Supplementary

Appendix 1

Search strategies for Cochrane database, EMBASE, and PubMed.

Cochrane: 646 results

#1 MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
#2 (lung OR pumlon):ti,ab,kw
#3 (cancer or carcinoma or neoplas):ti,ab,kw
#4 #2 AND #3
#5 #1 OR #4
#6 (perioperative OR neoadjuvant OR adjuvant):ti,ab,kw
#7 (pembrolizumab OR lambrolizumab OR Keytruda OR MK-3475 OR nivolumab OR MDX-1106 OR ONO-4538 OR BMS-936558 OR Opdivo OR atezolizumab OR MPDL3280A OR Tecentriq OR RG7446 OR RG-7446 OR Durvalumab OR Imfinzi OR MEDI4736 OR Camrelizumab OR SHR-1210 OR Tislelizumab OR Sintilimab OR 'IBI 308' OR 'anti-PDL1' OR 'anti-PD1' OR 'PD-1' OR PD-L1 OR 'Programmed Death 1' OR 'Programmed Cell Death 1 Receptor' OR 'Programmed Death-Ligand 1' OR 'programmed cell death 1 ligand 1 protein' OR 'immune checkpoint inhibitor' OR 'immune therapy' OR immunotherapy):ti, ab, kw
#8 #5 AND #6 AND #7
#9 (trial):ti,ab,kw OR (clinical trial):ti,ab,kw OR (phase):ti,ab,kw OR (random):ti,ab,kw
#10 #8 AND #9

Embase: 326 results

('pembrolizumab'/exp OR 'pembrolizumab' OR 'lambrolizumab':ab,ti OR 'keytruda':ab,ti OR 'mk-3475':ab,ti OR 'nivolumab'/exp OR 'mdx-1106':ab,ti OR 'ono-4538':ab,ti OR 'bms-936558':ab,ti OR 'opdivo':ab,ti OR 'atezolizumab'/exp OR 'mpdl3280a':ab,ti OR 'tecentriq':ab,ti OR 'rg7446':ab,ti OR 'rg-7446':ab,ti OR 'durvalumab':ab,ti OR 'imfinzi':ab,ti OR 'medi4736':ab,ti OR 'camrelizumab'/exp OR 'shr-1210':ab,ti OR 'tislelizumab'/exp OR 'sintilimab'/exp OR 'ibi 308':ab,ti OR 'anti-pdl1':ab,ti OR 'anti-pd1':ab,ti OR 'pd-1':ab,ti OR 'pd-l1':ab,ti OR 'programmed death 1':ab,ti OR 'programmed cell death 1 receptor':ab,ti OR 'programmed death-ligand 1':ab,ti OR 'programmed cell death 1 ligand 1 protein':ab,ti OR 'immune checkpoint inhibitor':ab,ti OR 'immune therapy':ab,ti OR 'immunotherapy':ab,ti) AND ('perioperative':ab,ti OR 'neoadjuvant':ab,ti OR 'adjuvant':ab,ti) AND ('non small cell lung cancer'/exp OR 'lung cancer':ab,ti OR 'nsclc':ab,ti OR 'non small cell':ab,ti OR 'non-small-cell':ab,ti OR 'non-small cell':ab,ti) AND 'randomized controlled trial'/exp

