

Legend of Additional Files

Search Strategy of PubMed for RCT

Additional File Figure S1. Flow chart of the search, selection, and inclusion of the studies.

Additional File Figure S2. Reconstruct Kaplan-Meier curve and original Kaplan-Meier curve (event-free survival/progression-free survival).

Additional File Figure S3. Reconstruct Kaplan-Meier curve and original Kaplan-Meier curve (overall survival).

Additional File Figure S4. Reconstruct Kaplan-Meier curve and original Kaplan-Meier curve (disease-free survival).

Additional File Figure S5. Cumulative Risk and Hazard Ratio (HR) of Primary Outcome.

Additional File Figure S6. Meta-analysis at the Study Level of Primary Outcome.

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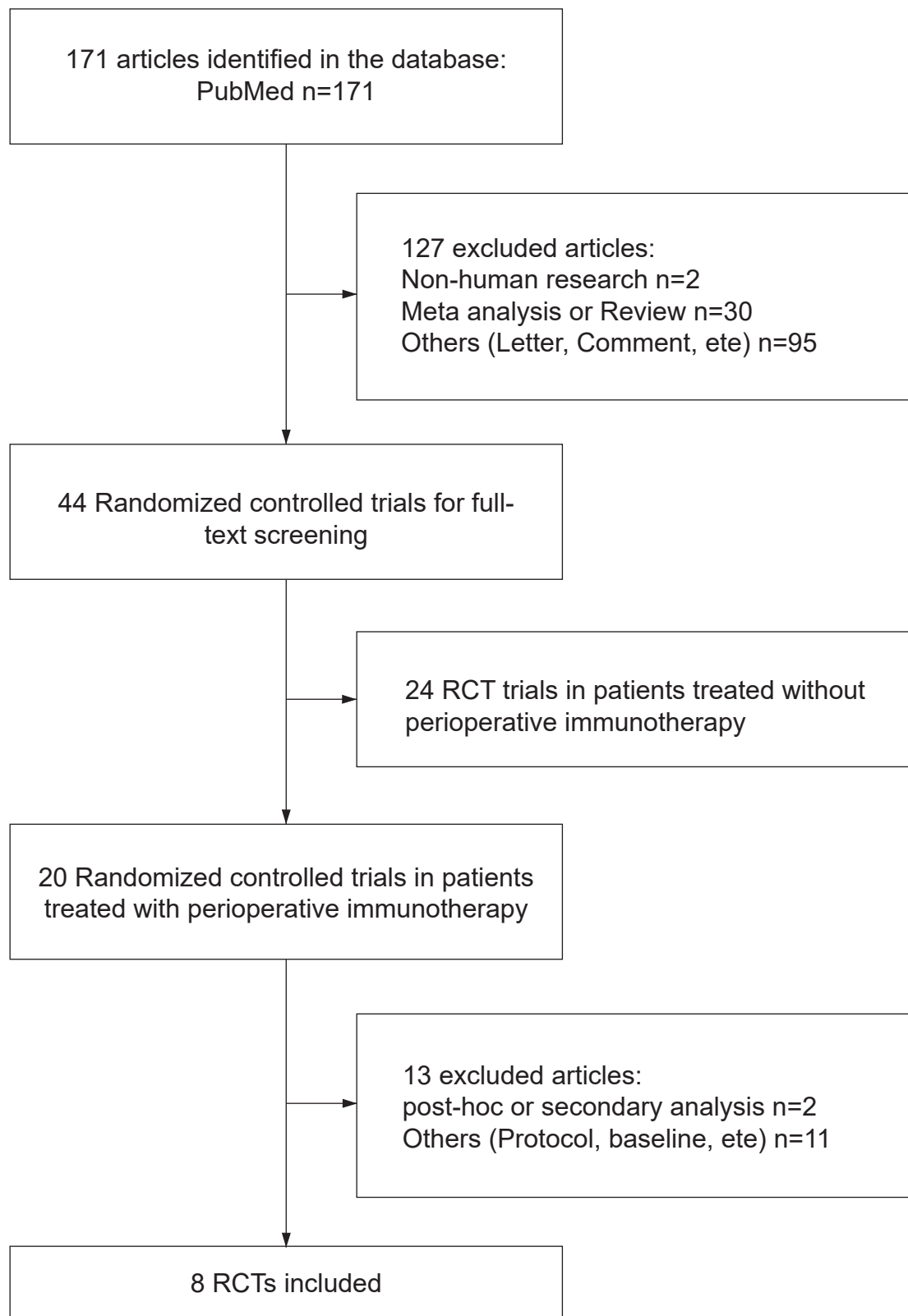
Additional File Table S2. Risk of Bias Assessment of included trial.

Additional File Table S3. Definition for the primary outcome for each include trial.

