# **Supplemental Online Content**

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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.

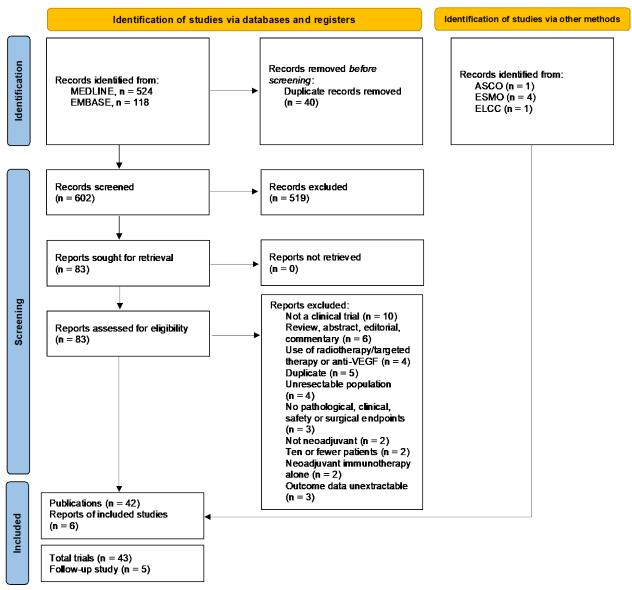
#### **Extracted Data**

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.

				Risk of bia	s domains		
		D1	D2	D3	D4	D5	Overall
	Forde 2022	+	+	+	+	+	+
	Wakelee 2023	+	+	+	+	+	+
	Provencio 2023	+	+	+	+	+	+
Study	Heymach 2023	+	+	+	+	-	-
Str	Lei 2023	-	+	+	+	+	-
	Lu 2023	+	+	?	+	?	?
	Cascone 2023	+	+	?	+	?	?
	Yue 2023	+	+	?	+	?	?

Domains:

D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.

D3: Bias due to missing outcome data. D4: Bias in measurement of the outcome.

D5: Bias in selection of the reported result.

Judgement

Some concerns

Low

? No information

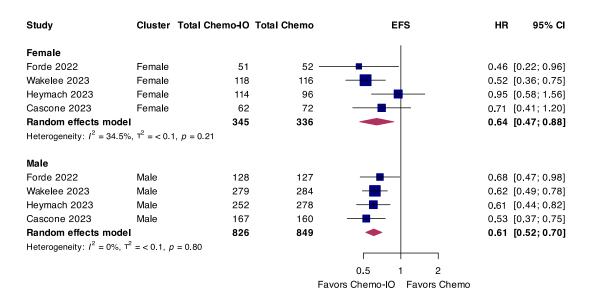
eFigure 3. Pooled hazard ratios of EFS across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by geographic region. \$For Wakelee 2023, the geographic region was East Asia.

Study	Cluster	Total Chemo-IO	Total Chemo	EFS	HR	95% CI
Forde 2022	North America	41	50	<del></del>	0.78	[0.38; 1.62]
Heymach 2023	North America	43	43	<del></del>	0.69	[0.27; 1.62]
Cascone 2023	North America	23	21	<del></del>	0.59	[0.25; 1.38]
Random effects model		107	114		0.69	[0.43; 1.10]
Heterogeneity: $I^2 = 0\%$ , $T^2$	=<0.1, p = 0.88	3				
Europe						
Forde 2022	Europe	41	25	<del></del>	0.80	[0.36; 1.77]
Heymach 2023	Europe	141	140	<del></del>	0.75	[0.49; 1.14]
Provencio 2023	Europe	57	29		0.47	[0.25; 0.88]
Cascone 2023	Europe	123	127	— <del>—</del>	0.61	[0.40; 0.92]
Random effects model		362	321	•	0.65	[0.50; 0.83]
Heterogeneity: $I^2 = 0\%$ , $T^2$	= < 0.1, p = 0.61	I				
Asia						
Forde 2022	Asia	85	92	-	0.45	[0.29; 0.71]
Wakelee 2023\$	Asia	123	121	-	0.63	[0.44; 0.91]
Heymach 2023	Asia	142	163	-	0.62	[0.41; 0.93]
Lu 2023	Asia	202	202	-	0.39	[0.27; 0.57]
Cascone 2023	Asia	65	50		0.47	[0.26; 0.86]
Random effects model		617	628	•	0.51	[0.41; 0.63]
Heterogeneity: $I^2 = 8.2\%$ ,	$T^2 = < 0.1, p = 0.$	36				
				į.		

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

Study	Cluster Tot	al Chemo-IO	Total Chemo	EI	FS	HR	95% CI
<65yr							
Forde 2022	<65yr	93	83		0.	57	[0.35; 0.93]
Wakelee 2023	<65yr	221	214		0.	51	[0.39; 0.67]
Random effects mode	I	314	297		0.	52	[0.41; 0.66]
Heterogeneity: $I^2 = 0\%$ , T	$^2 = < 0.1, p = 0$	.70					
≥65yr							
Forde 2022	≥65yr	86	96		<del> </del> 0.	.70	[0.45; 1.08]
Wakelee 2023	≥65yr	176	186		0.	70	[0.52; 0.92]
Random effects mode	I	262	282		0.	70	[0.55; 0.88]
Heterogeneity: $I^2 = 0\%$ , T	$^2 = < 0.1, p = 0$	.98					
				0.5	1 2		
				Favors Chemo-IO	Favors Chemo		

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.

	1 2	J	1.2	_	03					
Study	Cluster	Total Chemo-IO	Total Chemo		EFS			HR	95% CI	
Nonsquamous										
Forde 2022	Nonsquamous	92	84		_			0.50	[0.32; 0.79]	
Wakelee 2023	Nonsquamous	226	227		-			0.66	[0.51; 0.86]	
Heymach 2023	Nonsquamous	196	179		-			0.69	[0.48; 0.99]	
Provencio 2023	Nonsquamous	36	15		-			0.35	[0.15; 0.81]	
Lu 2023	Nonsquamous	45	45	_	-			0.54	[0.27; 1.10]	
Cascone 2023	Nonsquamous	113	114		-			0.72	[0.49; 1.07]	
Random effects mo	del	708	664		•			0.63	[0.54; 0.74]	
Heterogeneity: $I^2 = 0$ %	6, $T^2 = < 0.1$ , $p = 0.57$									
Squamous										
Forde 2022	Squamous	87	95		-			0.77	[0.49; 1.22]	
Wakelee 2023	Squamous	171	173					0.51	[0.38; 0.69]	
Heymach 2023	Squamous	169	191		-			0.71	[0.49; 1.03]	
Provencio 2023	Squamous	21	14	-	-	_		0.63	[0.24; 1.63]	
Lu 2023	Squamous	157	157		_			0.35	[0.24; 0.53]	
Cascone 2023	Squamous	116	118	-				0.46	[0.30; 0.72]	
Random effects mo	odel	721	748		•			0.54	[0.42; 0.70]	
Heterogeneity: $I^2 = 46$	$6.5\%$ , $T^2 = < 0.1$ , $p = 0$ .	10								
					1 1					
				0.2	0.5 1	2	5			
				Favors	Chemo-IO F	avors Ch	emo			

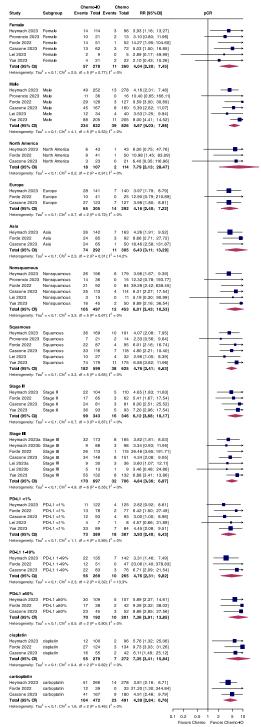
eFigure 7. Pooled hazard ratios of EFS across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by chemotherapy type.

Study	Cluster	Total Chemo-IO	Total Chemo		EFS	HR	95% CI
cisplatin							
Forde 2022	cisplatin	124	134	-	-	0.71	[0.49; 1.03]
Heymach 2023	cisplatin	100	96			0.59	[0.35; 1.00]
Cascone 2023	cisplatin	55	42		<del>-  </del>	0.61	[0.35; 1.08]
Random effects mode	el	279	272	<b>⋖</b>	<b></b>	0.66	[0.50; 0.86]
Heterogeneity: $I^2 = 0\%$ ,	$T^2 = < 0.1, p =$	0.83					
carboplatin							
Forde 2022	carboplatir	າ 39	33	-		0.31	[0.14; 0.67]
Heymach 2023	carboplatir	n 266	278	-	-	0.73	[0.54; 0.98]
Cascone 2023	carboplatir	n 167	180	-	_	0.53	[0.37; 0.75]
Random effects mode	əl	472	491		<b>-</b>	0.55	[0.37; 0.82]
Heterogeneity: $I^2 = 59.7^\circ$	$\%$ , $T^2 = < 0.1$ ,	p = 0.08					
				0.2 0.5	1 2	5	
				avors Chemo-	IO Favors Ch	nemo	

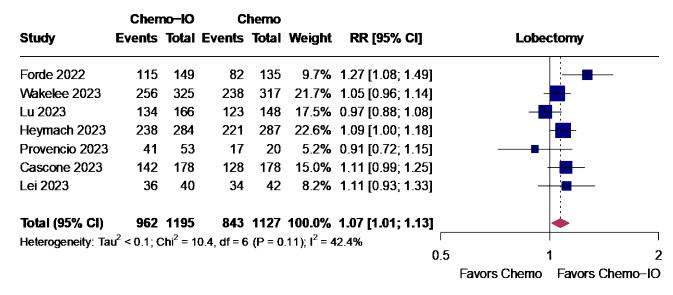
eFigure 8. Pooled risk ratios of MPR across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by sex, geographic region, histology, stage, PD-L1 status and chemotherapy type.