PubMed: 353 results

((("pembrolizumab" [Title/Abstract] OR "lambrolizumab" [Title/Abstract] OR "Keytruda" [Title/Abstract] OR "MK-3475" [Title/Abstract] OR "nivolumab" [Title/Abstract] OR "MDX-1106" [Title/Abstract] OR "ONO-4538" [Title/Abstract] OR "BMS-936558" [Title/Abstract] OR "Opdivo"[Title/Abstract] OR "atezolizumab"[Title/Abstract] OR "MPDL3280A"[Title/Abstract] OR "Tecentriq"[Title/Abstract] OR"RG7446"[Title/Abstract] OR "RG-7446"[Title/Abstract] OR "Durvalumab" [Title/Abstract] OR "Imfinzi" [Title/Abstract] OR "MEDI4736" [Title/Abstract] OR "Camrelizumab" [Title/Abstract] OR "SHR-1210" [Title/Abstract] OR "Tislelizumab" [Title/Abstract] OR "Sintilimab" [Title/Abstract] OR "anti-PDL1"[Title/Abstract] OR "anti-PD1"[Title/Abstract] OR "PD-1"[Title/Abstract] OR "PD-L1"[Title/Abstract] OR "Programmed Death 1"[Title/Abstract] OR "Programmed Cell Death 1 Receptor"[Title/Abstract] OR "Programmed Death-Ligand 1"[Title/Abstract] OR "programmed cell death 1 ligand 1 protein"[Title/Abstract] OR "immune checkpoint inhibitor"[Title/Abstract] OR "immune therapy"[Title/Abstract] OR "immunotherapy"[Title/Abstract]) AND (perioperative[Title/Abstract] OR neoadjuvant[Title/Abstract] OR adjuvant[Title/Abstract])) AND ((("nonsquamous"[Title/Abstract]) OR "lung cancer"[Title/Abstract]) OR ((NSCLC[Title/Abstract]) OR ("Non Small Cell"[Title/Abstract]) OR ("Non-Small-Cell"[Title/Abstract]) OR

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("Non-Small Cell"[Title/Abstract]) OR ("Carcinoma, Non-Small-Cell Lung"[Mesh]))))) AND ("clinical trials as topic"[MeSH Terms] OR "clinical trial"[Title/Abstract] OR "random"[Title/Abstract] OR "phase"[Title/Abstract])

Table S1 Quality assessment by Cochrane Collaboration's tool

Regimen	Trial	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other source of bias
12/13 cycles	KEYNOTE-671	Adequate	Adequate (central allocation)	Adequate	Adequate	Adequate	–
	AEGEAN	Adequate	Not clear	Adequate	Adequate	Adequate	–
	Neotorch	Adequate	Not clear	Adequate	Adequate	Adequate	–
	CheckMate 77T	Adequate	Adequate (central allocation)	Adequate	Adequate	Adequate	–
6/8 cycles	NADIM II	Adequate	Not clear	Adequate	Adequate	Adequate	–
	RATIONALE-315	Adequate	Not clear	Adequate	Adequate	Adequate	Data from conferences

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Table S2 Additional characteristics of patients and outcomes of included trials