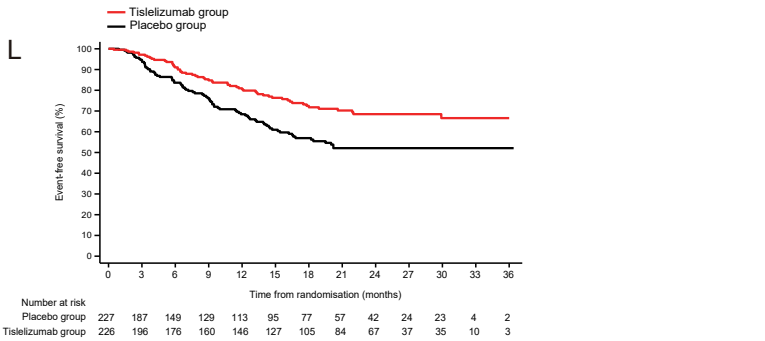
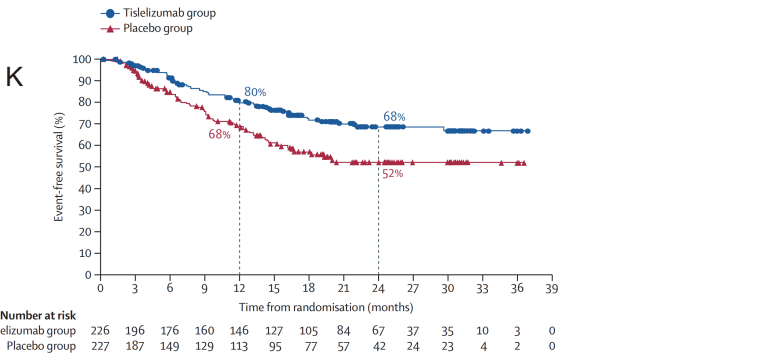
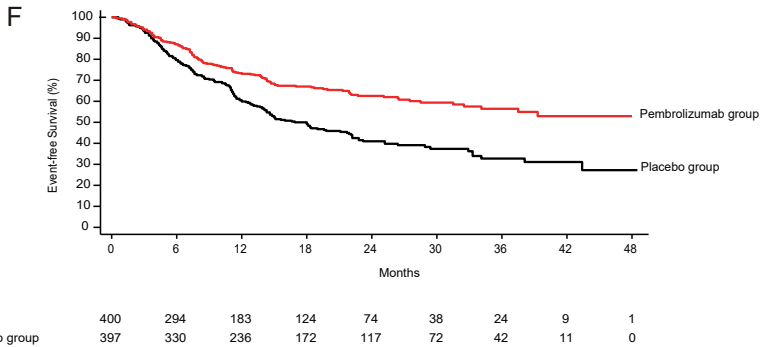
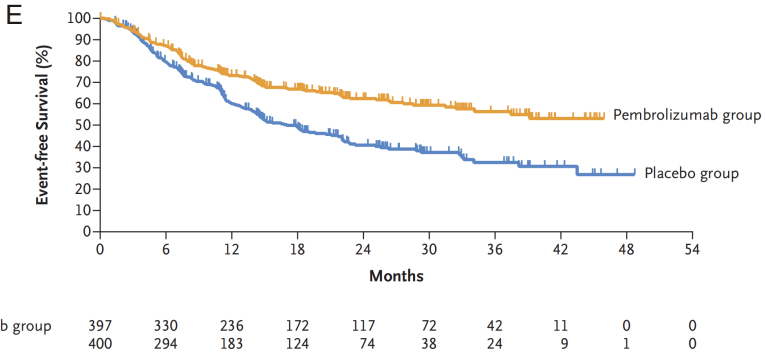
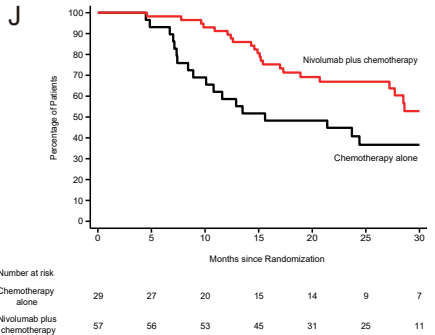
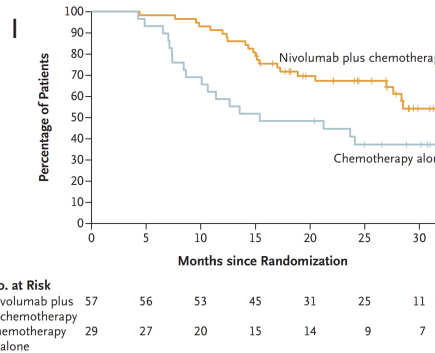
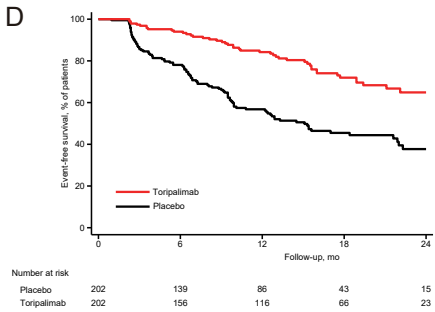
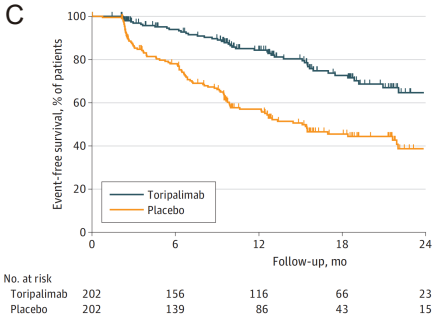
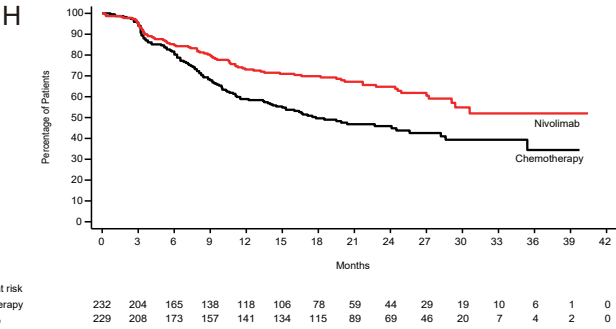
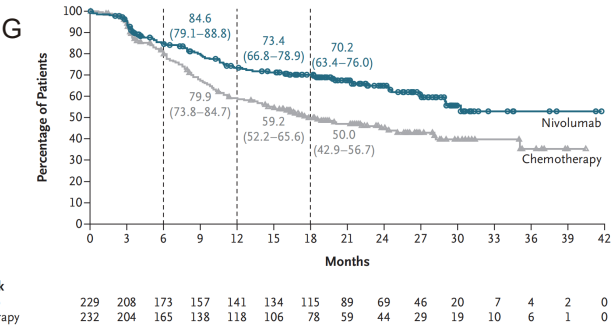
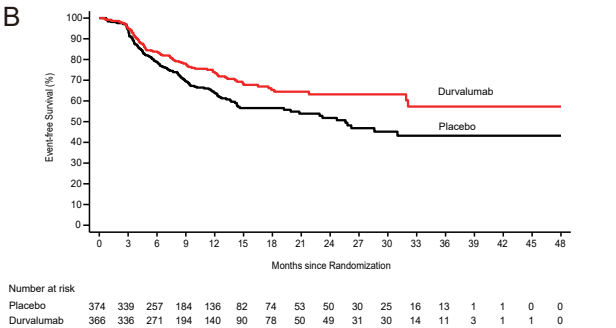
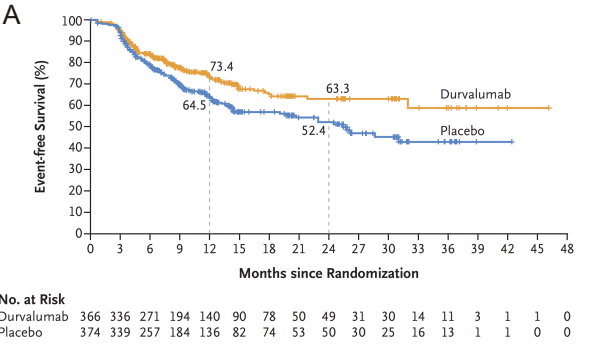
Search Strategy of PubMed for RCT

