	16156
46	(monoclonal antibody mpdl 3280a or monoclonal antibody mpdl3280a or mpdl 3280a or mpdl3280a or rg 7446 446 or ro 5541267 or ro5541267 or tecentriq or tecntriq).tw,kf,du.	1057
47	ipilimumab.tw,kf,du. or ipilimumab/	25821
48	(bms 734016 or bms734016 or cs 1002 or cs1002 or ibi 310 or ibi310 or "mdx 010" or mdx 101 or mdx010 or 01 or strentarga or yervoy).tw,kf,du.	1341
49	or/34-48	567967
50	chemotherap*.tw,kf.	822593
51	antineoplastic agent/ or antineoplastic agent.tw,kf.	372991
52	gemcitabine/ or (gemcitabine or Gemzar).tw,kf,dy.	76154
53	cisplatin/ or (cisplatin or platinol).tw,kf,dy.	231101
54	docetaxel/ or (docetaxel or Taxotere).tw,kf,dy.	76416
55	paclitaxel/ or (paclitaxel or Abraxane).tw,kf,dy.	140502
56	carboplatin/ or (carboplatin or Paraplatin).tw,kf,dy.	90486
57	or/50-56	1263609
58	26 and 29 and 33 and ((49 and 57) or 57)	4884
59	58 not limit 58 to conference abstracts	3025
60	limit 59 to dd=20130101-20231025	118

eTable 2. Search strategy for MEDLINE.

#	Query	Results
1	Carcinoma, Non-Small-Cell Lung/	71701
2	(NSCLC or ((cancer or carcinoma or tumo?r* or neoplasm*) adj2 (non-small cell or nonsmall cell or lung))).tw,kf.	243394
3	Lung Neoplasms/	260560
4	limit 3 to yr="1966 - 1986"	34104
5	1 or 2 or 4	273228
6	(neoadjuvant or neo-adjuvant or preoperative or pre-operative or induction).tw,kf.	944661
7	Neoadjuvant Therapy/	29030
8	exp Induction Chemotherapy/	3872
9	6 or 7 or 8	950079
10	(immunotherap* or chemoimmunotherap* or chemo-immunotherap*).tw,kf.	149010
11	immune checkpoint inhibitor*.tw,kf.	24383
12	(31yo63lbsn or bms 936558 or bms-936558 or bms936558 or mdx 1106 or mdx-1106 or mdx1106 or nivolumab or ono 4538 or ono-4538 or ono4538 or opdivo).tw,kf,nm. or Nivolumab/	9930
13	(pembrolizumab or Keytruda).tw,kf,nm. or pembrolizumab/	9254
14	exp Antineoplastic Agents, Immunological/ or antineoplastic agent immunological.tw,kf,nm.	73950
15	(cemiplimab or Libtayo).tw,kf,nm. or cemiplimab/	391
16	(durvalumab or Imfinzi).tw,kf,nm. or durvalumab/	1603
17	(atezolizumab or Tecentriq).tw,kf,nm. or atezolizumab/	3252
18	(6t8c155666 or anti ctla 4 mab ipilimumab or anti-ctla-4 mab ipilimumab or ipilimumab or ipilimumab, anti-ctla-4 mab or "mdx 010" or mdx ctla 4 or mdx-010 or mdx-ctla-4 or mdx010 or yervoy).tw,kf,nm. or Ipilimumab/	5663
19	or/10-18	222788
20	chemotherap*.tw,kf.	506937
21	gemcitabine/ or (gemcitabine or Gemzar).tw,kf,nm.	21128
22	exp Antineoplastic Agents/ or antineoplastic agents.tw,kf.	1254372
23	(cisplatin or Platinol).tw,kf,nm. or Cisplatin/	88362
24	docetaxel.tw,kf,nm. or Docetaxel/	20133
25	(15h5577cqd or 699121phca or docetaxel or docetaxel anhydrous or docetaxel hydrate or docetaxel trihydrate or docetaxol or n dibenzoyl n tert butoxycarbonyl 10 deacetyltaxol or n-debenzoyl-n-tert-butoxycarbonyl-10-deacetyltaxol or nsc 628503 or rp 56976 or rp-56976 or rp56976 or taxoltere metro or Taxotere).tw,kf,nm.	20321
26	Paclitaxel/ or (paclitaxel or Abraxane).tw,kf,nm.	45232
27	(carboplatin or Paraplatin).tw,kf,nm. or carboplatin/	20660
28	or/20-27	1563671
29	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase II or Clinical Trial, Phase III).pt.	722140
30	Randomized Controlled Trial/	601405
31	exp Randomized Controlled Trials as Topic/	168460
32	Controlled Clinical Trial/	95423
33	exp Controlled Clinical Trials as Topic/	174172
34	Randomization/	107032
35	Random Allocation/	107032
36	Double-Blind Studies/	176369
37	Single-Blind Studies/	32983
38	Placebos/	35932