Characteristic	NADIM II		RATIONALE-315		Neotorch		CheckMate 77T		AEGEAN		KEYNOTE-671	
	Nivo	Placebo	Tis	Placebo	Tori	Placebo	Nivo	Placebo	Durva	Placebo	Pembro	Placebo
Overall	57	29	226	227	202	202	229	232	366	374	397	400
Age												
<65 years	28, 0.49	15, 0.52	143, 0.63	129, 0.57	140, 0.69	138, 0.68	102, 0.45	100, 0.43	182, 0.5	186, 0.5	221, 0.56	214, 0.54
≥65 years	29, 0.51	14, 0.48	83, 0.37	98, 0.43	62, 0.31	64, 0.32	127, 0.55	132, 0.57	184, 0.5	188, 0.5	176, 0.44	186, 0.47
Sex												
Male	36, 0.63	16, 0.55	205, 0.91	205, 0.9	181, 0.9	189, 0.94	167, 0.73	160, 0.69	252, 0.69	278, 0.74	279, 0.7	284, 0.71
Female	21, 0.37	13, 0.45	21, 0.09	22, 0.1	21, 0.1	13, 0.06	62, 0.27	72, 0.31	114, 0.31	96, 0.26	118, 0.3	116, 0.29
ECOG												
0	31, 0.54	16, 0.55	142, 0.63	154, 0.68	70, 0.35	73, 0.36	147, 0.64	141, 0.61	251, 0.69	255, 0.68	253, 0.64	246, 0.62
1	26, 0.46	13, 0.45	83, 0.37	73, 0.32	132, 0.65	129, 0.64	82, 0.36	91, 0.39	115, 0.31	119, 0.32	144, 0.36	154, 0.39
Stage												
II	0	0	92, 0.41	91, 0.4	0	0	81, 0.35	81, 0.35	104, 0.28	110, 0.29	118, 0.3	121, 0.3
III	57, 1	29, 1	132, 0.58	133, 0.59	202, 1	202, 1	146, 0.64	149, 0.64	262, 0.72	264, 0.71	279, 0.7	279, 0.7
IIIA	44, 0.77	24, 0.83	132, 0.58	133, 0.59	136, 0.67	136, 0.67	NR	NR	173, 0.47	165, 0.44	NR	NR
IIIB	13, 0.23	5, 0.17	0	0	65, 0.32	64, 0.32	NR	NR	88, 0.24	98, 0.26	NR	NR
Histology												
Squamous	21, 0.37	14, 0.48	179, 0.79	175, 0.77	157, 0.78	157, 0.78	116, 0.51	118, 0.51	169, 0.46	191, 0.51	171, 0.43	173, 0.43
non-Squamous	36, 0.63	15, 0.52	45, 0.2	50, 0.22	45, 0.22	45, 0.22	113, 0.49	114, 0.49	196, 0.54	179, 0.48	226, 0.57	227, 0.57
PD-L1 expression												
<1%	13, 0.23	7, 0.24	89, 0.39	84, 0.37	51, 0.25	54, 0.27	93, 0.41	93, 0.4	122, 0.33	125, 0.33	138, 0.35	151, 0.38
≥1%	34, 0.6	19, 0.66	130, 0.58	132, 0.58	NR	NR	128, 0.56	128, 0.55	NR	NR	259, 0.65	249, 0.62
1–49%	NR	NR	59, 0.26	70, 0.31	69, 0.34	68, 0.34	83, 0.36	76, 0.33	135, 0.37	142, 0.38	127, 0.32	115, 0.29
≥50%	NR	NR	71, 0.31	62, 0.27	64, 0.32	64, 0.32	45, 0.2	52, 0.22	109, 0.3	107, 0.29	132, 0.33	134, 0.34
Smoking												
Current	30, 0.53	21, 0.72	43, 0.19	52, 0.23	NR	NR	NR	NR	95, 0.26	95, 0.25	96, 0.24	103, 0.26
Former	NR	NR	150, 0.66	138, 0.61	NR	NR	NR	NR	220, 0.6	223, 0.6	247, 0.62	250, 0.63
Current + former	NR	NR	NR	NR	174, 0.86	181, 0.9	212, 0.93	205, 0.88	NR	NR	NR	NR
Never + former	27, 0.47	8, 0.28	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Never	NR	NR	33, 0.15	37, 0.16	28, 0.14	21, 0.1	17, 0.07	27, 0.12	51, 0.14	56, 0.15	54, 0.14	47, 0.12
Pathologic response												
Complete	21, 0.37	2, 0.07	92, 0.41	13, 0.06	50, 0.25	2, 0.01	58, 0.25	11, 0.05	63, 0.17	16, 0.04	72, 0.18	16, 0.04
Incomplete + major	36, 0.63	27, 0.93	134, 0.59	214, 0.94	152, 0.75	200, 0.99	98, 0.43	148, 0.64	303, 0.83	358, 0.96	325, 0.82	384, 0.96

durva, durvalumab; ECOG, Eastern Cooperative Oncology Group; nivo, nivolumab; nivo, nivolumab; NR, not report; PD-L1, programmed death ligand 1; pembro, pembrolizumab; tis, tislelizumab; tori, toripalimab.

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Table S3 Results of sensitivity analyses

Sensitivity analysis strategy	Trials	Reference value	Direct meta	Indirect meta
Based on definitive surgery rate, >75% were included				
12/13 cycle	AEGEAN	76.70%	HR =0.61, 95% CI: 0.53–0.71	HR =1.07, 95% CI: 0.73–1.54
	KEYNOTE-671	79.40%		
	CheckMate 77T	76.70%		
6/8 cycle	RATIONALE-315	76.20%	HR =0.57, 95% CI: 0.41–0.8	
Based on adjuvant initiation rate, >70% were included				
12/13 cycle	Neotorch	71.80%	HR =0.5, 95% CI: 0.43–0.63	HR =0.95, 95% CI: 0.67–1.34
	KEYNOTE-671	73.20%		
6/8 cycle	RATIONALE-315	74%	HR =0.55, 95% CI: 0.41–0.73	
	NADIM II	74%		
Based on median follow-up duration, >24 months were included				
12/13 cycle	AEGEAN	25.9 months	HR =0.61, 95% CI: 0.53–0.71	HR =1.30, 95% CI: 0.68–2.48
	KEYNOTE-671	36.6 months		
	CheckMate 77T	25.4 months		
6/8 cycle	NADIM II	26.1 months	HR =0.47, 95% CI: 0.25–0.88	

CI, confidence interval; HR, hazard ratio.