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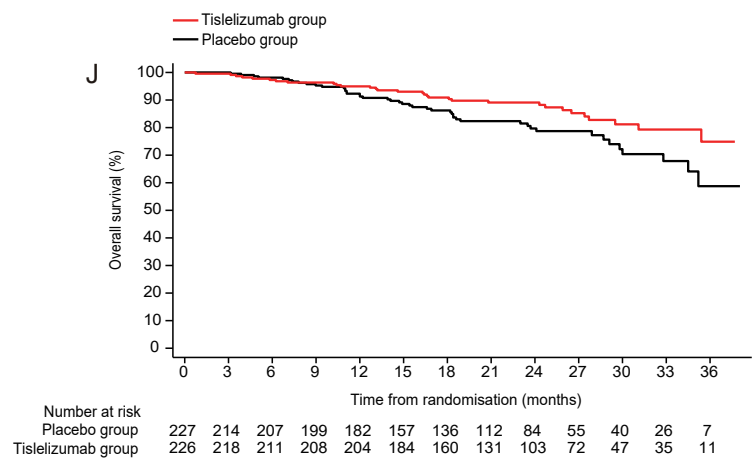
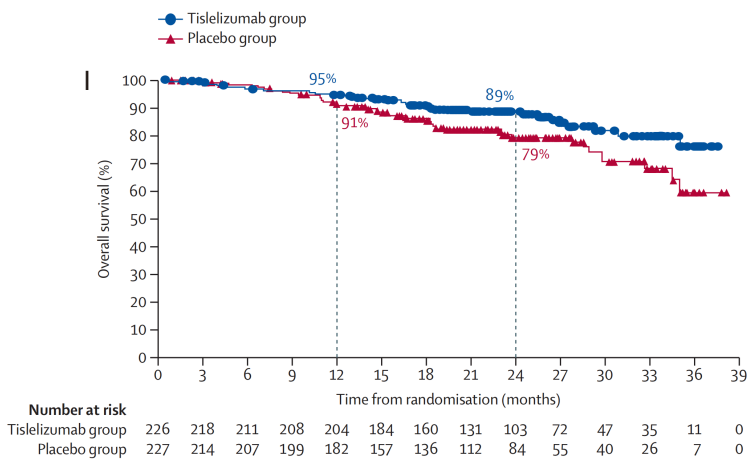
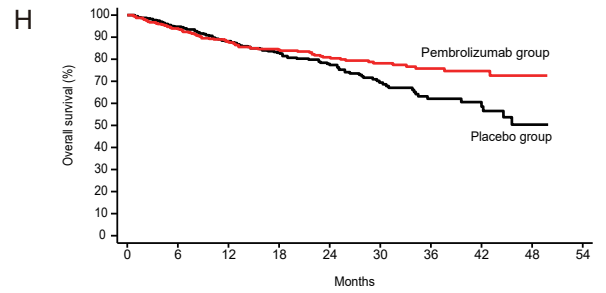
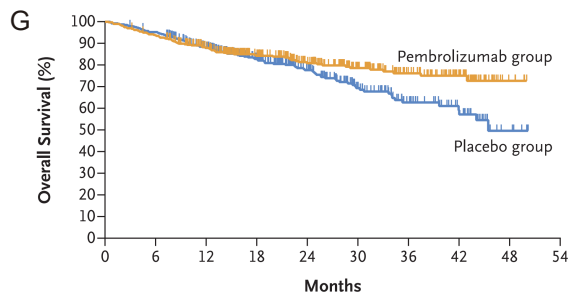
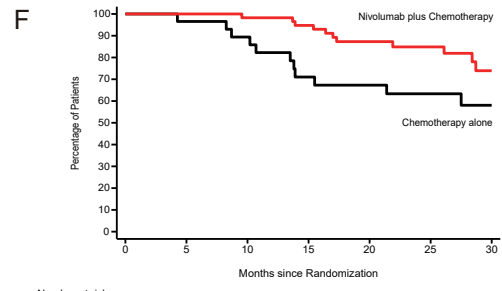
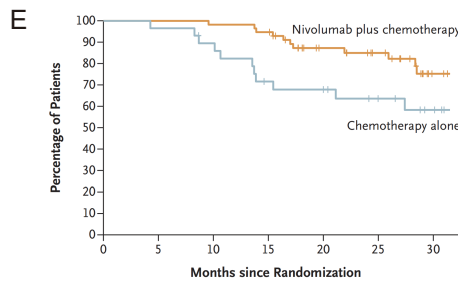
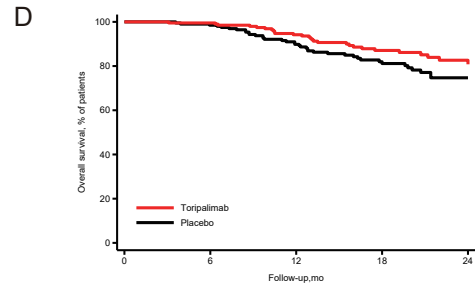
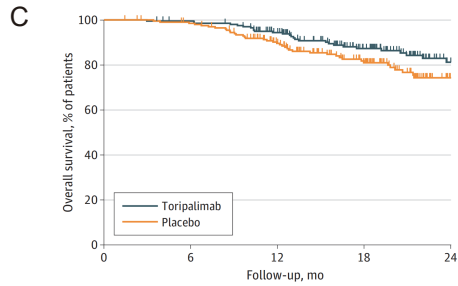
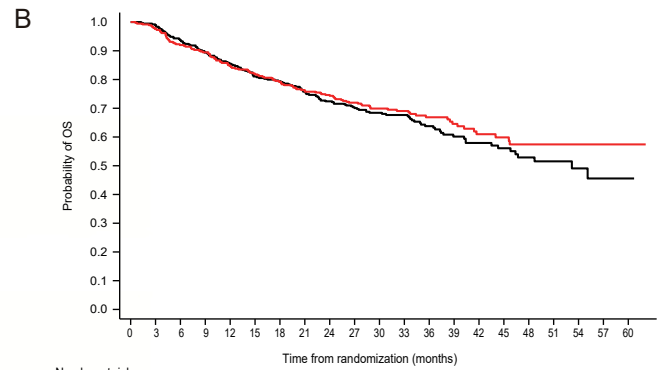
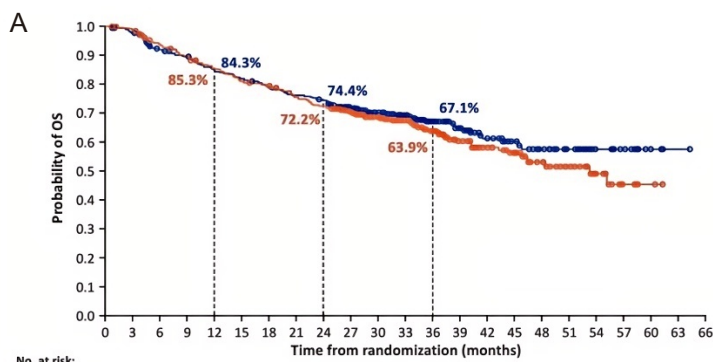


Additional File Figure S1. Flow chart of the search, selection, and inclusion of the studies