		• J P	٠.				
Study	Subgroup	Chen Events			nemo Total	RR [95%CI]	MPR
leymach 2023	Female	28	114	10	96	2.36 [1.21; 4.60]	<b></b>
orde 2022	Female	19	51	6	52	3.23 [1.40; 7.42]	
ei 2023	Female	6	9	1	5	3.33 [0.54; 20.43]	<del>  _•</del>
ue 2023 otal (95% CI)	Female	7 <b>60</b>	21 195	3 <b>20</b>	22 175	2.44 [0.73; 8.22] 2.67 [1.68; 4.25]	
	$a^2 = < 0.1$ ; $Chi^2 = 0$					2.07 [1.00, 4.25]	
Male							
leymach 2023	Male	94	252	36	278	2.88 [2.04; 4.06]	-
orde 2022	Male	47	128	10	127	4.66 [2.47; 8.82]	
ei 2023	Male	22	34	6	40	4.31 [1.98; 9.39]	-
'ue 2023 'otal (95% Cl)	Male	120 <b>283</b>	205 <b>619</b>	31 <b>83</b>	205 <b>650</b>	3.87 [2.74; 5.46] 3.56 [2.82; 4.50]	•
leterogeneity: Tau	$i^2 = < 0.1$ ; $Chi^2 = :$	2.6, df = 3	(P = 0.	46); $I^2 = 0$	%		
lorth America							
leymach 2023	North America	9 13	43 41	8 5	43 50	1.12 [0.48; 2.64]	<del>-</del> -
orde 2022 otal (95% CI)	North America	22	84	13	93	3.17 [1.23; 8.16] 1.85 [0.67; 5.10]	
	$u^2 = 0.3$ ; $Chi^2 = 2.3$					1100 [0107; 0170]	
urope							
leymach 2023	Europe	51	141	17	140	2.98 [1.81; 4.89]	-
orde 2022	Europe	18	41	2	25		
otal (95% CI) eterogeneity: Tau	i <sup>2</sup> = < 0.1; Chi <sup>2</sup> = i	69 0.7. df = 1	182 P = 0.	19 41): I <sup>2</sup> = 0	165 %	3.20 [2.00; 5.10]	
	, 0	, =====	0.	.,,. = 0	-		
sia eymach 2023	Asia	53	142	19	163	3.20 [1.99; 5.14]	
orde 2022	Asia	33	85	8	92	4.46 [2.19; 9.12]	
otal (95% CI)	2 .04 21 2	86	227	27	255	3.54 [2.39; 5.26]	-
eterogeneity: Tau	i <sup>2</sup> = < 0.1; Chi <sup>2</sup> = i	U.6, df = 1	(P = 0.	45); I* = 0	%6		
onsquamous	Nonograma		100	4.0	170	4 57 [0 47: 0 17]	_
eymach 2023 orde 2022	Nonsquamous Nonsquamous	55 36	196 92	11 3	179 84	4.57 [2.47; 8.44] 10.96 [3.50; 34.26	,   -
ei 2023	Nonsquamous	7	15	1	11	5.13 [0.73; 35.92]	
ue 2023	Nonsquamous	18	45	5	50	4.00 [1.62; 9.89]	
otal (95% CI)		116	348	20	324	5.10 [3.25; 8.01]	-
eterogeneity: Tau	1 <sup>2</sup> = < 0.1; Chi <sup>2</sup> = :	z.1, df = 3	P = 0.	55); I* = 0	%		
quamous	Caucam		100	0.5	101	0 40 14 50- 0 0 2	_
eymach 2023 orde 2022	Squamous Squamous	66 30	169 87	35 13	191 95	2.13 [1.50; 3.04] 2.52 [1.41; 4.51]	
ei 2023	Squamous	20	27	6	32	3.95 [1.86; 8.41]	
'ue 2023	Squamous	107	179	29	175	3.61 [2.53; 5.14]	-
otal (95% CI)	i <sup>2</sup> = < 0.1; Chi <sup>2</sup> = :	223 5.2 df = 3	462 P - 0	83 16): I <sup>2</sup> = 4	493	2.85 [2.09; 3.90]	•
	. =<0.1, OIII =:	v.c, ul = 3	, = U.	.0), 1 = 4	176		
tage II leymach 2023	Stage II	36	104	12	110	3.17 [1.75; 5.76]	
orde 2022	Stage II	20	65	5	62	3.82 [1.53; 9.54]	
ue 2023	Stage II	49	93	17	93	2.88 [1.80; 4.62]	-
otal (95% CI)	i <sup>2</sup> = < 0.1; Chi <sup>2</sup> = i	105	262 P = 0	34 86): 1 <sup>2</sup> = 0	265	3.09 [2.20; 4.36]	-
	. = < 0.1, 0111 =1	, ul = 2	. = 0.	,. = U			
itage III leymach 2023a	Stage III	62	173	21	165	2.82 [1.80; 4.40]	
leymach 2023b		24	88	13	98	2.06 [1.12; 3.79]	
orde 2022	Stage III	46	113	11	115	4.26 [2.33; 7.79]	
ei 2023a	Stage III	20	30	5	36	4.80 [2.05; 11.25]	
ei 2023b	Stage III	8	13	2	9	2.77 [0.76; 10.12]	+
ue 2023 otal (95% Cl)	Stage III	77 <b>237</b>	132 549	17 <b>69</b>	132 555	4.53 [2.84; 7.22] 3.40 [2.54; 4.55]	
	$s^2 = < 0.1$ ; $Chi^2 = 0$					,	
D-L1 <1%							
eymach 2023	PD-L1 <1%	23	122	14	125	1.68 [0.91; 3.12]	<del>  • </del>
orde 2022	PD-L1 <1%	23	78	11	77	2.06 [1.08; 3.94]	<del></del>
ei 2023 ue 2023	PD-L1 <1% PD-L1 <1%	6 43	7 89	3 14	8 84	2.29 [0.89; 5.88]	
otal (95% CI)	. D L 1 < 170	95	296	42	294	2.24 [1.63; 3.09]	•
	$i^2 = < 0.1$ ; $Chi^2 =$						
D-L1 1-49%							
leymach 2023		44	135	19		2.44 [1.50; 3.95]	-
orde 2022	PD-L1 1-49%	21	51	2		9.68 [2.40; 39.05]	
otal (95% CI) eterogeneity: Tau	i <sup>2</sup> = 0.7; Chi <sup>2</sup> = 3.	65 4, df = 1 (P	186 = 0.07	21 '); I <sup>2</sup> = 70.		4.13 [1.11; 15.37]	
D-L1 ≥50% eymach 2023	PD-L1 ≥50%	55	109	13	107	4.15 [2.41; 7.14]	
orde 2022	PD-L1 ≥50%	19	38	3	42	7.00 [2.25; 21.80]	
otal (95% CI)	i <sup>2</sup> = < 0.1; Chi <sup>2</sup> = i	74	147	16	149	4.58 [2.80; 7.47]	
eterogeneity: Tau	=<0.1; ChF=	v.7, at = 1	r = 0.	42); I = 0	76		
isplatin	pipplatic	00	100	_	00	4 20 12 04: 0 12	_
leymach 2023 orde 2022	cisplatin cisplatin	32 45	100 124	7 12	96 134	4.39 [2.04; 9.46] 4.05 [2.25; 7.30]	
UIUE 2022	ospiauri	45 77	124 224	19		4.05 [2.25; 7.30] 4.17 [2.62; 6.66]	
otal (95% CI)	$a^2 = < 0.1$ ; $Chi^2 = 0$						
otal (95% CI) leterogeneity: Tau arboplatin							l
arboplatin leymach 2023	carboplatin	90	266	39		2.41 [1.72; 3.38]	-
arboplatin leymach 2023 orde 2022	carboplatin carboplatin	16	39	3	33	4.51 [1.44; 14.15]	-
eterogeneity: Tau arboplatin leymach 2023 orde 2022 otal (95% CI)		16 <b>106</b>	39 <b>305</b>	3 <b>42</b>	33 <b>311</b>		-

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.



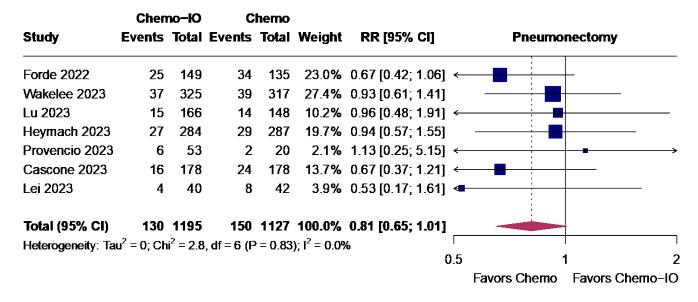
eFigure 10. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who received a lobectomy.