39	Control Group/	2044
40	(random* or sham or placebo*).ti,ab,hw,kf.	1846289
41	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.	270225
42	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.	1687
43	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf.	1250932
44	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.	55816
45	allocated.ti,ab,hw.	85621
46	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.	45829
47	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.	12543
48	(pragmatic study or pragmatic studies).ti,ab,hw,kf.	618
49	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.	7924
50	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.	12752
51	(phase adj3 (II or III or "2" or "3") adj3 (study or studies or trial*)).ti,hw,kf.	86301
52	or/29-51	2674296
53	5 and 9 and ((19 and 28) or 28) and 52	1496
54	limit 53 to dt=20130101-20231025	524

eTable 3. Non-randomized study characteristics.

Treatment mode	First author	Publication year	NCT number	Clinical trial	Study phase	Study design	Neoadjuvent treatment regimen	Main inclusion criteria	Sample size	Proportion of males (%)	Median age, years	Proportion of SCC (%)	Proportion of stage III (%)
Chemotherapy	Chen	2013	NA	NA	NA	Single-arm	Mitomycin + cisplatin + vindesine	Stage I-IIIA resected NSCLC	179	74	61	44	37
Chemotherapy	Westeel	2013	NCT00198354	IFCT 0002	III	Single-arm	Preoperative chemotherapy	Stage IA-II resectable NSCLC	267	81	Pre: 60	Pre: 43	Pre: 0
Chemotherapy	Westeel	2013	NCT00198354	IFCT 0002	III	Single-arm	Perioperative chemotherapy	Stage IA-II resectable NSCLC	261	81	Peri: 62	Peri: 44	Peri: 0
Chemotherapy	Dy	2014	NA	NA	II	Single-arm	Cisplatin + pemetrexed	Stage IB-IIIA resectable NSCLC	38	50	62.5	26	50
Chemotherapy	Li	2015	NA	NA	NA	Single-arm	Docetaxel + cisplatin	NSCLC	93	77	NR	53	100
Chemotherapy	Pless	2015	NCT00030771	NA	III	Single-arm	Cisplatin + docetaxel	Stage IIIA N2 resectable NSCLC	115	67	59	31	100
Chemotherapy	Chaft	2016	NA	NEOSCAN	II	Single-arm	Platinum-doublet chemotherapy	Stage IB-IIIA resectable lung cancer	40	35	63	18	80
Chemotherapy	Zhao	2016	NCT02497118	NA	NA	Single-arm	Cisplatin + vinorelbine	Stage IIIA N2 resectable NSCLC	10	90	58	30	100
Chemotherapy	Zhu	2017	NA	NA	NA	Single-arm	Gemcitabine hydrochloride and cisplatin	Stage I-II NSCLC	48	54	NA	NA	0
Chemotherapy	Chen	2018	NA	NA	NA	Single-arm	Pemetrexed + cisplatin	EGFR mutant lung adenocarcinoma	43	28	NA	0	100
Chemotherapy	Hainsworth	2018	NA	NA	II	Single-arm	Pemetrexed + carboplatin	Resectable non-squamous NSCLC	46	39	65	0	52
Chemotherapy	Cascone	2018	NCT00254384	NA	II	Single-arm	Cisplatin + docetaxel	Stage I-III resectable NSCLC	47	62	64	38	40
Chemoimmunotherapy	Yang	2018	NCT01820754	TOP1201	II	Single-arm	Ipilimumab + paclitaxel + cisplatin or ipilimumab + paclitaxel + carboplatin	Stage IB-IIIA NSCLC	24	50	65	38	79
Chemotherapy	Ma	2019	NA	NA	NA	Single-arm	Docetaxel + cisplatin	Stage IIIA NSCLC	41	NA	NA	NA	100
Chemotherapy	Romine	2019	NCT00227539	NA	II	Single-arm	Cisplatin + pemetrexed	Stage IB-IIIB resectable NSCLC	25	48	62	12	76
Chemotherapy	Xiong	2019	NCT01217619	NA	NA	Single-arm	Cisplatin doublet chemotherapy + vinorelbine or gemcitabine or paclitaxel or docetaxel or permetrexed	Stage IIIA N2 NSCLC	16	63	60	0	100
Chemoimmunotherapy	Shu	2020	NCT02716038	NA	II	Single-arm	Atezolizumab + nab-paclitaxel + carboplatin	Stage IB-IIIA resectable NSLC	30	50	67	40	77
Chemoimmunotherapy	Tfayli	2020	NCT03480230	NA	NA	Single-arm	Avelumab + chemotherapy	Stage IB-IIIA resectable NSCLC	15	47	65	13	53
Chemoimmunotherapy	Shen	2021	NA	NA	NA	Single-arm	Pembrolizumab + albumin-paclitaxel + carboplatin	Stage IIB to IIIB resectable squamous NSCLC	37	95	63	100	NA
Chemotherapy	Zhu	2021	NA	NA	II	Single-arm	Nab-paclitaxel + carboplatin	Stage IIIA N2 resectable squamous NSCLC	36	100	58	100	100
Chemotherapy	Mittal	2021	NA	NA	II	Single-arm	Paclitaxel and carboplatin	Stage IB-IIIB NSCLC	37	57	55	35	81

