

### Electronic search strategy

1. We used a search strategy for randomized controlled trials (RCT) in Medline through Pubmed. The same search was then modified for RCT searches in other databases (Scopus, Controlled Cochrane Trial Register - CCTR).

The query was adapted from Robinson & coll: [Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. *International journal of epidemiology* 2002;31:150-153].

("Lung Neoplasms"[Mesh] OR "Carcinoma, Non-Small-Cell Lung"[Mesh] OR "lung cancer"[tiab] OR "lung neoplasms"[tiab] OR "lung tumor"[tiab] OR "Non-small-cell lung cancer"[tiab] OR "Non small cell lung cancer"[tiab] OR NSCLC[tiab]) AND ("Neoplasm Metastasis"[Mesh] OR "Recurrence"[Mesh] OR "neoplasm metastasis"[tiab] OR metastas\*[tiab] OR "stage 4"[tiab] OR "stage IV"[tiab] OR "advanced"[tiab] OR Recurrence\*[tiab] OR relapse\*[tiab] AND ("Biomarkers, Tumor/analysis"[Mesh] OR PD-L1 [tiab] OR PD L1[tiab]) AND (expression[tiab] OR "antibody"[tiab] OR diagnostic\*[tiab] OR "testing"[tiab]) AND ("pembrolizumab" [Supplementary Concept] OR "Pembrolizumab"[tiab] OR "atezolizumab" [Supplementary Concept] OR "atezolizumab"[tiab] OR "nivolumab" [Supplementary Concept] OR "nivolumab"[tiab] OR "durvalumab" [Supplementary Concept] OR "durvalumab"[tiab] OR "ipilimumab" [Supplementary Concept] OR "ipilimumab"[tiab] OR "tremelimumab" [Supplementary Concept] OR "tremelimumab"[tiab] "Programmed Cell Death 1 Ligand 2 Protein"[Mesh] OR "PD-1"[tiab] OR "PD-L1"[tiab] OR "Drug Therapy/therapeutic use"[Mesh] OR "Drug therapy/therapy"[Mesh] OR "Drug Therapies"[tiab] OR "Chemotherapy"[tiab] OR Chemotherapies[tiab])

AND

("Randomized Controlled Trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR randomized[Title/Abstract] OR randomised[Title/Abstract] OR placebo[Title/Abstract] OR randomly[Title/Abstract] OR groups[Title/Abstract] OR trial[Title/Abstract] OR "drug therapy"[Subheading]))

## 2. Cochrane Database search strategy

		View fewer lines		Print
+	#1	lung neoplasms	S	MeSH
-	#2	NSCLC		Limits
-	#3	Non-small-cell lung cancer		Limits
-	#4	#1 #2 OR #3		Limits
-	#5	metastasis		Limits
-	#6	MeSH descriptor: [Neoplasm Metastasis] explode all trees		MeSH
-	#7	recurrence		Limits
-	#8	advanced		Limits
-	#9	MeSH descriptor: [Recurrence] explode all trees		MeSH
-	#10	stage IV		Limits
-	#11	Stage 4		Limits
-	#12	#5 OR #6 OR #7 OR #8 OR #9 OR #10		Limits
-	#13	pd 1		Limits
-	#14	pd 1		Limits
-	#15	pd 11		Limits
-	#16	pd 11		Limits
-	#17	MeSH descriptor: [Programmed Cell Death 1 Receptor] explode all trees		MeSH
-	#18	MeSH descriptor: [B7-1 Antigen] explode all trees		MeSH
-	#19	#13 OR #14 OR #15 OR #16 OR #17 OR #18		Limits
-	#20	avelumab		Limits
-	#21	pembrolizumab		Limits
-	#22	nivolumab		Limits
-	#23	atezolizumab		Limits
-	#24	ipilimumab		Limits
-	#25	durvalumab		Limits
-	#26	tremelimumab		Limits
-	#27	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26		Limits
-	#28	therapy		Limits
-	#29	chemotherapy		Limits
-	#30	treatment		Limits
-	#31	MeSH descriptor: [Drug Therapy] explode all trees		MeSH
-	#32	#28 OR #29 OR #30 OR #31		Limits
-	#33	randomized		Limits
-	#34	MeSH descriptor: [Randomized Controlled Trial] explode all trees		MeSH
-	#35	rcs		Limits
-	#36	#33 OR #34 OR #35		Limits
-	#37	#4 AND #12 AND #19 AND #27 AND #32 AND #36		Limits
-	#38	Type a search term or use the S or MeSH buttons to compose		Limits