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.

	Chen	10-10	C	hemo								
Study	Events	Total	Events	Total	Weight	RR [95% CI]	Full	neoad	iuvan	t treat	ment	
Forde 2022	165	179	149	179	11.6%	1.11 [1.02; 1.20]			-			
Wakelee 2023	295	397	297	400	11.0%	1.00 [0.92; 1.09]			•			
Heymach 2023	318	366	331	374	17.4%	0.98 [0.93; 1.04]			+			
Provencio 2023	53	57	28	29	8.4%	0.96 [0.87; 1.06]						
Lei 2023	42	47	45	47	6.6%	0.93 [0.83; 1.05]						
Lu 2023	176	202	185	202	13.9%	0.95 [0.89; 1.02]			+			
Yue 2023	211	226	210	227	18.3%	1.01 [0.96; 1.06]			+			
Cascone 2023	194	229	205	232	12.8%	0.96 [0.89; 1.03]						
Total (95% CI)	1454	1703	1450	1690	100.0%	0.99 [0.96; 1.02]						
Heterogeneity: $Tau^2 < 0.1$ ; $Chi^2 = 1$		1.9, df = 7	(P = 0	$(.10); I^2 = 4$	l1.4%		I					
						0.1	1 0.2	0.5	1	2	5	10
							Favor	s Chem	io Fa	avors (	Chemo	-IO

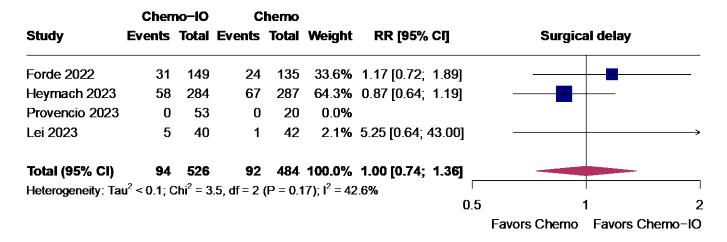
eFigure 12. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who received a pneumonectomy.



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

	Chen	no-IO	C	hemo						
Study	Events	Total	Events	Total	Weight	RR [95%	CI]		Bilobe	ectomy
Forde 2022	3	149	4	135	7.0%	0.68 [0.15;	2.98]	<b>←</b>	-	<b></b>
Wakelee 2023	26	325	26	317	56.5%	0.98 [0.58;	1.64]		-	
Heymach 2023	13	284	20	287	33.3%	0.66 [0.33;	1.29]	<del></del>		
Provencio 2023	3	53	1	20	3.2%	1.13 [0.12; 1	0.26]	<b>←</b>	:	•
Lei 2023	0	40	0	42	0.0%					
Total (95% CI)	45	851	51	801	100.0%	0.84 [0.57;	1.24]			
Heterogeneity: Ta	u <sup>2</sup> = 0 <del>,</del> Ch	i <sup>2</sup> = 1.0	), df = 3 (F	P = 0.81	); $I^2 = 0.09$	%				
							0	.5	,	1 2
									Favors Chemo	Favors Chemo-IO

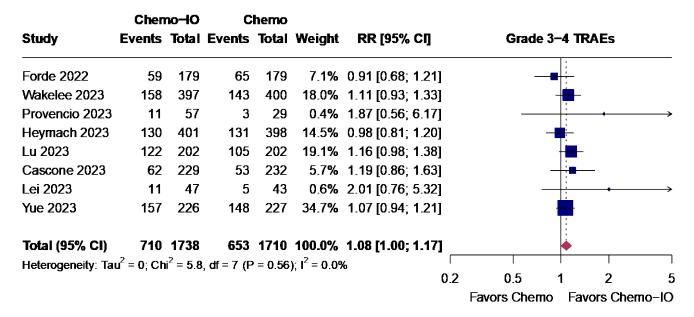
eFigure 14. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who had surgical delay.



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

	Chen	no-IO	С	hemo				
Study	Events	Total	Events	Total	Weight	RR [95% CI]	Open s	surgery
Forde 2022	88	149	85	135	40.0%	0.94 [0.78; 1.13]	- :	
Heymach 2023	145	284	153	287	56.0%	0.96 [0.82; 1.12]		<u> </u>
Lei 2023	15	40	14	42	4.0%	1.12 [0.63; 2.02]		<b>→</b>
Total (95% CI)		473				0.96 [0.85; 1.08]	-	
Heterogeneity: Ta	au² = 0 <del>;</del> Cl	ni² = 0.3	3, df = 2 (F	P = 0.84	$1); 1^2 = 0.0$	% ' 0.5	<del>,</del> .	1 2
						0.0		Favors Chemo-IO

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.

	Chen	no-IO	C	hemo									
Study	<b>Events</b>	Total	Events	Total	Weight	RR [95% CI]			Grade	e 5 TF	RAEs		
Forde 2022	0	179	3	179	6.5%	0.14 [0.01; 2.75]	<b>←</b>						
Wakelee 2023	3	397	3	400	22.2%	1.01 [0.20; 4.96]					:		
Heymach 2023	7	401	2	398	23.0%	3.47 [0.73; 16.62]					-	_	<b>→</b>
Lu 2023	6	202	4	202	36.1%	1.50 [0.43; 5.24]					Ĺ		
Cascone 2023	2	229	0	232	6.1%	5.07 [0.24; 104.93]				_		_	<b>→</b>
Lei 2023	0	47	0	43	0.0%						}		
Yue 2023	2	226	0	227	6.1%	5.02 [0.24; 104.02]					:	-	$\rightarrow$
Total (95% CI)	20	1681	12	1681	100.0%	1.66 [0.78; 3.52]					:	_	
Heterogeneity: Ta	au <sup>2</sup> < 0.1; •	Chi <sup>2</sup> = 4	4.9, df = 5	(P = 0.	42); I <sup>2</sup> = 0	.0%				İ			
						(	0.1	0.2	0.5	1	2	5	10
								Favor	s Chem	o Fa	avors C	hemo	-IO

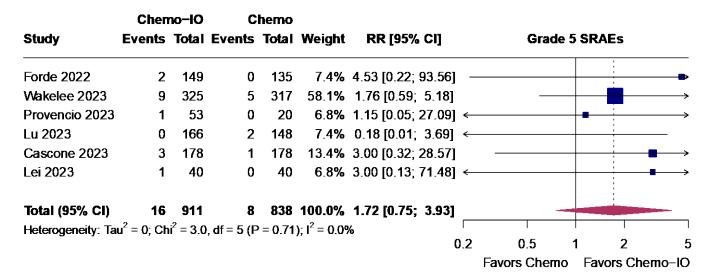
eFigure 18. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who had treatment-related adverse events.

	Chen	no-IO	C	hemo					
Study	Events	Total	Events	Total	Weight	RR [95% CI]	Total	TRAEs	
Forde 2022	145	179	156	179	1.7%	0.93 [0.85; 1.02]	-	•	
Wakelee 2023	379	397	374	400	12.1%	1.02 [0.99; 1.06]		þ	
Provencio 2023	50	57	26	29	0.6%	0.98 [0.84; 1.14]	-	+	
Heymach 2023	348	401	321	398	3.7%	1.08 [1.01; 1.14]		=	
Lu 2023	201	202	199	202	35.0%	1.01 [0.99; 1.03]		+	
Cascone 2023	197	229	197	232	2.4%	1.01 [0.94; 1.09]		+	
Lei 2023	41	47	40	43	0.7%	0.94 [0.82; 1.08]	_	+	
Yue 2023	224	226	225	227	43.8%	1.00 [0.98; 1.02]		+	
Total (95% CI)	1585	1738	1538	1710	100.0%	1.01 [1.00; 1.02]			
Heterogeneity: Ta	u <sup>2</sup> < 0.1; (	Chi <sup>2</sup> = 1	0.0, df = 7	(P = 0	$(.19); I^2 = 3$	30.3%			
						0.2	0.5	1	2 5
							Favors Chemo	Favor	s Chemo-IO

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.

	Chen	no-IO	C	hemo						
Study	Events	Total	Events	Total	Weight	RR [95% CI]		Grade 3-	-4 SRAE	s
Forde 2022	17	149	20	135	12.3%	0.77 [0.42; 1.41]				
Wakelee 2023	75	325	63	317	50.8%	1.16 [0.86; 1.56]		_		
Lu 2023	36	166	28	148	23.0%	1.15 [0.74; 1.78]			<del> </del>	
Cascone 2023	21	178	21	178	13.9%	1.00 [0.57; 1.76]			<u> </u>	
Lei 2023	0	40	0	40	0.0%				1	
Total (95% CI)	149	858	132	818	100.0%	1.08 [0.87; 1.33]		<		
Heterogeneity: Ta	au <sup>2</sup> = 0; C	$hi^2 = 1.$	6, df = 3 (l	P = 0.66	6); $I^2 = 0.0$	<b>)%</b>				
			•		•	0.	.2	0.5	1 2	2 5
								Favors Chemo	Favors	Chemo-IO

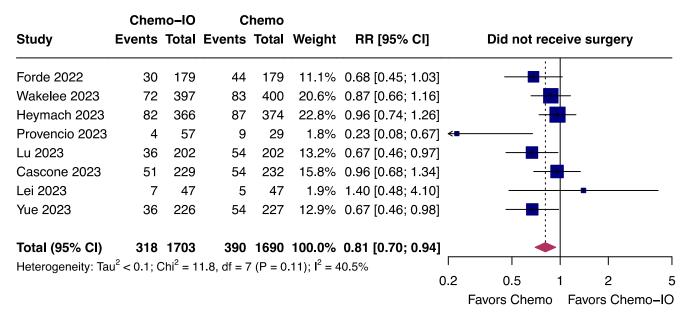
eFigure 20. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who had grade 5 surgery-related adverse events.