Chemoimmunotherapy	Rothschild	2021	NCT02572843	SAKK 16/14	II	Single-arm	Durvalumab + cisplatin + docetaxel	Stage IIIA N2 NSCLC	67	52	61	33	100
Chemoimmunotherapy	Zhao	2021	NCT04304248	NA	II	Single-arm	Toripalimab + carboplatin + pemetrexed/nab-paclitaxel	Stage IIIA-IIIB resectable NSCLC	33	82	61	55	100
Chemoimmunotherapy	Zhang	2022	ChiCTR1900023758	NA	II	Single-arm	Sintilimab + carboplatin + pemetrexed or sintilimab + carboplatin + gemcitabine	Stage IB-IIIA resectable NSCLC	50	88	NA	56	100
Chemoimmunotherapy	Zhu	2022	ChiCTR190002401	LungMate 002	II	Single-arm	Toripalimab + chemotherapy	Stage II-IIIB resectable NSCLC	50	84	66	64	92
Chemoimmunotherapy	Cui	2022	NA	NA	II	Single-arm	Toripalimab + nabpaclitaxel or toripalimab + pemetrexed & carboplatin	Stage IIIA or T3-4N2 IIIB resectable NSCLC	30	80	NA	50	100
Chemoimmunotherapy	Hou	2022	NA	NA	I	Single-arm	Toripalimab + platinum-paclitaxel	Stage II-IIIB resectable NSCLC	11	91	63	82	64
Chemotherapy	Gu	2022	NCT04197076	NA	NA	Single-arm	Chemotherapy	Stage IIB-IIIB resectable NSCLC	19	84	64	63	89
Chemoimmunotherapy	Yan	2022	NCT04316364	NA	IB	Single-arm	Adebrelimab + nab-paclitaxel + carboplatin	Stage II-IIIB resectable NSCLC	37	95	63	84	70
Chemoimmunotherapy	Sun	2022	NCT04326153	NA	II	Single-arm	Sintilimab + nab-paclitaxel + carboplatin	Stage IIIA-IIIB resectable NSCLC	20	90	59.5	80	100
Chemoimmunotherapy	Cascone	2023	NCT03158129	NEOSTAR	II	Single-arm	Nivolumab + cisplatin & docetaxel or pemetrexed	Stage IB-IIIA NSCLC	22	45	69.5	23	50
Chemoimmunotherapy	Cascone	2023	NCT03158129	NEOSTAR	II	Single-arm	Ipilimumab + nivolumab + cisplatin & docetaxel or pemetrexed	Stage IB-IIIA resectable NSCLC	22	68	63.1	23	59
Chemoimmunotherapy	Li	2023	NCT04422392	NA	II	Single-arm	Sintilimab + platimum-doublet chemotherapy	Stage IIIA-N2 resectable NSCLC	39	97	62-64	67	100
Chemoimmunotherapy	Shao	2023	NCT04459611	neoSCORE	II	Single-arm	Sintilimab + chemotherapy (2 cycles)	Stage IB-IIIA NSCLC	29	86	66	66	62
Chemoimmunotherapy	Shao	2023	NCT04459611	neoSCORE	II	Single-arm	Sintilimab + chemotherapy (3 cycles)	Stage IB-IIIA NSCLC	31	74	63	55	45
Chemoimmunotherapy	Tao	2023	NCT04606303	Renaissance	II	Single-arm	Toripalimab + platinum-doublet chemotherapy	Stage IIB-IIIB NSCLC	55	91	62	80	71
Chemotherapy	Zhong	2019_2023	NCT01407822	EMERGING-CTONG 1103	II	Single-arm	Gemcitabine + cisplatin	EGFR mutant stage IIIA-N2 resectable NSCLC	35	23	58	NA	100
Chemoimmunotherapy	Provencio	2020_2022	NCT03081689	NADIM	II	Single-arm	Nivolumab + paclitaxel + carboplatin	Stage IIIA resectable NSCLC	46	74	63	35	100

eTable 4. Johanna Brigs bias assessment.