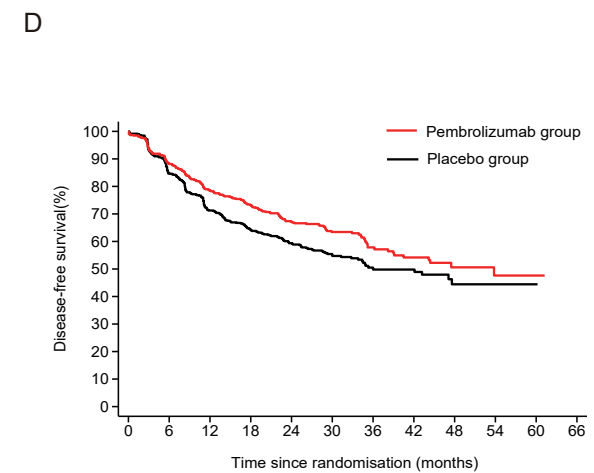
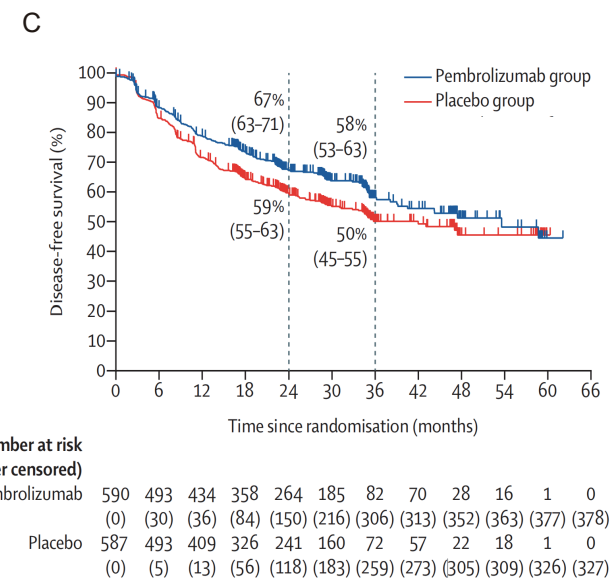
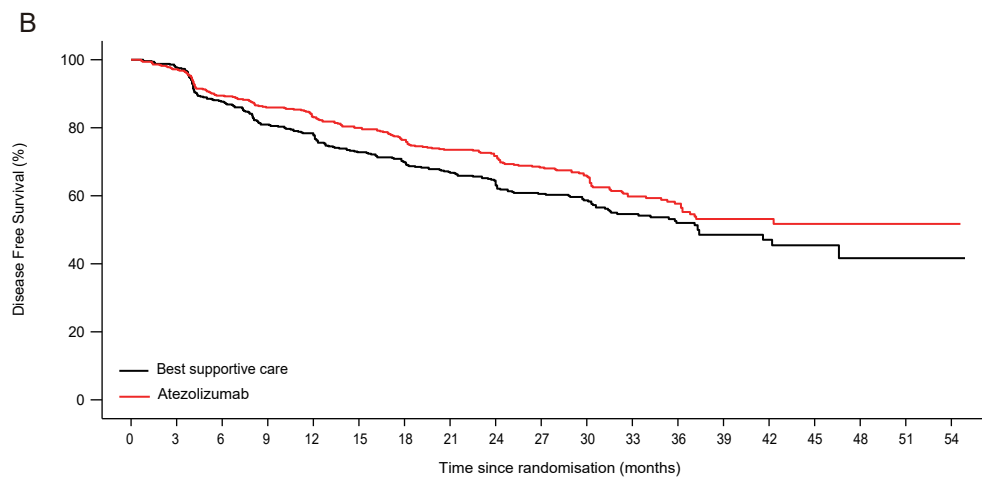
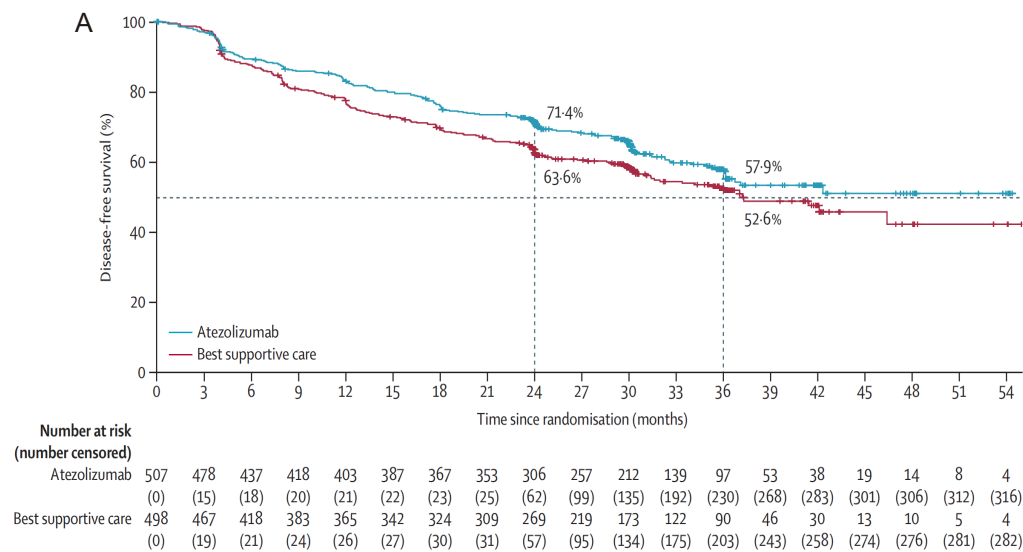
Additional File Figure S2. Reconstruct Kaplan-Meier curve and original Kaplan-Meier curve (event-free survival/progression-free survival)

(A) Original Kaplan-Meier curve (AEGEAN), (B) Reconstruct Kaplan-Meier curve (AEGEAN), (C) Original Kaplan-Meier curve (Neotorch), (D) Reconstruct Kaplan-Meier curve (Neotorch), (E) Original Kaplan-Meier curve (KEYNOTE-671), (F) Reconstruct Kaplan-Meier curve (KEYNOTE-671), (G) Original Kaplan-Meier curve (CheckMate-77T), (H) Reconstruct Kaplan-Meier curve (CheckMate-77T), (I) Original Kaplan-Meier curve (NADIM II), (J) Reconstruct Kaplan-Meier curve (NADIM II), (K) Original Kaplan-Meier curve (RATIONALE-315), (L) Reconstruct Kaplan-Meier curve (RATIONALE-315).