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

	Chen	no-IO	С	hemo							
Study	Events	Total	Events	Total	Weight	RR [95% CI]		Total	SRA	Es	
Forde 2022	62	149	63	135	7.7%	0.89 [0.69; 1.16]		_			
Wakelee 2023	231	325	226	317	54.5%	1.00 [0.90; 1.10]					
Lu 2023	124	166	104	148	28.1%	1.06 [0.93; 1.22]					
Cascone 2023	73	178	69	178	8.1%	1.06 [0.82; 1.37]			<u> </u>		
Lei 2023	16	40	14	40	1.6%	1.14 [0.65; 2.02]			•		
Total (95% CI)	506	858	476	818	100.0%	1.01 [0.94; 1.09]			•		
Heterogeneity: Ta	au <sup>2</sup> = 0; C	hi <sup>2</sup> = 1.	8, df = 4 (l	P = 0.7	8); $I^2 = 0.0$	)%			1		
						(	0.2	0.5	1	2	5
								Favors Chemo	Fav	vors Che	mo-IO

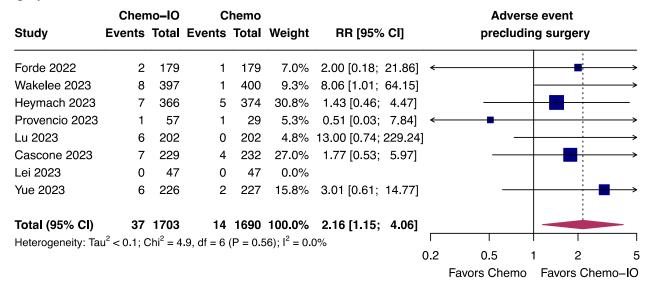
eFigure 22. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients who did not receive surgery.



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

	Chen	no-IO	С	hemo			Disease progression
Study	Events	Total	Events	Total	Weight	RR [95% CI]	precluding surgery
Forde 2022	12	179	17	179	16.5%	0.71 [0.35; 1.43]	
Wakelee 2023	10	397	17	400	15.4%	0.59 [0.27; 1.28]	<del></del>
Heymach 2023	35	366	42	374	22.8%	0.85 [0.56; 1.30]	<del></del>
Provencio 2023	0	57	4	29	2.1%	0.06 [0.00; 1.02]	<b>←</b>
Lu 2023	5	202	31	202	12.7%	0.16 [0.06; 0.41]	<b></b>
Cascone 2023	13	229	22	232	17.5%	0.60 [0.31; 1.16]	<del>- :</del>
Lei 2023	0	47	1	47	1.8%	0.33 [0.01; 7.98]	<b>←</b>
Yue 2023	5	226	12	227	11.2%	0.42 [0.15; 1.17]	<b>←</b>
Total (95% CI)	80	1703	146	1690	100.0%	0.51 [0.33; 0.79]	
Heterogeneity: Ta	$u^2 = 0.2; 0$	$Chi^2 = 1$	3.7, df = 7	P = 0	.06); $I^2 = 4$	19.0%	
						0	0.2 0.5 1 2 5
							Favors Chemo Favors Chemo-IC

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



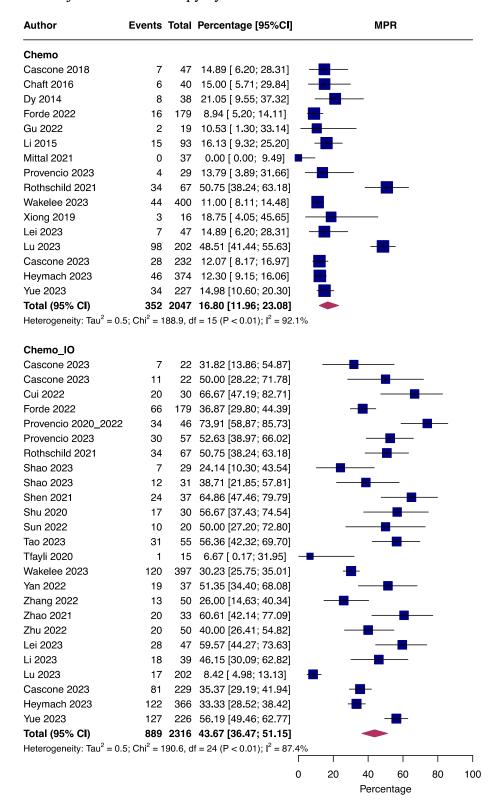
eFigure 25. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patient refusals precluding surgery.

	Chen	no-IO	С	hemo				Patient	refusal	
Study	Events	Total	Events	Total	Weight	RR [95% CI]		precludir	ng surgery	
Forde 2022	9	179	11	179	12.2%	0.82 [0.35; 1.93]				
Wakelee 2023	4	397	6	400	5.6%	0.67 [0.19; 2.36]	←	-		
Heymach 2023	12	366	17	374	17.0%	0.72 [0.35; 1.49]				
Lu 2023	18	202	13	202	19.0%	1.38 [0.70; 2.75]		<u>:</u>	1	_
Cascone 2023	8	229	18	232	13.5%	0.45 [0.20; 1.01]	<b>←</b>	•	 	
Lei 2023	2	47	2	47	2.4%	1.00 [0.15; 6.81]	<b>←</b>			<b></b>
Yue 2023	20	226	28	227	30.2%	0.72 [0.42; 1.24]				
Total (95% CI)	73	1646	95	1661	100.0%	0.78 [0.58; 1.05]	l		-	
Heterogeneity: Ta	$au^2 = 0$ ; Ch	$ni^2 = 4.7$	7, df = 6 (F)	= 0.58	3); $I^2 = 0.0$	%				
							0.2	0.5	1 2	5
								Favors Chemo	Favors Ch	nemo-IO

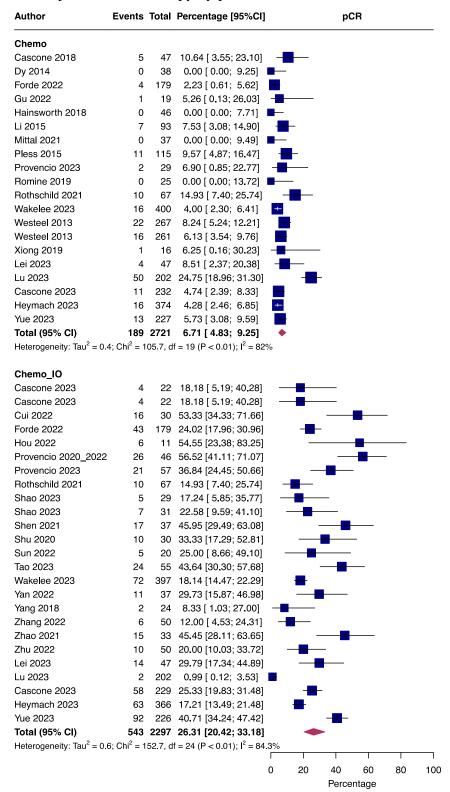
eFigure 26. Pooled risk ratios across RCTs comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by the number of patients with other reasons precluding surgery.

	Chen	no-IO	С	hemo				Other r	eason		
Study	Events	Total	Events	Total	Weight	RR [95% CI]		precludin	g surg	ery	
Forde 2022	4	179	7	179	9.7%	0.57 [0.17; 1.92]	<del></del>			-	
Wakelee 2023	1	397	4	400	3.3%	0.25 [0.03; 2.24]	<b>←</b>	-		_	
Heymach 2023	36	366	30	374	36.1%	1.23 [0.77; 1.95]		<u>:</u>		-	
Lu 2023	7	202	10	202	14.6%	0.70 [0.27; 1.80]		<del></del>			
Cascone 2023	15	229	16	232	23.5%	0.95 [0.48; 1.88]				-	
Lei 2023	0	47	0	47	0.0%			:			
Yue 2023	5	226	12	227	12.8%	0.42 [0.15; 1.17]	<b>←</b>	-	_		
Total (95% CI)	68	1646	79	1661	100.0%	0.82 [0.54; 1.23]					
Heterogeneity: Ta	$au^2 < 0.1;$	$Chi^2 = 6$	6.0, df = 5	(P = 0.	31); $I^2 = 1$	6.5%					
						(	0.2	0.5		2	5
								Favors Chemo	Favors	s Chemo	)–IO

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



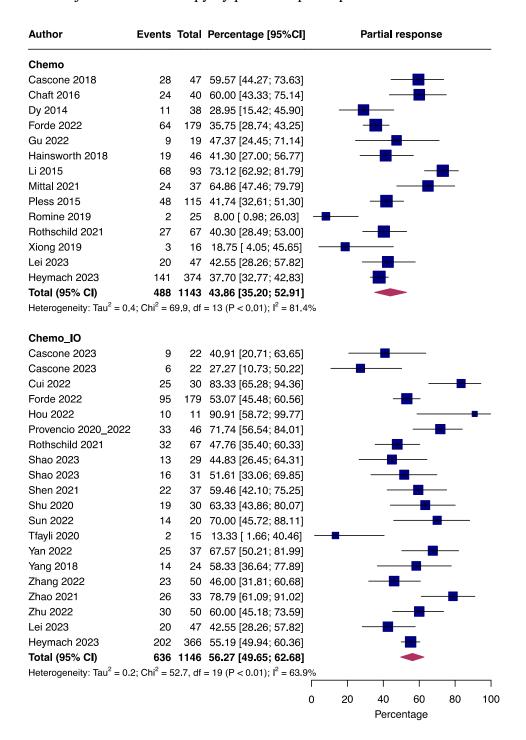
eFigure 28. Pooled proportions across all studies comparing neoadjuvant chemoimmunotherapy to neoadjuvant chemotherapy by pCR.