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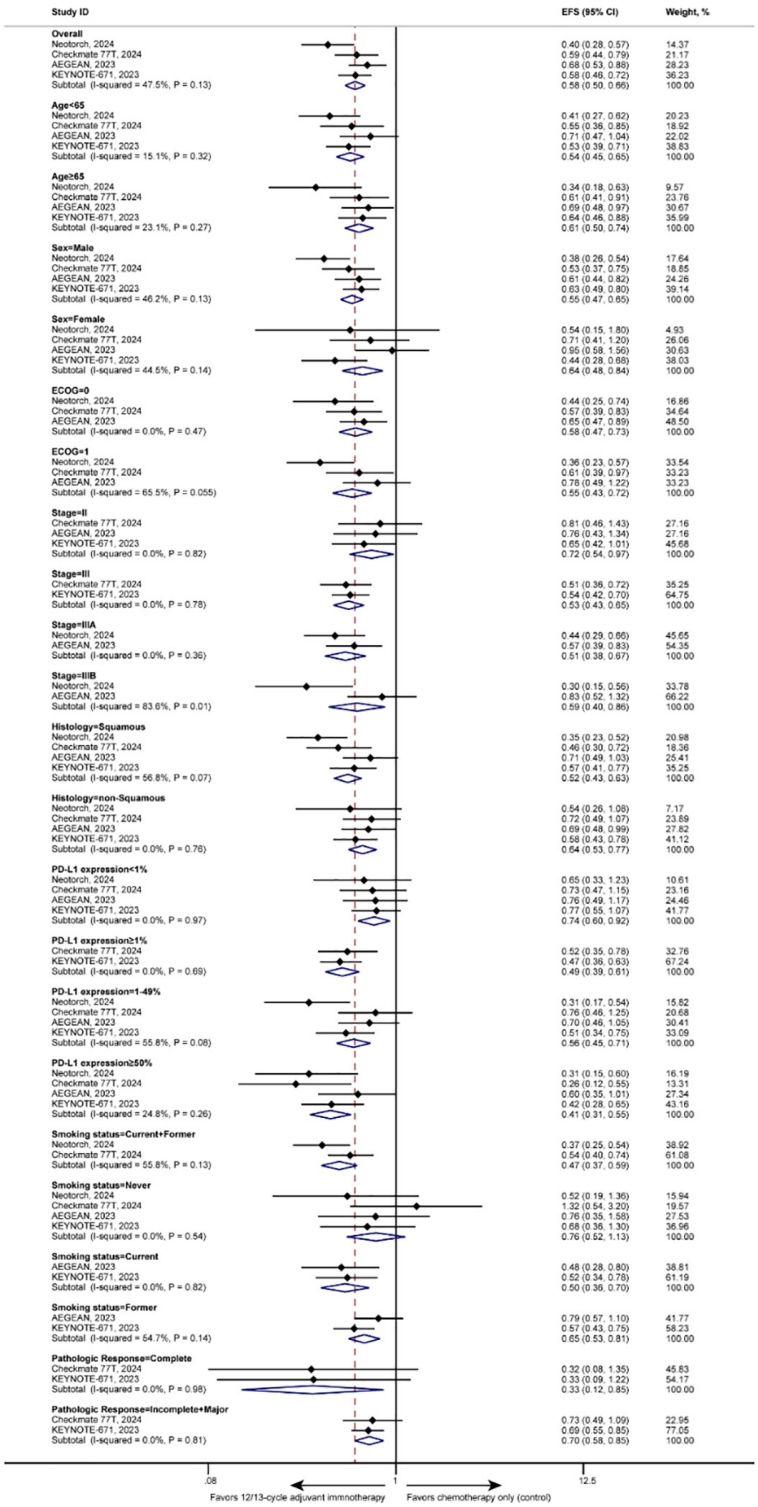