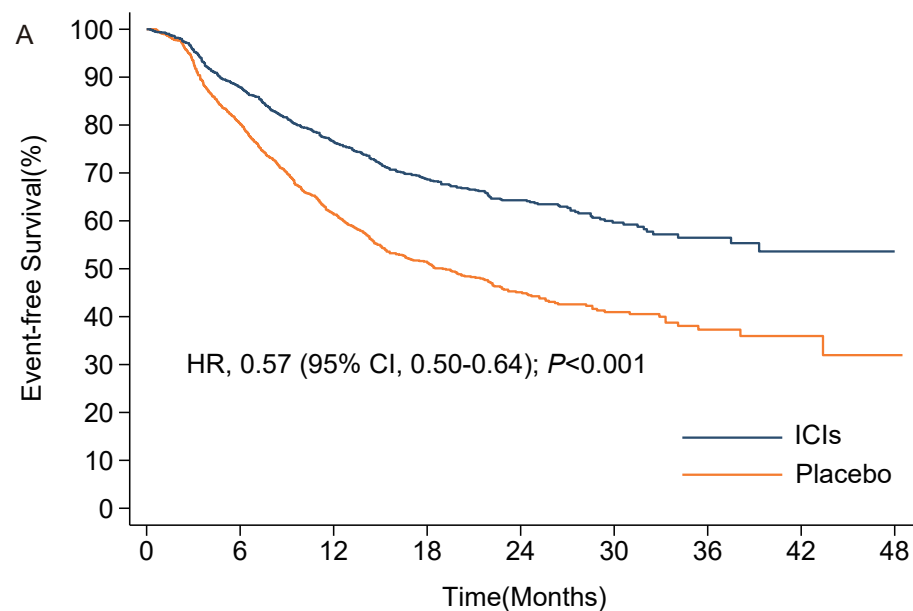
Additional File Figure S3. Reconstruct Kaplan-Meier curve and original Kaplan-Meier curve(overall survival)

(A) Original Kaplan-Meier curve (AEGEAN), (B) Reconstruct Kaplan-Meier curve (AEGEAN), (C) Original Kaplan-Meier curve (Neotorch), (D) Reconstruct Kaplan-Meier curve (Neotorch), (E) Original Kaplan-Meier curve (NADIM II), (F) Reconstruct Kaplan-Meier curve (NADIM II), (G) Original Kaplan-Meier curve (KEYNOTE-671), (H) Reconstruct Kaplan-Meier curve (KEYNOTE-671), (I) Original Kaplan-Meier curve (ATIONALE-315), (J) Reconstruct Kaplan-Meier curve (ATIONALE-315).

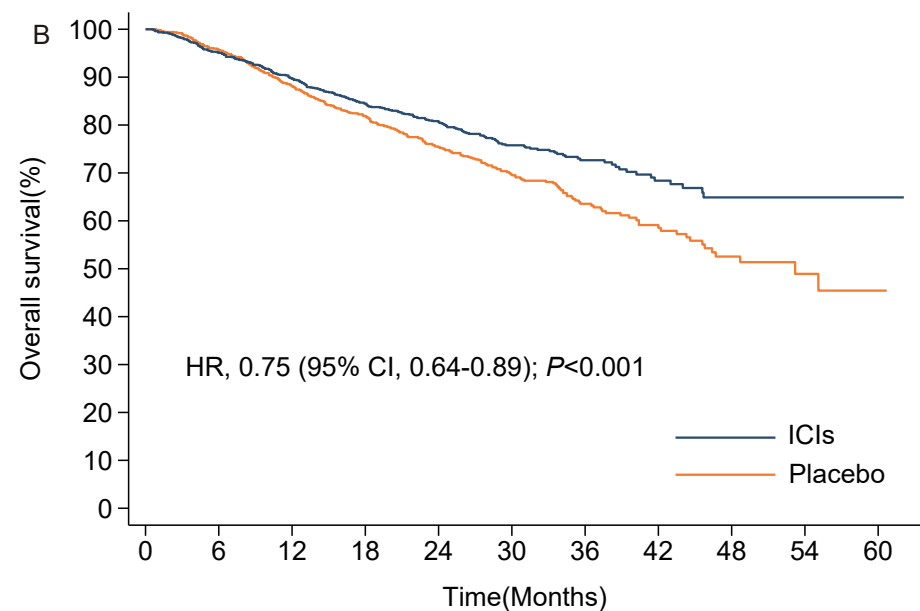


Additional File Figure S4. Reconstruct Kaplan-Meier curve and original Kaplan-Meier curve (disease-free survival)

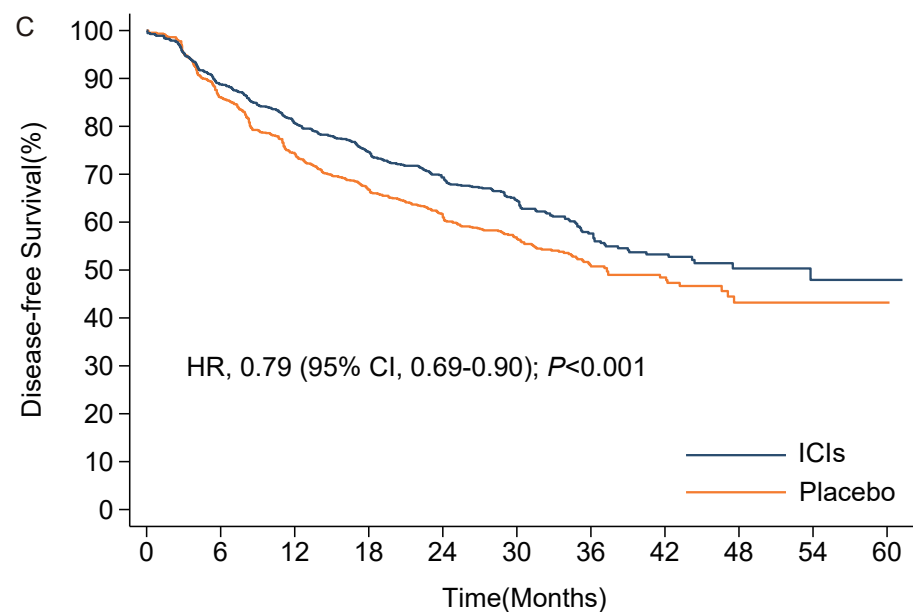
(A) Original Kaplan-Meier curve (IMpower010), (B) Reconstruct Kaplan-Meier curve (IMpower010), (C) Original Kaplan-Meier curve (KEYNOTE-091), (D) Reconstruct Kaplan-Meier curve (KEYNOTE-091).