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

Author	Events	Total	Percentage [95%CI]	Complete response
Chemo				
Cascone 2018	0	47	0.00 [ 0.00; 7.55]	<b>-</b>
Dy 2014	0	38	0.00 [ 0.00; 9.25]	<b>—</b>
Forde 2022	3	179	1.68 [ 0.35; 4.82]	-
Hainsworth 2018	0	46	0.00 [ 0.00; 7.71]	<b>-</b>
Li 2015	7	93	7.53 [ 3.08; 14.90]	-
Mittal 2021	4	37	10.81 [ 3.03; 25.42]	
Pless 2015	2	115	1.74 [ 0.21; 6.14]	-
Romine 2019	0	25	0.00 [ 0.00; 13.72]	<b></b>
Rothschild 2021	2	67	2.99 [ 0.36; 10.37]	-
Xiong 2019	0	16	0.00 [ 0.00; 20.59]	
Lei 2023	4	47	8.51 [ 2.37; 20.38]	-
Heymach 2023	1	374	0.27 [ 0.01; 1.48]	<b>+</b>
Total (95% CI)	23	1084	2.95 [ 1.50; 5.71]	<b>•</b>
Heterogeneity: $Tau^2 = 0$ .	7; Chi <sup>2</sup> = 2	3.6, df	= 11 (P = 0.01); $I^2$ = 53.49	%
Chemo_IO				
Cascone 2023	0	22	0.00 [ 0.00; 15.44]	<del></del>
Cascone 2023	0	22	0.00 [ 0.00; 15.44]	<b></b>
Cui 2022	2	30	6.67 [ 0.82; 22.07]	_
Forde 2022	1	179	0.56 [ 0.01; 3.07]	•
Hou 2022	0	11	0.00 [ 0.00; 28.49]	<del></del>
Provencio 2020_2022	2	46	4.35 [ 0.53; 14.84]	-
Rothschild 2021	4	67	5.97 [ 1.65; 14.59]	-
Shao 2023	0	29	0.00 [ 0.00; 11.94]	<del></del>
Shao 2023	0	31	0.00 [ 0.00; 11.22]	<b></b>
Shen 2021	10	37		<del></del>
Shu 2020	0	30	0.00 [ 0.00; 11.57]	
Sun 2022	0	20		<b></b>
Tfayli 2020	1	15	6.67 [ 0.17; 31.95]	<del></del>
Yan 2022	1	37	2.70 [ 0.07; 14.16]	<del></del>
Yang 2018	0	24	0.00 [ 0.00; 14.25]	<b></b>
Zhang 2022	0	50	0.00 [ 0.00; 7.11]	<b>I</b> —
Zhao 2021	3	33	9.09 [ 1.92; 24.33]	_
Zhu 2022	8	50		_
Lei 2023	11	47	23.40 [12.30; 38.03]	
Heymach 2023	4	366	· · · · · · · · · · · · · · · · · · ·	<u> </u>
Total (95% CI)		1146	•	•
			= 19 (P < 0.01); $I^2$ = 72.69	%
- ,				
				0 20 40 60 80 100

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.

Author	Events	Total	Percentage [95%CI]	Stable disease
Chemo				
Cascone 2018	18	47	38.30 [24.51; 53.62]	<del></del>
Dy 2014	23	38	60.53 [43.39; 75.96]	<del></del>
Forde 2022	88	179	49.16 [41.63; 56.73]	-
Gu 2022	9	19	47.37 [24.45; 71.14]	<del></del>
Hainsworth 2018	22	46	47.83 [32.89; 63.05]	<del></del>
Li 2015	14	93	15.05 [ 8.48; 23.97]	-
Mittal 2021	5	37	13.51 [ 4.54; 28.77]	<del></del>
Pless 2015	45	115	39.13 [30.16; 48.67]	<del>-</del>
Romine 2019	14	25	56.00 [34.93; 75.60]	
Rothschild 2021	30		44.78 [32.60; 57.42]	
Xiong 2019	12		75.00 [47.62; 92.73]	
Lei 2023	15		31.91 [19.09; 47.12]	<del></del>
Heymach 2023	189		50.53 [45.35; 55.71]	
Total (95% CI)	484		42.21 [33.16; 51.82]	
			= 12 (P < 0.01); $I^2$ = 80.4%	6
Chemo_IO				<u>_</u>
Cascone 2023	13		59.09 [36.35; 79.29]	<del></del> -
Cascone 2023	14		63.64 [40.66; 82.80]	
Cui 2022	3	30	10.00 [ 2.11; 26.53]	<del></del> _
Forde 2022	70	179	39.11 [31.91; 46.67]	<del></del>
Hou 2022	1	11	9.09 [ 0.23; 41.28]	
Provencio 2020_2022	11	46	23.91 [12.59; 38.77]	<del></del>
Rothschild 2021	16	67	23.88 [14.31; 35.86]	<del></del>
Shao 2023	13	29	44.83 [26.45; 64.31]	<del></del>
Shao 2023	12	31	38.71 [21.85; 57.81]	<del></del>
Shen 2021	5	37	13.51 [ 4.54; 28.77]	_
Shu 2020	9	30	30.00 [14.73; 49.40]	<del></del>
Sun 2022	4	20	20.00 [ 5.73; 43.66]	<del></del>
Tfayli 2020	8	15	53.33 [26.59; 78.73]	
Yan 2022	10	37	27.03 [13.79; 44.12]	<del></del>
Yang 2018	8	24	33.33 [15.63; 55.32]	<del></del>
Zhang 2022	24	50	48.00 [33.66; 62.58]	<del></del>
Zhao 2021	3	33	9.09 [ 1.92; 24.33]	-
Zhu 2022	10	50	20.00 [10.03; 33.72]	<del></del>
Lei 2023	9	47	19.15 [ 9.15; 33.26]	<del></del>
Heymach 2023	124	366	33.88 [29.04; 38.98]	-
Total (95% CI)			30.34 [24.00; 37.52]	•
			= 19 (P < 0.01); $I^2$ = 69.4%	6
			1	00 40 00 00 10
			C	
				Percentage

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

Author	Events	Total	Percentage [95%CI]	Progressive disease
Chemo	,			
Cascone 2018	1	47	2.13 [0.05; 11.29]	-
Dy 2014	4	38	10.53 [2.94; 24.80]	<del></del>
Forde 2022	11	179	6.15 [3.11; 10.73]	<b>-</b>
Gu 2022	1	19	5.26 [0.13; 26.03]	<del>-</del>
Hainsworth 2018	6	46	13.04 [4.94; 26.26]	<del></del>
Li 2015	4	93	4.30 [1.18; 10.65]	<b>■</b>
Mittal 2021	4	37	10.81 [3.03; 25.42]	-
Pless 2015	16	115	13.91 [8.17; 21.61]	-
Romine 2019	1	25	4.00 [0.10; 20.35]	-
Rothschild 2021	3	67	4.48 [0.93; 12.53]	-
Xiong 2019	1	16	6.25 [0.16; 30.23]	-
Lei 2023	4	47	8.51 [2.37; 20.38]	
Heymach 2023	15	374	4.01 [2.26; 6.53]	+
Total (95% CI)	71	1103	7.14 [5.09; 9.94]	•
Heterogeneity: $Tau^2 = 0$ .	2; Chi <sup>2</sup> = 2	0.9, df	= 12 (P = 0.05); $I^2$ = 42.6	5%
Chemo_IO				
Cascone 2023	0	22	0.00 [0.00; 15.44]	
Cascone 2023	1	22	4.55 [0.12; 22.84]	
Cui 2022	0	30	0.00 [0.00; 11.57]	
Forde 2022	8	179	4.47 [1.95; 8.62]	-
Provencio 2020_2022		46	0.00 [0.00; 7.71]	
Rothschild 2021	4	67	5.97 [1.65; 14.59]	-
Shao 2023	0	29	0.00 [0.00; 11.94]	-
Shao 2023	1	31	3.23 [0.08; 16.70]	•
Shen 2021	0	37	0.00 [0.00; 9.49]	_
Shu 2020	2	30	6.67 [0.82; 22.07]	
Sun 2022	2	20	10.00 [1.23; 31.70]	
Tfayli 2020	3	15	20.00 [4.33; 48.09]	<u> </u>
Yan 2022	1	37	2.70 [0.07; 14.16]	-
Yang 2018	2	24	8.33 [1.03; 27.00]	
Zhang 2022	2	50	4.00 [0.49; 13.71]	-
Zhao 2021	1	33	3.03 [0.08; 15.76]	
Zhu 2022	2	50	4.00 [0.49; 13.71]	_
Lei 2023	0	47	0.00 [0.00; 7.55]	<u>-</u>
Heymach 2023	11	366	3.01 [1.51; 5.31]	_ 
Total (95% CI)		1135	4.46 [3.23; 6.13]	•
Heterogeneity: Tau <sup>2</sup> = <				* %
e.orogonolty. rau = <		10.2,	= 10 (1 = 0.00), 1 = 0	
				0 20 40 60 80 100
				Percentage