Figure S1 Forest plot of HR in subgroup analyses comparing EFS in patients who received 12/13-cycle adjuvant immunotherapy versus chemotherapy alone. The horizontal line crossing the dot represents the 95% CI of the pooled HR in each subgroup-analysis. I-squared (P) shows the heterogeneity in each subgroup meta-analysis. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; HR, hazard ratio; PD-L1, programmed cell death-ligand 1.

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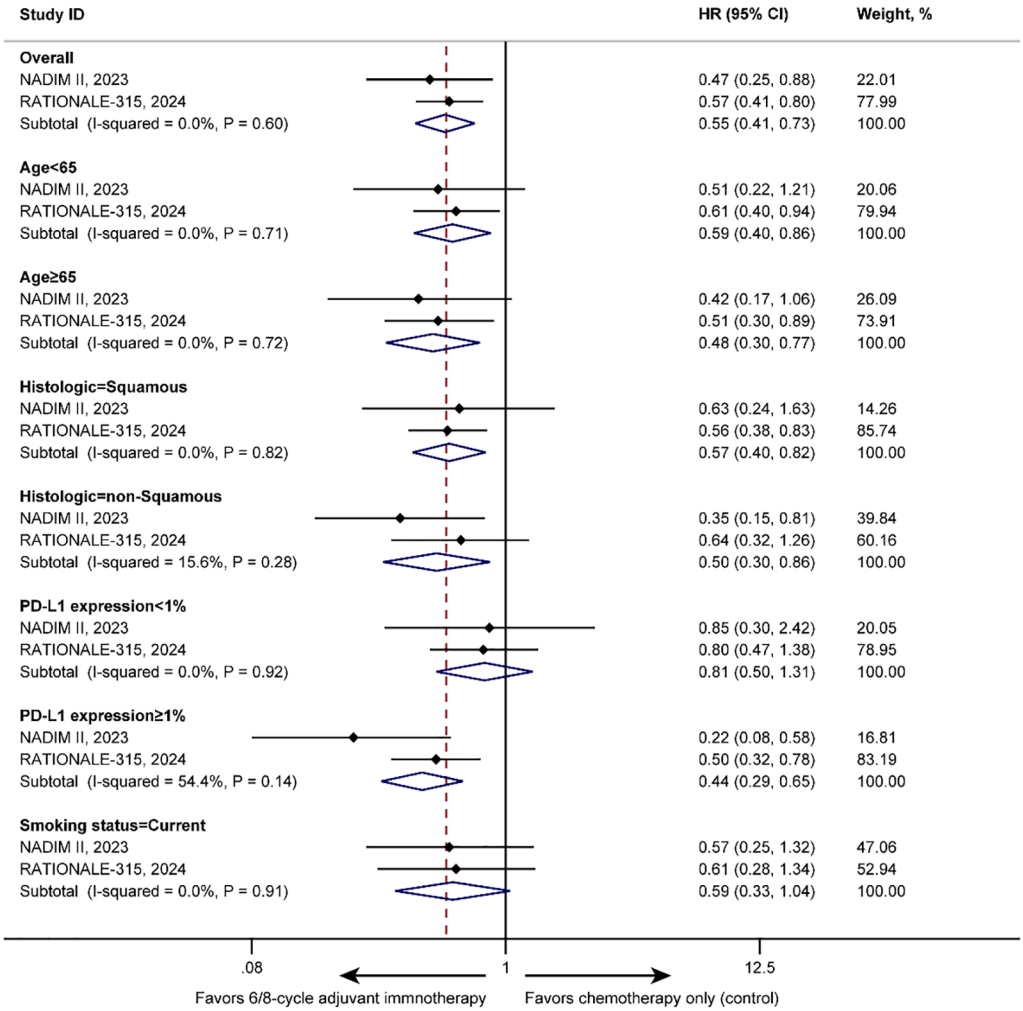

Figure S2 Forest plot of HR in subgroup-analyses comparing EFS in patients who received 6/8-cycle adjuvant immunotherapy versus chemotherapy. The horizontal line crossing the dot represents the 95% CI of the pooled HR in each subgroup analysis. I-squared (P) shows the heterogeneity in each subgroup meta-analysis. EFS, event-free survival; HR, hazard ratio; PD-L1, programmed cell death-ligand 1.