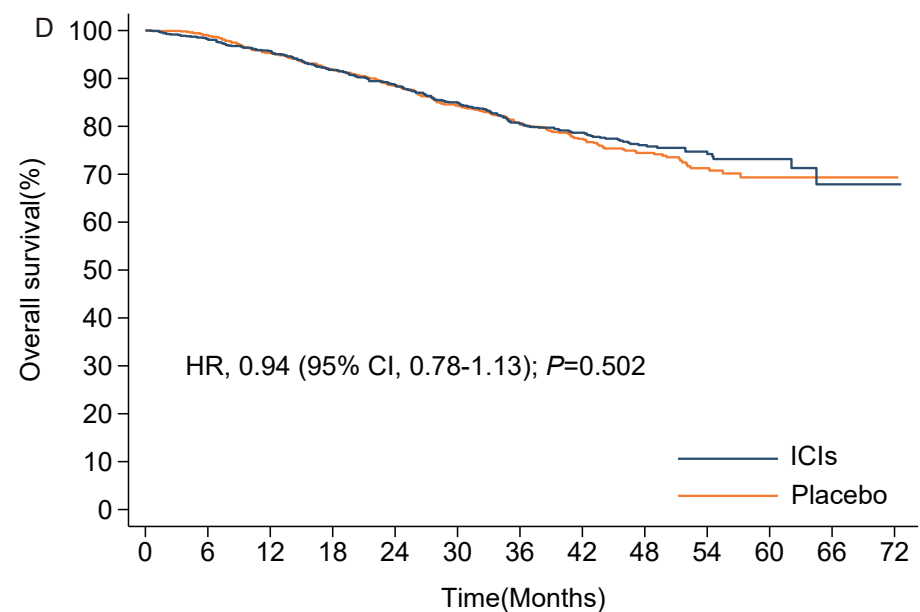
Number at risk										
Placebo	1464	1033	653	410	239	113	46	11	3	
ICIs	1477	1162	831	573	352	168	63	12	12	



Number at risk											
Placebo	1232	1150	988	765	546	323	179	98	49	17	3
ICIs	1248	1163	1040	822	615	364	198	103	45	20	3



Number at risk											
Placebo	1085	911	774	651	512	333	164	87	32	22	1
ICIs	1097	931	837	725	572	397	179	108	42	20	1



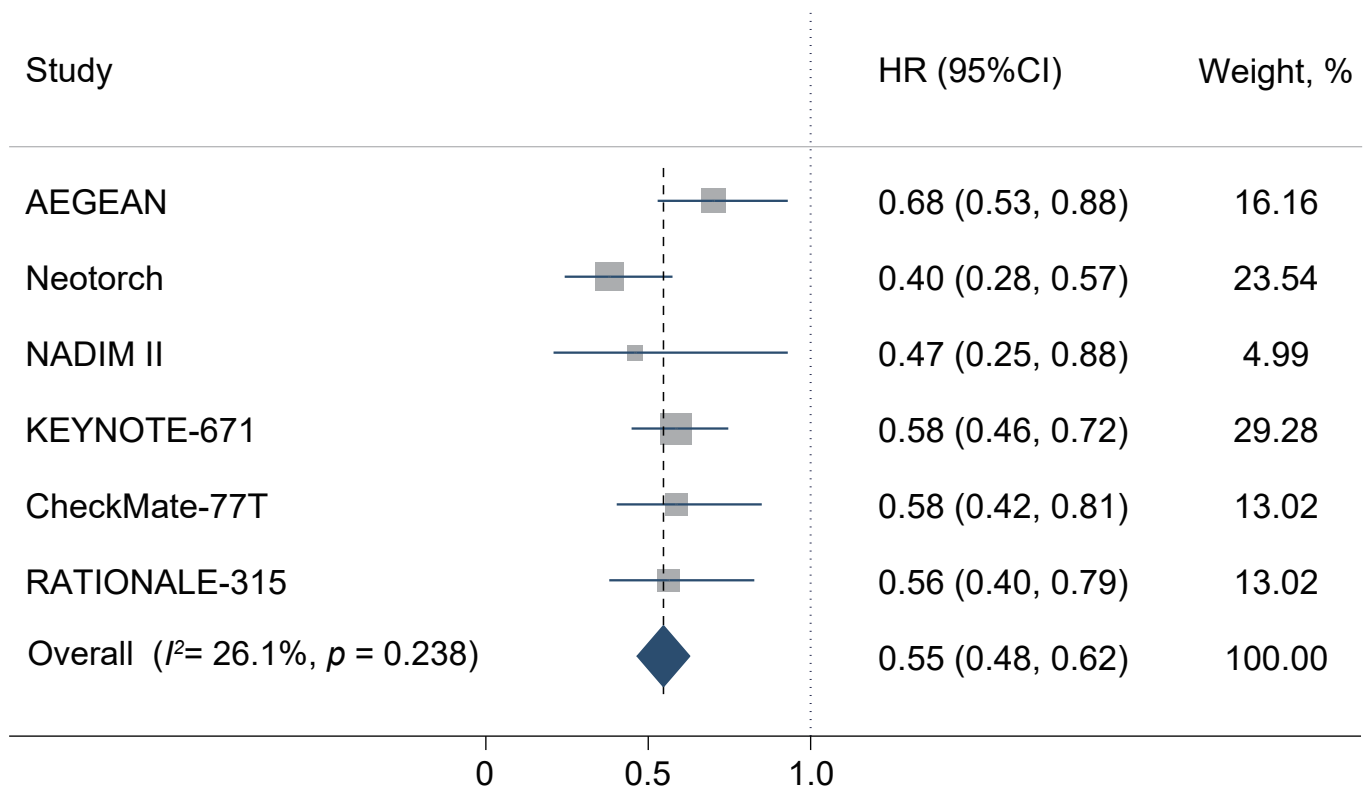
Number at risk													
Placebo	1085	1055	1008	961	841	700	584	460	287	145	44	12	1
ICIs	1097	1060	1020	970	851	726	607	476	289	148	56	11	1

Additional File Figure S5. Cumulative Risk and Hazard Ratio (HR) of Primary Outcome