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

Author	Events	Total	Percentage [95%CI]	Surgical resection
Chemo	-			
Cascone 2018	37	47	78.72 [64.34; 89.30]	
Chaft 2016	32	40	80.00 [64.35; 90.95]	
Chen 2013	148	179	82.68 [76.33; 87.92]	<u>-</u>
Dy 2014	34	38	89.47 [75.20; 97.06]	
Forde 2022	135	179	75.42 [68.44; 81.54]	
Gu 2022	16	173	84.21 [60.42; 96.62]	
Hainsworth 2018	27	46		
	90		58.70 [43.23; 73.00]	
_i 2015		93	96.77 [90.86; 99.33]	_
Mittal 2021	17	37	45.95 [29.49; 63.08]	
Pless 2015	94	115	81.74 [73.45; 88.33]	
Provencio 2023	20	29	68.97 [49.17; 84.72]	
Romine 2019	14	25	56.00 [34.93; 75.60]	
Wakelee 2023	317	400	79.25 [74.94; 83.12]	<b>=</b> _
Westeel 2013	257	267	96.25 [93.22; 98.19]	<u>=</u>
Westeel 2013	252	261	96.55 [93.56; 98.41]	_ =
Xiong 2019	8	16	50.00 [24.65; 75.35]	<del></del>
Zhu 2017	48	48	100.00 [92.60; 100.00]	-
_ei 2023	42	47	89.36 [76.90; 96.45]	<del></del>
_u 2023	148	202	73.27 [66.60; 79.23]	<del></del>
Cascone 2023	178	232	76.72 [70.75; 82.00]	-
Heymach 2023	302	374	80.75 [76.38; 84.62]	-
Yue 2023	173	227	76.21 [70.13; 81.60]	-
Total (95% CI)	2389	2921	81.18 [74.08; 86.69]	•
Heterogeneity: Tau <sup>2</sup> = 0.	3; Chi <sup>-</sup> = 1	50.5, d	$f = 21 (P < 0.01); I^2 = 86.1\%$	
Chemo_IO				
Cascone 2023	22	22	100.00 [84.56; 100.00]	
Cascone 2023	20	22	90.91 [70.84; 98.88]	
Cui 2022	30	30	100.00 [88.43; 100.00]	
Forde 2022	149	179	83.24 [76.95; 88.40]	-
Hou 2022	11		100.00 [71.51; 100.00]	
Provencio 2020_2022		46	89.13 [76.43; 96.38]	
Provencio 2023	53	57	92.98 [83.00; 98.05]	
Rothschild 2021	55	67	82.09 [70.80; 90.39]	
Shao 2023	26	29	89.66 [72.65; 97.81]	
Shao 2023	29	31	93.55 [78.58; 99.21]	
Shen 2021	37		100.00 [90.51; 100.00]	
	26		-	
Shu 2020		30	86.67 [69.28; 96.24]	
Sun 2022	16	20	80.00 [56.34; 94.27]	
Tao 2023	48	55	87.27 [75.52; 94.73]	
Tfayli 2020	11	15	73.33 [44.90; 92.21]	<del></del> -
Wakelee 2023	325	397	81.86 [77.71; 85.53]	<b>=</b> _
Yan 2022	34	37	91.89 [78.09; 98.30]	_
Yang 2018	13	24	54.17 [32.82; 74.45]	<del></del>
Zhang 2022	30	50	60.00 [45.18; 73.59]	<del></del>
Zhao 2021	30	33	90.91 [75.67; 98.08]	
Zhu 2022	36	50	72.00 [57.51; 83.77]	<del></del>
_ei 2023	40	47	85.11 [71.69; 93.80]	<del></del>
	166	202	82.18 [76.19; 87.19]	-
_u 2023			77.73 [71.78; 82.95]	
_u 2023 Cascone 2023	178	229	77.73 [71.76, 62.93]	
	178 295	229 366		<u> </u>
Cascone 2023	295	366	80.60 [76.17; 84.53]	1
Cascone 2023 Heymach 2023 Yue 2023	295 190	366 226		•
Cascone 2023 Heymach 2023 Yue 2023 <b>Total (95% CI)</b>	295 190 <b>1911</b>	366 226 <b>2312</b>	80.60 [76.17; 84.53] 84.07 [78.64; 88.59]	•
Cascone 2023 Heymach 2023 Yue 2023 <b>Total (95% CI)</b>	295 190 <b>1911</b>	366 226 <b>2312</b>	80.60 [76.17; 84.53] 84.07 [78.64; 88.59] 83.28 [79.61; 86.41]	20 40 60 80 10

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

Author	Events	Total	Percentage [95%CI]	R0 resection
Chemo				
Cascone 2018	35	37	94.59 [81.81; 99.34]	-
Chaft 2016	29	32	90.62 [74.98; 98.02]	
Dy 2014	32	34	94.12 [80.32; 99.28]	
Forde 2022	105	135	77.78 [69.82; 84.48]	<del> </del>
Gu 2022	15	16	93.75 [69.77; 99.84]	
Hainsworth 2018	25	27	92.59 [75.71; 99.09]	
Mittal 2021	17	17	100.00 [80.49; 100.00]	
Pless 2015	76	94	80.85 [71.44; 88.24]	<del></del>
Provencio 2023	17	20	85.00 [62.11; 96.79]	
Wakelee 2023	267	317	84.23 [79.74; 88.06]	-
Westeel 2013	244	257	94.94 [91.51; 97.28]	=
Westeel 2013	240	252	95.24 [91.83; 97.52]	=
Lei 2023	36	42	85.71 [71.46; 94.57]	<del></del>
Lu 2023	137	148	92.57 [87.09; 96.23]	-
Cascone 2023	161	178	90.45 [85.15; 94.34]	-
Heymach 2023	262	302	86 75 [82 40; 90 37]	-
Total (95% CI)	1698	1908	89.65 [86.15; 92.34]	•
Heterogeneity: $Tau^2 = 0.3$	3; Chi <sup>2</sup> = 5	3.3, df	= 15 (P < 0.01); $I^2$ = 71.9%	
Chemo_IO				
Cascone 2023	20	22	90.91 [70.84; 98.88]	
Cascone 2023	19	20	95.00 [75.13; 99.87]	
Forde 2022	124	149	83.22 [76.24; 88.84]	-
Hou 2022	11	11	100.00 [71.51; 100.00]	
Provencio 2020_2022	41		100.00 [91.40; 100.00]	
Provencio 2023	50	53	94.34 [84.34; 98.82]	
Rothschild 2021	51	55	92 73 [82 41; 97 98]	
Shao 2023	26	26	100.00 [86.77; 100.00]	
Shao 2023	29		100.00 [88.06; 100.00]	
Shen 2021	37		100.00 [90.51; 100.00]	
Shu 2020	26		100.00 [86.77; 100.00]	
Sun 2022	16		100.00 [79.41; 100.00]	
Tao 2023	48		100.00 [92.60; 100.00]	
Wakelee 2023	299	325	92.00 [88.50; 94.71]	<u></u>
Yan 2022	32	34	94.12 [80.32; 99.28]	
Yang 2018	13		100.00 [75.29; 100.00]	
Zhang 2022	30		100.00 [88.43; 100.00]	
Zhao 2021	29	30	96.67 [82.78; 99.92]	
Zhu 2022	36		100.00 [90.26; 100.00]	
Lei 2023	37		92 50 [79.61; 98.43]	
Lu 2023	159		95.78 [91.50; 98.29]	-
Cascone 2023	159	178	89.33 [83.83; 93.45]	<b>=</b>
Heymach 2023	269	295	91.19 [87.35; 94.16]	-
Total (95% CI)			93.35 [90.94; 95.15]	
			= 22 (P = 0.04); I <sup>2</sup> = 36.2%	
			0	20 40 60 80 100
			0	Percentage