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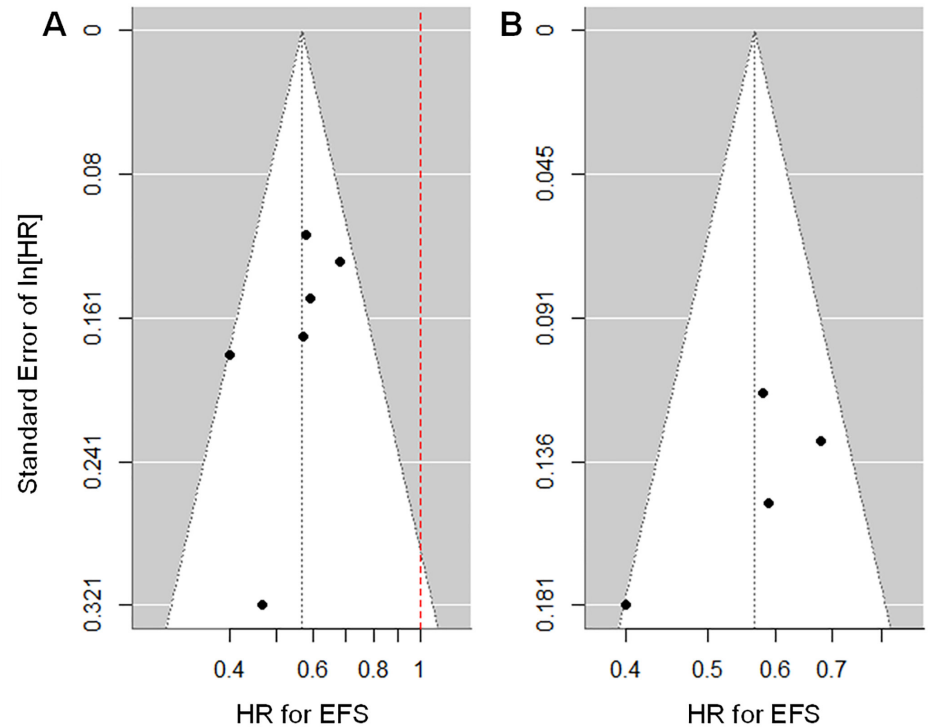

Figure S3 Funnel plot assessing publication bias for EFS. (A) Funnel plot including all eligible studies evaluating perioperative chemoimmunotherapy with adjuvant PD-1/PD-L1 inhibitors versus neoadjuvant chemotherapy alone. (B) Funnel plot restricted to studies using 12/13-cycle adjuvant immunotherapy regimens. Each study's effect estimate plotted against its standard error. The outer dashed lines represent the confidence interval boundary within which 95% of studies are expected to lie in the absence of bias or heterogeneity. The gray vertical dashed line represents the summary treatment effect. EFS, event-free survival; HR, hazard ratio; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

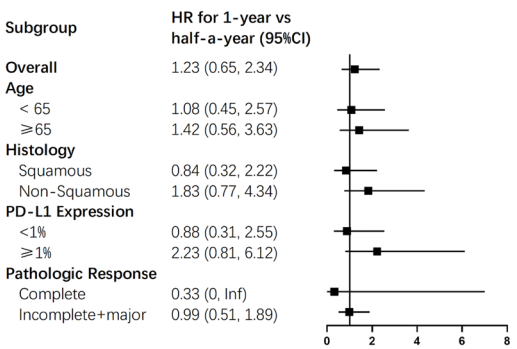

Figure S4 Forest plot of HR in subgroup-analyses comparing EFS in patients who received 1-year versus half-a-year adjuvant immunotherapy. CI, confidence interval; EFS, event-free survival; HR, hazard ratio; PD-L1, programmed death-ligand 1.

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