Author (Year)	1. Were the two/three groups similar and recruited from the same population?	2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	3. Was the exposure measured in a valid and reliable way?	4. Were confounding factors identified?	5. Were strategies to deal with confounding factors stated?	6. Were the groups/participants free of the outcome at the start of the study?	7. Were the outcomes measured in a valid and reliable way?	8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	10. Were strategies to address incomplete follow up utilized?	11. Was appropriate statistical analysis used?
Cascone (2018)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Cascone (2023)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Chaft (2016)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Chen (2013)	N/A	N/A	N/A	U	Y	Y	Y	Y	Y	N/A	Y
Chen (2018)	N/A	N/A	N/A	N	N/A	Y	Y	Y	Y	N/A	Y
Cui (2022)	N/A	N/A	N/A	N	N/A	Y	Y	N/A	N/A	N/A	Y
Dy (2014)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Gu (2022)	N/A	N/A	N/A	U	U	Y	Y	Y	N	U	Y
Hainsworth (2018)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Hou (2022)	N/A	N/A	N/A	U	U	Y	Y	Y	Y	N/A	Y
Li (2015)	N/A	N/A	N/A	N	N/A	Y	Y	Y	Y	N/A	Y
Li (2023)	N/A	N/A	N/A	U	U	Y	Y	U	N	U	Y
Ma (2019)	N/A	N/A	N/A	N	N/A	Y	Y	U	U	U	Y
Mittal (2021)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Pless (2015)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Provencio (2020)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Provencio (2022)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Romine (2019)	N/A	N/A	N/A	N	N/A	Y	Y	Y	Y	N/A	Y
Rothschild (2021)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Shao (2023)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Shen (2021)	N/A	N/A	N/A	U	U	Y	Y	N	U	U	Y
Shu (2020)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Sun (2022)	N/A	N/A	N/A	U	U	Y	Y	N	N	N	Y
Tao (2023)	N/A	N/A	N/A	N	N/A	Y	Y	N	U	Y	
Tfayli (2020)	N/A	N/A	N/A	N	N/A	Y	Y	U	U	U	Y
Westeel (2013)	N/A	N/A	N/A	N	N/A	Y	Y	Y	Y	N/A	Y
Xiong (2019)	N/A	N/A	N/A	N	N/A	Y	Y	U	N	U	Y
Yang (2018)	N/A	N/A	N/A	N	N/A	Y	Y	U	U	U	Y
Yan (2022)	N/A	N/A	N/A	U	U	Y	Y	Y	N	U	Y

Zhang (2022)	N/A	N/A	N/A	U	U	Y	Y	Y	N	U	Y
Zhao (2016)	N/A	N/A	N/A	U	U	Y	Y	U	N	U	Y
Zhao (2021)	N/A	N/A	N/A	N	N/A	Y	Y	N	U	U	Y
Zhong (2019)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Zhong (2023)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Zhu (2017)	N/A	N/A	N/A	N	N/A	Y	U	Y	U	U	Y
Zhu (2021)	N/A	N/A	N/A	U	U	Y	Y	Y	Y	N/A	Y
Zhu (2022)	N/A	N/A	N/A	N	N/A	Y	Y	N	N	U	Y

eTable 5. Surgical and efficacy outcomes for RCTs.

First author	ITT Chemo IO	ITT Chemo	Surgical resection Chemo IO	Surgical resection Chemo	R0 resection Chemo IO	R0 resection Chemo	MPR Chemo IO	MPR Chemo	pCR Chemo IO	pCR Chemo	Median follow up time (months)	PFS/EFS HR	OS HR
Forde 2022	179	179	149	135	124	105	66	16	43	4	41.4	0.68 (95% 0.49-0.93)	0.57 (95% CI 0.38-0.87)
Wakelee 2023	397	400	325	317	299	267	120	44	72	16	36.6	0.59 (95% 0.48-0.72)	0.72 (95% CI 0.56-0.93)
Heymach 2023	366	374	295	302	269	262	122	46	63	16	11.7	0.68 (95% CI 0.53-0.88)	NA
Provencio 2023	57	29	53	20	50	17	30	4	21	2	26.1	0.47 (95% CI 0.25-0.88)	0.43 (95% CI 0.19-0.98)
Lu 2023	202	202	166	148	159	137	98	17	50	2	18.25	0.4 (95% CI 0.27-0.57)	0.62 (95% CI 0.38-0.999)
Cascone 2023	229	232	178	178	159	161	81	28	58	11	25.4	0.59 (95% CI 0.44-0.79)	NA
Lei 2023	47	47	40	42	37	36	28	7	14	4	14.1	0.52 (95% CI 0.21-1.29)	NA
Yue 2023	226	227	190	173	NA	NA	127	34	92	13	16.8	NA	NA