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

Author	Events	Total	Percentage [95%CI]	Lobectomy
Chemo				
Cascone 2018	31	37	83.78 [67.99; 93.81]	<del></del>
Chen 2013	68	148	45.95 [37.73; 54.32]	<del>-</del>
Dy 2014	26	34	76.47 [58.83; 89.25]	<del></del>
Forde 2022	82	135	60.74 [51.97; 69.03]	-
Hainsworth 2018	19	27	70.37 [49.82; 86.25]	<del></del>
Li 2015	39	90	43.33 [32.92; 54.20]	
Mittal 2021	14	17	82.35 [56.57; 96.20]	
Pless 2015	59	94	62.77 [52.18; 72.52]	— <del></del>
Provencio 2023	17	20	85.00 [62.11; 96.79]	<del></del>
Wakelee 2023	238	317	75.08 [69.94; 79.74]	-
Lei 2023	34	42	80.95 [65.88; 91.40]	
Lu 2023	123	148	83.11 [76.08; 88.76]	-
Cascone 2023	128	178	71.91 [64.70; 78.38]	
Heymach 2023	221	302	73.18 [67.80; 78.09]	-
Total (95% CI)	1099	1589	70.79 [63.23; 77.35]	•
•			= 13 (P < 0.01); $I^2$ = 86.6%	
Chemo_IO				
Cascone 2023	17	22	77.27 [54.63; 92.18]	
Cascone 2023	18	20	90.00 [68.30; 98.77]	
Forde 2022	115	149	77.18 [69.60; 83.65]	-
Hou 2022	11		100.00 [71.51; 100.00]	<del></del>
Provencio 2020_2022		41	92.68 [80.08; 98.46]	
Provencio 2023	41	53	77.36 [63.79; 87.72]	
Rothschild 2021	43	55	78.18 [64.99; 88.19]	
Shao 2023	20	26	76.92 [56.35; 91.03]	
Shao 2023	23	29	79.31 [60.28; 92.01]	
Shen 2021	22	37	59.46 [42.10; 75.25]	
Shu 2020	19	26	73.08 [52.21; 88.43]	
Sun 2022	13	16	81.25 [54.35; 95.95]	
Wakelee 2023	256	325	78.77 [73.92; 83.09]	_
Yan 2022	24	34	70.59 [52.52; 84.90]	
Yang 2018	10	13	76.92 [46.19; 94.96]	
Zhang 2022	24	30	80.00 [61.43; 92.29]	
Zhao 2021	22	30	73.33 [54.11; 87.72]	
Zhu 2022	35	36	97.22 [85.47; 99.93]	
Lei 2023	36	40	90.00 [76.34; 97.21]	
Lu 2023	134	166	80.72 [73.89; 86.43]	<b>—</b>
Cascone 2023	142	178	79.78 [73.12; 85.41]	
Heymach 2023	238	295	80.68 [75.70; 85.02]	<u>=</u>
Total (95% CI)		1632		•
			If = 21 (P = 0.19); $I^2$ = 20.9%	•
	.,			
			0	20 40 60 80 100
				Percentage

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

Author	Events	Total	Percentage [95%CI]	Pneumonectomy
Chemo				
Cascone 2018	4	37	10.81 [ 3.03; 25.42]	-
Chen 2013	75	148	50.68 [42.34; 58.98]	-
Dy 2014	6	34	17.65 [ 6.76; 34.53]	
Forde 2022	34		25.19 [18.11; 33.38]	
Hainsworth 2018	3		11.11 [ 2.35; 29.16]	<del></del>
Li 2015	32		35.56 [25.74; 46.35]	
Mittal 2021	3	17	17.65 [ 3.80; 43.43]	_ <del></del>
Pless 2015	19		20.21 [12.63, 29.75]	
Provencio 2023	2	20	10.00 [ 1.23; 31.70]	
Wakelee 2023	39	317	12.30 [ 8.90; 16.43]	
Lei 2023	8	42	19.05 [ 8.60; 34.12]	
Lu 2023	14	148	9.46 [ 5.27; 15.36]	
Cascone 2023	24	178	13.48 [ 8.83; 19.39]	
Heymach 2023	29	302	9.60 [ 6.53; 13.50]	<b>_</b>
Total (95% CI)			17.76 [12.68; 24.32]	
` ,			$f = 13 (P < 0.01); I^2 = 90.$	69/
rieterogeneity. rau = 0.	4, OIII = 1	36.4, u	1 = 13 (F < 0.01), 1 = 90.	0 /0
Chemo_IO				
Cascone 2023	2	22	9.09 [ 1.12; 29.16]	-
Cascone 2023	1	20	5.00 [ 0.13; 24.87]	-
Forde 2022	25	149	16.78 [11.16; 23.76]	<del></del>
Hou 2022	0	11	0.00 [ 0.00; 28.49]	<b>-</b>
Provencio 2020_2022	3	41	7.32 [ 1.54; 19.92]	-
Provencio 2023	6	53	11.32 [ 4.27; 23.03]	<del></del>
Rothschild 2021	5	55	9.09 [ 3.02; 19.95]	-
Shao 2023	0	26	0.00 [ 0.00; 13.23]	<b></b>
Shao 2023	2	29	6.90 [ 0.85; 22.77]	-
Shen 2021	2	37	5.41 [ 0.66; 18.19]	-
Shu 2020	3	26	11.54 [ 2.45; 30.15]	-
Sun 2022	3	16	18.75 [ 4.05; 45.65]	
Wakelee 2023	37	325	11 38 [ 8 14; 15 35]	<u> </u>
Yan 2022	2	34	5.88 [ 0.72; 19.68]	<del>-</del>
Yang 2018	1	13	7.69 [ 0.19; 36.03]	_
Zhang 2022	4	30	13.33 [ 3.76; 30.72]	
Zhao 2021	6	30	20.00 [ 7.71; 38.57]	
Zhu 2022	0	36	0.00 [ 0.00; 9.74]	<u> </u>
Lei 2023	4	40	10.00 [ 2.79; 23.66]	_
Lu 2023	15	166	9.04 [ 5.15; 14.47]	<u>=</u>
Cascone 2023	16	178	8.99 [ 5.23; 14.19]	-
Heymach 2023	27	295	9.15 [ 6.12; 13.04]	
Total (95% CI)			10.58 [ 8.94; 12.49]	<u> </u>
			If = 21 (P = 0.54); $I^2 = 0\%$	· ·
notorogenous, rad = <	o. 1, Oili –	, .	– 2. (1 – 0.04), 1 – 0 /	
				0 20 40 60 80 10

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

Author	Events	Months	Total	Events per 100 person-months [95% CI]	Incidence of death
Chemo					
Cascone 2018	29	62.00	47	0.47 [0.33; 0.67]	
Chen 2013	128	53.80	179	2.38 [2.00; 2.83]	-
Dy 2014	15	37.10	38	0.40 [0.24; 0.67]	<del>1</del>
Li 2015	33	60.00	93	0.55 [0.39; 0.77]	<del></del>
Pless 2015	64	52.00	115	1.23 [0.96; 1.57]	-
Provencio 2023	11	26.10	29	0.42 [0.23; 0.76]	<b>-</b>
Romine 2019	8	95.00	25	0.08 [0.04; 0.17]	<b>=</b>
Rothschild 2021	15	28.60	67	0.52 [0.32; 0.87]	<del>-</del>
Total (95% CI)			<b>59</b> 3	0.54 [0.28; 1.04]	•
Heterogeneity: Ta	u <sup>2</sup> = 0.8; C	chi <sup>2</sup> = <b>200</b> .3	3, df = 7	$7 (P < 0.01); i^2 = 96.5\%$	
Chemo_IO					
Provencio 2023	12	26.10	57	0.46 [0.26; 0.81]	<del></del>
Rothschild 2021	15	28.60	67	0.52 [0.32; 0.87]	<del>-</del>
Shen 2021	0	7.00	37	0.00 [0.00; 1.14]	<b>-</b>
Shu 2020	4	12.90	30	0.31 [0.12; 0.83]	<del></del>
Sun 2022	2	27.00	20	0.07 [0.02; 0.30]	<b>-</b>
Yan 2022	1	12.10	37	0.08 [0.01; 0.59]	<b>-</b>
Zhang 2022	6	13.60	50	0.44 [0.20; 0.98]	<del></del>
Zhao 2021	1	10.30	33	0.10 [0.01; 0.69]	<b>-</b>
Zhu 2022	14	22.00	50	0.64 [0.38; 1.07]	<del></del>
Total (95% CI)			381	0.34 [0.22; 0.54]	•
Heterogeneity: Ta	u <sup>2</sup> = 0.2; C	chi <sup>2</sup> = 16, d	f=8 (F	$P = 0.04$ ); $I^2 = 49.9\%$	
Test for subgroup	difference	s: Chi <sup>2</sup> = 1.	.2, df =		
				-3	-2 -1 0 1 2 3

eTable 1. Search strategy for Embase.