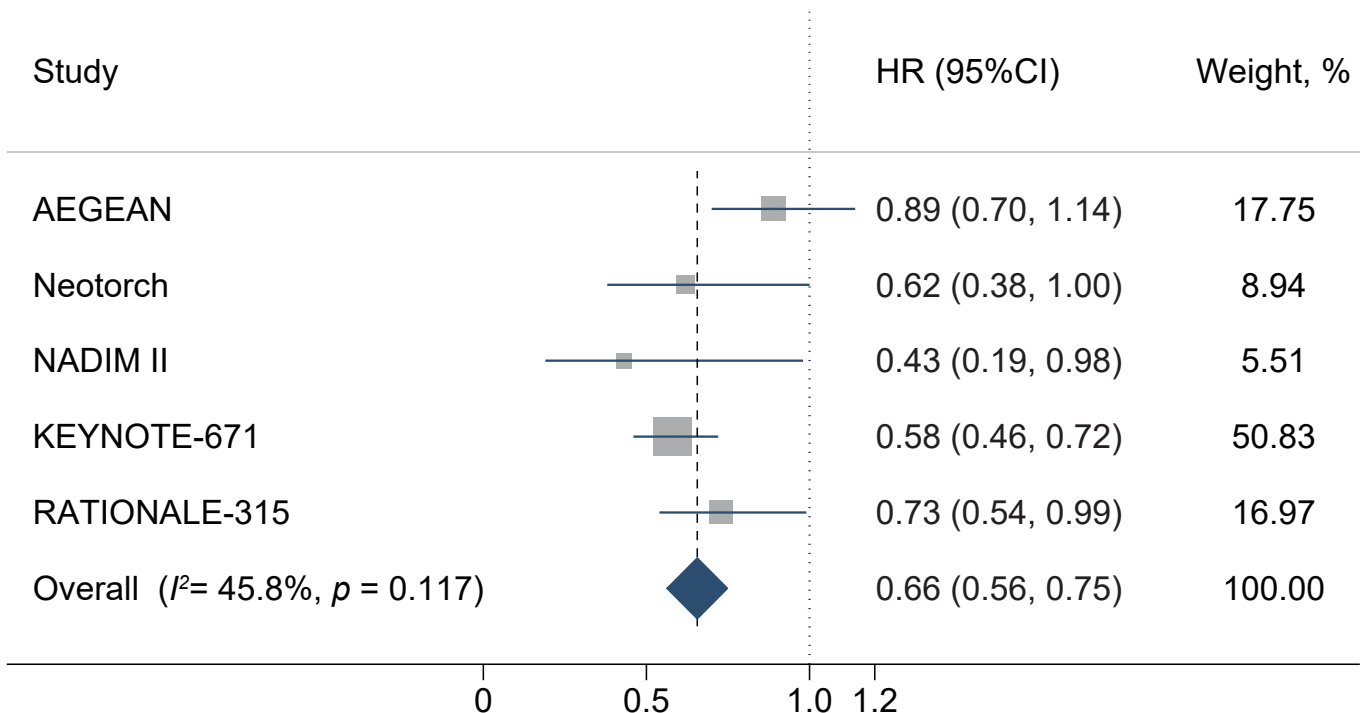
(A) Kaplan-Meier plots of event-free survival of perioperative immunotherapy combined with chemotherapy vs chemotherapy alone; (B) Kaplan-Meier plots of overall survival of perioperative immunotherapy combined with chemotherapy vs chemotherapy alone; (C) Kaplan-Meier plots of disease-free survival of adjuvant immunotherapy combined with chemotherapy vs chemotherapy alone; (D) Kaplan-Meier plots of overall survival of adjuvant immunotherapy combined with chemotherapy vs chemotherapy alone.

ICIs, Immune checkpoint inhibitors. The ICIs group refers to immunotherapy combined with chemotherapy. The Placebo group refers to chemotherapy alone.

A. Event-free survival



B. Overall survival



Additional File Figure S6. Meta-analysis at the Study Level of Primary Outcome

(A) Meta-analysis of event-free survival of perioperative immunotherapy combined with chemotherapy vs chemotherapy alone; (B) Meta-analysis of overall survival of perioperative immunotherapy combined with chemotherapy vs chemotherapy alone.

Additional File Table S1. Characteristics of Included Studies

Supplementary Table 1. Characteristics of Included Studies

Characteristic, year	IMpower010,2021 NCT02486718		KEYNOTE-091,2022 NCT02504372		AEGEAN,2023 NCT03800134		Neotorch,2024 NCT04158440		NADIM II,2023 NCT03838159		KEYNOTE-671,2023 NCT03425643		CheckMate 77T,2024 NCT04025879		RATIONALE-315,2025 NCT04379635	
	Atezolizumab	BSC	Pembrolizumab	Placebo	Durvalumab	Placebo	Toripalimab	Placebo	Nivolumab	BSC	Pembrolizumab	Placebo	Nivolumab	Placebo	Pembrolizumab	Placebo
Countries	Multinational	Multinational	Multinational	Multinational	Multinational	Multinational	China	China	Spain	Spain	Multinational	Multinational	Multinational	Multinational	China	China
Study population	NSCLC	NSCLC	NSCLC	NSCLC	NSCLC	NSCLC	NSCLC	NSCLC	NSCLC	NSCLC	NSCLC	NSCLC	NSCLC	NSCLC	NSCLC	NSCLC
Regimen	Adjuvant	Adjuvant	Adjuvant	Adjuvant	Perioperative	Perioperative	Perioperative	Perioperative	Perioperative	Perioperative	Perioperative	Perioperative	Perioperative	Perioperative	Perioperative	Perioperative
No. of participants	507	498	590	587	366	374	202	202	57	29	397	400	229	232	226	227
Age, median (IQR), y	62(57-67)	62(56-68)	65(59-70)	65(59-70)	65(30-88)	65(39-85)	62(56-65)	61(56-65)	65(58-70)	63(57-66)	63(26-83)	64(35-81)	66(37-83)	66(35-86)	62(57-67)	63(56-68)
Sex, No. (%)																
Male	337(66)	335(67)	401(68)	403(69)	252(69)	278(74)	181(90)	189(94)	36(63)	16(55)	279(70)	284(71)	167(73)	160(69)	205(91)	205(90)
Female	170(34)	164(33)	189(32)	184(31)	114(31)	96(26)	21(10)	13(6)	21(37)	13(45)	118(30)	116(29)	62(27)	72(31)	21(9)	22(10)
ECOG performance status, No. (%)																
0	273(54)	283(57)	380(64)	343(58)	251(69)	255(68)	70(35)	73(36)	31(54)	16(55)	253(64)	246(62)	147(64)	141(61)	142(63)	154(68)
1	232(46)	214(43)	210(36)	244(42)	115(31)	119(32)	132(65)	129(64)	26(46)	13(45)	144(36)	154(39)	82(36)	91(39)	83(37)	73(32)
Disease stage, No. (%)																
II	237(47)	232(47)	329(56)	338(58)	104(28)	110(29)	0	0	0	0	118(30)	121(30)	81(35)	81(35)	92(41)	91(40)
III	205(40)	208(42)	177(30)	162(28)	261(71)	263(70)	201	200	57	29	279(70)	279(70)	146(64)	149(64)	132(58)	133(59)
Regional lymph node stage, No. (%)																
N0	NA	NA	233(39)	257(44)	110(30)	102(27)	17(8)	18(9)	6(11)	9(31)	148(37)	142(36)	80(35)	87(38)	60(27)	54(24)
N1	NA	NA	233(39)	223(38)	75(21)	87(23)	46(23)	39(19)	10(18)	4(14)	81(20)	71(18)	56(25)	52(22)	84(37)	93(41)
N2	NA	NA	124(21)	107(18)	181(50)	185(49)	138(68)	145(72)	41(72)	16(55)	168(42)	187(47)	91(40)	91(39)	82(36)	79(35)
Smoking status, No. (%)																
Current	76(15)	86(17)	75(13)	90(15)	95(26)	95(25)	30(15)	23(11)	30(53)	21(72)	96(24)	103(26)	212/229(93)	205/232(88)	43(19)	52(23)
Previous	317(63)	304(61)	428(73)	431(73)	220(60)	223(60)	144(71)	158(78)	22(39)	8(28)	247(62)	250(63)	212/229(93)	205/232(88)	150(66)	138(61)
Never	114(23)	108(22)	87(15)	66(11)	51(14)	56(15)	28(14)	21(10)	5(9)	0	54(14)	47(12)	17/229(7)	27/232(12)	33(15)	37(16)
PD-L1 expression, No. (%)																
< 1%	210(41)	234(47)	233(39)	232(40)	122(33)	125(33)	69(34)	70(35)	20(40)	8(35)	138(35)	151(38)	101(44)	104(45)	96(42)	95(42)
≥1%	283(56)	252(51)	357(61)	355(60)	244(67)	249(67)	133(66)	132(65)	30(60)	15(65)	259(65)	249(62)	128(56)	128(55)	130(58)	132(58)</

Abbreviations: BSC, best supportive care (observation and regular scans for disease recurrence). ECOG, Eastern Cooperative Oncology Group, performance-status scores range from 0 to 5, with higher scores indicating greater disability. NSCLC, non-small-cell lung cancer. DFS, disease-free survival. EFS, event-free survival. PFS, progression-free survival. NA, not available. NE, not estimable. HR, hazard ratio.