eTable 6. Definition of EFS, PFS and criteria used for pathological endpoints. Abbreviations: EFS, event-free survival; PFS, progression-free survival; irPRC, immune-related pathologic response criteria; IASLC, International Association for the Study of Lung Cancer.

First author	EFS or PFS definition	Pathological endpoints criteria
Forde 2022	Event-free survival was defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression of disease in the absence of surgery, or death from any cause; data on patients with subsequent therapy were censored at the last tumor assessment that could be evaluated on or before the date of subsequent therapy. EFS was based on BICR assessment per RECIST v1.1	irPRC
Wakelee 2023	Event-free survival was defined the time from randomization to the first occurrence of local progression that precluded the planned surgery, unresectable tumor, progression or recurrence according to the Response Evaluation Criteria in Solid Tumors, version 1.1, by the investigator's assessment, or death from any cause	IASLC 2020
Provencio 2023	Progression-free survival was defined as the time from randomization to progression of disease, recurrence of disease, or death from any cause	NA
Heymach 2023	Event-free survival was defined as the time from randomization to the earliest of the following: progressive disease that precluded surgery, progressive disease that was discovered and reported by the investigator when attempting surgery and that prevented completion of the surgery, local or distant recurrence assessed independently according to RECIST, or death from any cause.	IASLC 2020
Lu 2023	EFS is defined as the time from randomization until radiographic disease progression, local progression precluding surgery, inability to resect the tumor, local or distant recurrence, or death due to any cause.	NA
Cascone 2023	NA	irPRC
Lei 2023	EFS (defined as the time from randomization to the first occurrence of disease progression or recurrence, or death from any cause	NA
Yue 2023	NA	NA

eTable 7. Reasons precluding surgery.

First author	ITT Chemo IO	ITT Chemo	Did not receive surgery, n (%) Chemo IO	Did not receive surgery, n (%) Chemo	Disease progression, n(%) Chemo IO	Disease progression, n(%) Chemo	Patient refusal, n(%) Chemo IO	Patient refusal, n(%) Chemo	Adverse event, n(%) Chemo IO	Adverse event, n(%) Chemo	Other, n (%) Chemo IO	Other, n (%) Chemo
Forde 2022	179	179	30 (16.8)	44 (24.6)	12 (6.7)	17 (9.5)	9 (5.0)	11 (6.1)	2 (1.1)	1 (0.6)	4 (2.2)	7 (3.9)
Wakelee 2023	397	400	72 (18.1)	83 (20.8)	10 (2.5)	17 (4.3)	4 (1.0)	6 (1.5)	8 (2.0)	1 (0.3)	1 (0.3)	4 (1.0)
Heymach 2023	366	374	71 (19.4)	72 (19.3)	27 (7.4)	30 (8.0)	12 (3.3)	13 (3.5)	7 (1.9)	5 (1.3)	22 (6.0)	23 (6.1)
Provencio 2023	57	29	4 (7.0)	9 (31.0)	0 (0)	4 (13.8)	1 (1.8)	0 (0)	1 (1.8)	1 (1.8)	2 (3.5)	4 (13.8)
Lu 2023	202	202	36 (17.8)	54 (26.7)	5 (2.5)	31 (15.3)	18 (8.9)	13 (6.4)	6 (3.0)	0 (0)	7 (3.5)	10 (5.0)
Cascone 2023	229	232	51 (22.3)	54 (23.3)	13 (5.7)	22 (9.5)	11 (4.8)	18 (7.8)	7 (3.1)	4 (1.7)	15 (6.6)	16 (6.9)
Lei 2023	47	47	7 (14.9)	5 (2.1)	0 (0)	1 (2.1)	2 (4.3)	2 (4.3)	0 (0)	0 (0)	0 (0)	0 (0)
Yue 2023	226	227	36 (15.9)	54 (23.8)	5 (2.2)	12 (5.3)	20 (8.8)	28 (12.3)	6 (2.7)	2 (0.9)	5 (2.2)	12 (5.3)