#	Query	Results
1	(random* or factorial* or placebo* or assign* or allocat* or crossover*).tw.	2572740
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
-	randomization/	99085
14	placebo/	414590
	exp clinical trial/	1869347
	parallel design/	18809
	latin square design/	491
	randomized controlled trial/	791270
19	"randomized controlled trial (topic)"/	264085
	controlled clinical trial/	471606
21	"controlled clinical trial (topic)"/	13456
-	or/1-21	6567900
-	exp animal/ or exp nonhuman/ or exp animal experiment/ or exp animal model/	35123223
24	exp human/	27044216
	23 not 24	8079007
	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
	lung non small cell cancer/ or non small cell lung cancer/	163890
_	27 or 28	439985
30	(neoadjuvant or neo-adjuvant or preoperative or pre-operative or induction).tw,kf.	1335880
	exp neoadjuvant therapy/	52738
	exp induction chemotherapy/	18384
	30 or 31 or 32	1350877
	(immunotherap* or chemoimmunotherap* or chemo-immunotherap*).tw,kf.	229384
	immune checkpoint inhibitor*.tw,kf.	38043
36	exp immunological antineoplastic agent/ or immunological antineoplastic agent.tw,kf. or immune checkpoint or/	387482
	(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 o).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
⊤∠	(Liouayo oi regii 2010 oi regii2010 oi sai +3700+ oi sai+3700+).tw,ki,uy.	443

42	1 1 1 101 1 1 1 1	10004
	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 1 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
3	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 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	(duryalumab or Imfinzi),tw.kf.nm. or duryalumab/	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, 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
<i>-</i> 1	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	NCT001 98354	IFCT 0002	III	Single- arm	Preoperative chemotherapy	Stage IA-II resectable NSCLC	267	81	Pre: 60	Pre: 43	Pre: 0
Chemotherapy	Westeel	2013	NCT001 98354	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	NCT000 30771	NA	III	Single- arm	Cisplatin + docetaxel	Stage IIIA N2 resectable NSCLC	115	67	59	31	100
Chemotherapy	Chaft	2016	NA	NEOSC AN	II	Single- arm	Platinum-doublet chemotherapy	Stage IB-IIIA resectable lung cancer	40	35	63	18	80
Chemotherapy	Zhao	2016	NCT024 97118	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 adenocarcino ma	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	NCT002 54384	NA	II	Single- arm	Cisplatin + docetaxel	Stage I-III resectable NSCLC	47	62	64	38	40
Chemoimmunoth erapy	Yang	2018	NCT018 20754	TOP120 1	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	NCT002 27539	NA	II	Single- arm	Cisplatin + pemetrexed	Stage IB-IIIB resectable NSCLC	25	48	62	12	76
Chemotherapy	Xiong	2019	NCT012 17619	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
Chemoimmunoth erapy	Shu	2020	NCT027 16038	NA	II	Single- arm	Atezolizumab + nab- paclitaxel + carboplatin	Stage IB-IIIA resectable NSLC	30	50	67	40	77
Chemoimmunoth erapy	Tfayli	2020	NCT034 80230	NA	NA	Single- arm	Avelumab + chemotherapy	Stage IB-IIIA resectable NSCLC	15	47	65	13	53
Chemoimmunoth erapy	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

			•			•		•			•		
Chemoimmunoth erapy	Rothschild	2021	NCT025 72843	SAKK 16/14	II	Single- arm	Durvalumab + cisplatin + docetaxel	Stage IIIA N2 NSCLC	67	52	61	33	100
Chemoimmunoth erapy	Zhao	2021	NCT043 04248	NA	II	Single- arm	Toripalimab + carboplatin + pemetrexed/nab- paclitaxel	Stage IIIA- IIIB resectable NSCLC	33	82	61	55	100
Chemoimmunoth erapy	Zhang	2022	ChiCTR 1900023 758	NA	II	Single- arm	Sintilimab + carboplatin + pemetrexed or sintilimab + carboplatin + gemeitabine	Stage IB-IIIA resectable NSCLC	50	88	NA	56	100
Chemoimmunoth erapy	Zhu	2022	ChiCTR 1900024 01	LungMat e 002	II	Single- arm	Toripalimab + chemotherapy	Stage II-IIIB resectable NSCLC	50	84	66	64	92
Chemoimmunoth erapy	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
Chemoimmunoth erapy	Hou	2022	NA	NA	I	Single- arm	Toripalimab + platinum-paclitaxel	Stage II-IIIB resectable NSCLC	11	91	63	82	64
Chemotherapy	Gu	2022	NCT041 97076	NA	NA	Single- arm	Chemotherapy	Stage IIB-IIIB resectable NSCLC	19	84	64	63	89
Chemoimmunoth erapy	Yan	2022	NCT043 16364	NA	IB	Single- arm	Adebrelimab + nab- paclitaxel + carboplatin	Stage II-IIIB resectable NSCLC	37	95	63	84	70
Chemoimmunoth erapy	Sun	2022	NCT043 26153	NA	II	Single- arm	Sintilimab + nab- paclitaxel + carboplatin	Stage IIIA- IIIB resectable NSCLC	20	90	59.5	80	100
Chemoimmunoth erapy	Cascone	2023	NCT031 58129	NEOST AR	II	Single- arm	Nivolumab + cisplatin & docetaxel or pemetrexed	Stage IB-IIIA NSCLC	22	45	69.5	23	50
Chemoimmunoth erapy	Cascone	2023	NCT031 58129	NEOST AR	II	Single- arm	Ipilimumab + nivolumab + cisplatin & docetaxel or pemetrexed	Stage IB-IIIA resectable NSCLC	22	68	63.1	23	59
Chemoimmunoth erapy	Li	2023	NCT044 22392	NA	II	Single- arm	Sintilimab + platimum-doublet chemotherapy	Stage IIIA-N2 resectable NSCLC	39	97	62-64	67	100
Chemoimmunoth erapy	Shao	2023	NCT044 59611	neoSCO RE	II	Single- arm	Sintilimab + chemotherapy (2 cycles)	Stage IB-IIIA NSCLC	29	86	66	66	62
Chemoimmunoth erapy	Shao	2023	NCT044 59611	neoSCO RE	II	Single- arm	Sintilimab + chemotherapy (3 cycles)	Stage IB-IIIA NSCLC	31	74	63	55	45
Chemoimmunoth erapy	Tao	2023	NCT046 06303	Renaissa nce	II	Single- arm	Toripalimab + platinum-doublet chemotherapy	Stage IIB-IIIB NSCLC	55	91	62	80	71
Chemotherapy	Zhong	2019_2023	NCT014 07822	EMERG ING- CTONG 1103	II	Single- arm	Gemcitabine + cisplatin	EGFR mutant stage IIIA-N2 resectable NSCLC	35	23	58	NA	100
Chemoimmunoth erapy	Provencio	2020_2022	NCT030 81689	NADIM	II	Single- arm	Nivolumab + paclitaxel + carboplatin	Stage IIIA resectable NSCLC	46	74	63	35	100

eTable 4. Johanna Brigs bias assessment.

		1			1				1		
		2. Were the									
	1. Were the	exposures					7. Were	8. Was the	9. Was follow		
	two/three	measured				6. Were the	the	follow up time	up complete,	10. Were	11. Was
	groups	similarly to	3. Was the	4. Were		groups/parti	outcomes	-		strategies	appropri
		assign people		confound	5 Were				were the	to address	
	recruited	to both	_		strategies to	of the			reasons to loss		
											statistica 1
	from the	exposed and			deal with		and		to follow up	e follow	l
Author		unexposed			confounding		reliable		described and		analysis
(Year)	population?	groups?	way?	?	factors stated?	the study?	way?	occur?	explored?	utilized?	used?
Cascone											
(2018)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Cascone											
	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	IJ	Y
Chaft	1 1/11	1 1/1 1	1 1/2 1		1 1/2 1	1	1	1	- 1		_
(2016)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
	N/A	IN/A	IN/A	IN	IN/A	1	I	I	IN	U	1
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	Y	Y	N/A	N/A		Y
	N/A	N/A	N/A		N/A	Y	Y		N	U	Y
Gu (2022)	N/A	N/A	N/A	U	U	Y	Y		N	U	Y
		IN/A	IN/A	U	U	Y	Y	Y	IN	U	Y
Hainswort											
h (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	-	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	IJ	Y
	11/71	IV/A	1 V/ /A	11	11/71	1	1	1	11	C	1
Provencio	NT/A	NT / A	D.T./.A	N.T.	NT / A	3.7	X 7	<b>3</b> 7	<b>3</b> T	<b>T</b> T	<b>3</b> 7
(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	1						]			<u> </u>	
		N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Shao							İ			İ	
(2023)	N/A	N/A	N/A	N	N/A	Y	Y	Y	N	U	Y
Shen	11/11	11/11	11/11	1 1	1 1/ 1 1		1	*	± 1		-
	NT/A	NT/A	NT/A	T T	T T	v	V	N	T T	T T	v
(2021)	N/A	N/A	N/A		U	Y	Y		U		Y
Shu (2020)		N/A	N/A		N/A	Y	Y		N	U	Y
Sun (2022)		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	11/11	11/11	11/11	1	L 1/ L L	*	*	ř			1
	NT/A	NT/A	NT/A	N.T.	NT/A	W	NZ	N/	N/	NT/A	v.
	N/A	N/A	N/A	N	N/A	Y	Y	Y	Y	N/A	Y
Xiong	L	L					L	L		L	
(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		U	Y	Y		N	U	Y
1411 (2022)	1/ 1 1	11/11	11/11	$\sim$	<u>                                     </u>	l T	1.4	1.	<u>+ 1</u>	<u> </u>	1

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	ITT Chemo IO	ITT Chemo	Surgical resection Chemo IO	resection		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	IAD D	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		0.68 (95% CI 0.53-0.88)	NA
Provencio 2023	57	29	53	20	50	17	30	4	21	2		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		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		0.59 (95% CI 0.44-0.79)	NA
Lei 2023	47	47	40	42	37	36	28	7	14	4		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(%)	Adverse event, n(%) Chemo IO	Adverse event, n(%)	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)