Additional File Table S2. Risk of Bias Assessment of included trials

Supplementary Table 2. Risk of Bias Assessment of included trials								
	Impower010	AEGEAN	Neotorch	KEYNOTE-091	NADIM II	KEYNOTE-671	CheckMate-77T	RATIONALE-315
Random sequence generation	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Allocation concealment	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Blinding of participants and personnel	HIGH	LOW	LOW	LOW	HIGH	LOW	LOW	LOW
Blinding of outcome assessment	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Incomplete outcome data	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Selective reporting	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Overall	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW

Additional File Table S3. Definition for the primary outcome for each include trial

Supplementary Table 3. Definition for the primary outcome for each include trial

Trial	Definition
IMpower010	IMpower010 was a randomised, multicentre, open-label, phase 3 study done at 227 sites in 22 countries and regions. Eligible patients were 18 years or older with completely resected stage IB (tumours ≥ 4 cm) to IIIA NSCLC per the Union Internationale Contre le Cancer and American Joint Committee on Cancer staging system (7th edition). Patients were randomly assigned (1:1) by a permuted-block method (block size of four) to receive adjuvant atezolizumab (1200 mg every 21 days; for 16 cycles or 1 year) or best supportive care (observation and regular scans for disease recurrence) after adjuvant platinum-based chemotherapy (one to four cycles). The primary endpoint, investigator-assessed disease-free survival, was tested hierarchically first in the stage II–IIIA population subgroup whose tumours expressed PD-L1 on 1% or more of tumour cells.
KEYNOTE-091	In this randomised, triple-blind, phase 3 trial, patients were recruited from 196 medical centres in 29 countries. Eligible patients were aged 18 years or older, with completely resected, pathologically confirmed stage IB (tumours of ≥ 4 cm in diameter), II, or IIIA NSCLC per the American Joint Committee on Cancer staging system (7th edition) of any histology or PD-L1 expression level, and an Eastern Cooperative Oncology Group performance status of 0 or 1; adjuvant chemotherapy was to be considered for stage IB disease and was strongly recommended for stage II and IIIA disease, according to national and local guidelines. Using a central interactive voice-response system, eligible participants were randomly assigned (1:1), using a minimisation technique and stratified by disease stage, previous adjuvant chemotherapy, PD-L1 expression, and geographical region, to pembrolizumab 200 mg or placebo, both administered intravenously every 3 weeks for up to 18 cycles. Dual primary endpoints were disease-free survival in the overall population and in the population with PD-L1 tumour proportion score (TPS) of 50% or greater. This study randomly assigned patients with resectable NSCLC (stage II to IIIB [N2 node stage] according to the eighth edition of the AJCC Cancer Staging Manual) to receive platinum-based chemotherapy plus durvalumab or placebo administered intravenously every 3 weeks for 4 cycles before surgery, followed by adjuvant durvalumab or placebo intravenously every 4 weeks for 12 cycles. Randomization was stratified according to disease stage (II or III) and programmed death ligand 1 (PD-L1) expression ($\geq 1\%$ or $< 1\%$). Primary end points were event-free survival (defined as the time to the earliest occurrence of progressive disease that precluded surgery or prevented completion of surgery, disease recurrence [assessed in a blinded fashion by independent central review], or death from any cause) and pathological complete response (evaluated centrally).
AEGEAN	This randomized clinical trial enrolled patients with stage II or III resectable NSCLC (without EGFR or ALK alterations for nonsquamous NSCLC) at 50 participating hospitals in China. Patients were randomized in a 1:1 ratio to receive 240 mg of toripalimab or placebo once every 3 weeks combined with platinum-based chemotherapy for 3 cycles before surgery and 1 cycle after surgery, followed by toripalimab only (240 mg) or placebo once every 3 weeks for up to 13 cycles. The primary outcomes were event-free survival (assessed by the investigators) and the major pathological response rate (assessed by blinded, independent pathological review).
Neotorch	This study conducted a randomized, double-blind, phase 3 trial to evaluate perioperative pembrolizumab in patients with early-stage NSCLC. Participants with resectable stage II, IIIA, or IIIB (N2 stage) NSCLC were assigned in a 1:1 ratio to receive neoadjuvant pembrolizumab (200 mg) or placebo once every 3 weeks, each of which was given with cisplatin-based chemotherapy for 4 cycles, followed by surgery and adjuvant pembrolizumab (200 mg) or placebo once every 3 weeks for up to 13 cycles. The dual primary end points were event-free survival (the time from randomization to the first occurrence of local progression that precluded the planned surgery, unresectable tumor, progression or recurrence, or death) and overall survival.
KEYNOTE-671	In this phase 3, randomized, double-blind trial, we assigned adults with resectable stage IIA to IIIB NSCLC to receive neoadjuvant nivolumab plus chemotherapy or neoadjuvant chemotherapy plus placebo every 3 weeks for 4 cycles, followed by surgery and adjuvant nivolumab or placebo every 4 weeks for 1 year. The primary outcome was event-free survival according to blinded independent review.
CheckMate-77T	RATIONALE-315 is a randomised, double-blind, placebo-controlled phase 3 trial conducted at 50 sites (hospitals or academic research centres) in China. Patients (aged ≥ 18 years) with untreated stage II–IIIA squamous or non-squamous NSCLC were randomly assigned (1:1) to neoadjuvant tislelizumab 200 mg or placebo intravenously every 3 weeks, plus platinum-based doublet chemotherapy followed by surgery and adjuvant tislelizumab 400 mg or placebo every 6 weeks. Dual primary endpoints were major pathological response rate and event-free survival, analysed by intention to treat.
RATIONALE-315	In this open-label, phase 2 trial, we randomly assigned patients with resectable stage IIIA or IIIB NSCLC to receive neoadjuvant nivolumab plus platinum-based chemotherapy (experimental group) or chemotherapy alone (control group), followed by surgery. Patients in the experimental group who had R0 resections received adjuvant treatment with nivolumab for 6 months. The primary end point was a pathological complete response (0% viable tumor in resected lung and lymph nodes).
NADIM II	