S

MeSH

Limits

N/A

Clear all

Highlight orphan line

3. We used the free text strategy

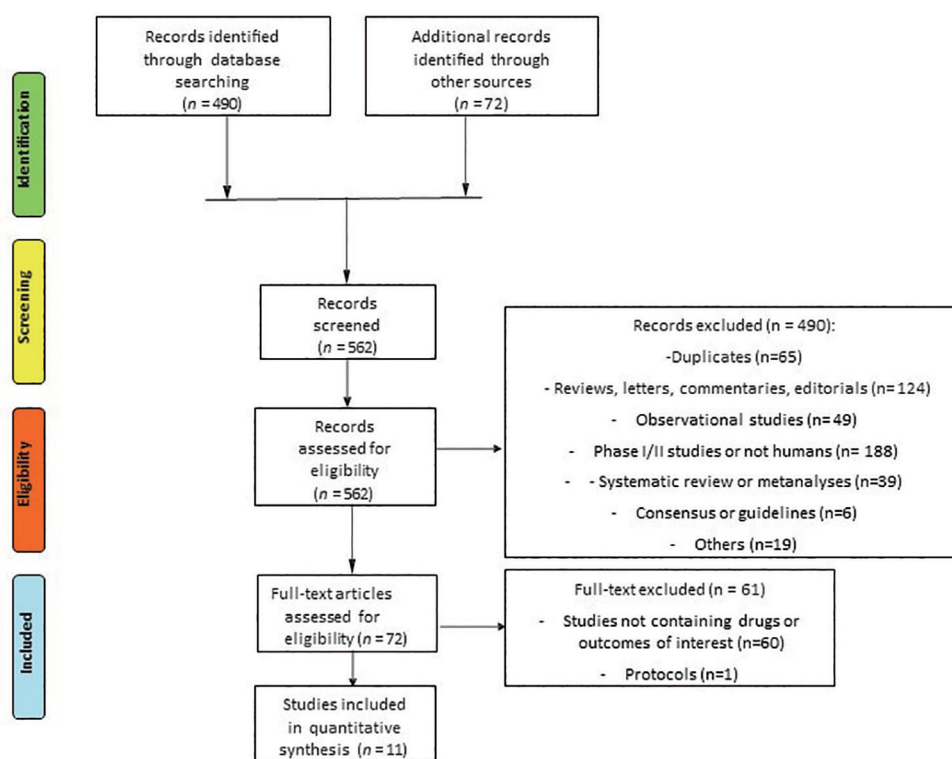
### Immunotherapy and advanced NSCLC survival response toxicity

4. We searched meta-analyses for any other published data concerning immunotherapy in the references cited. The strategy in Pubmed for meta-analysis searching was

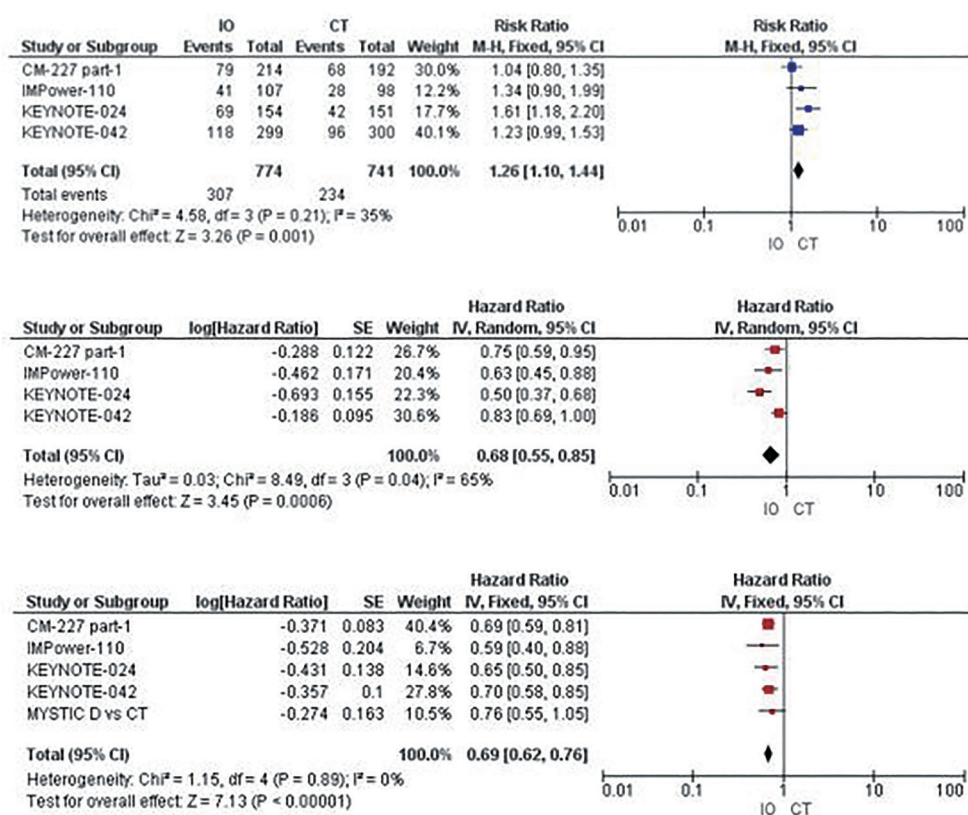
Immunotherapy [tiab] AND NSCLC [tiab] AND meta-analysis [pt]

for RCT on-line searches in Clinical Trials registers ([www.clinicaltrials.gov](http://www.clinicaltrials.gov))

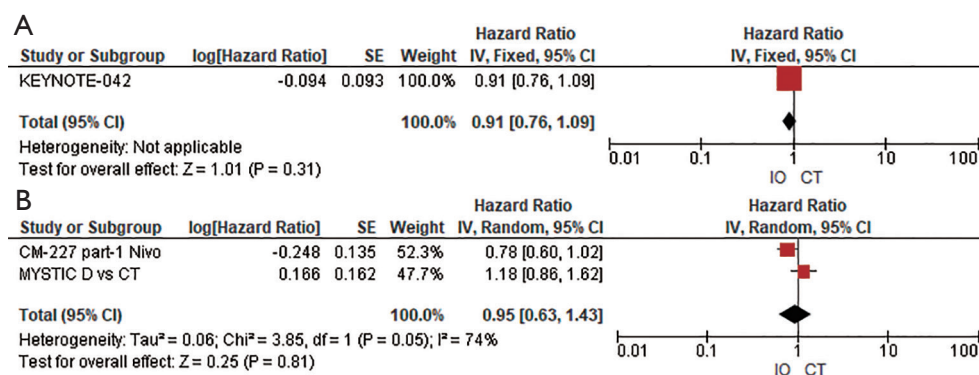
**Figure S1** Electronic search strategy.



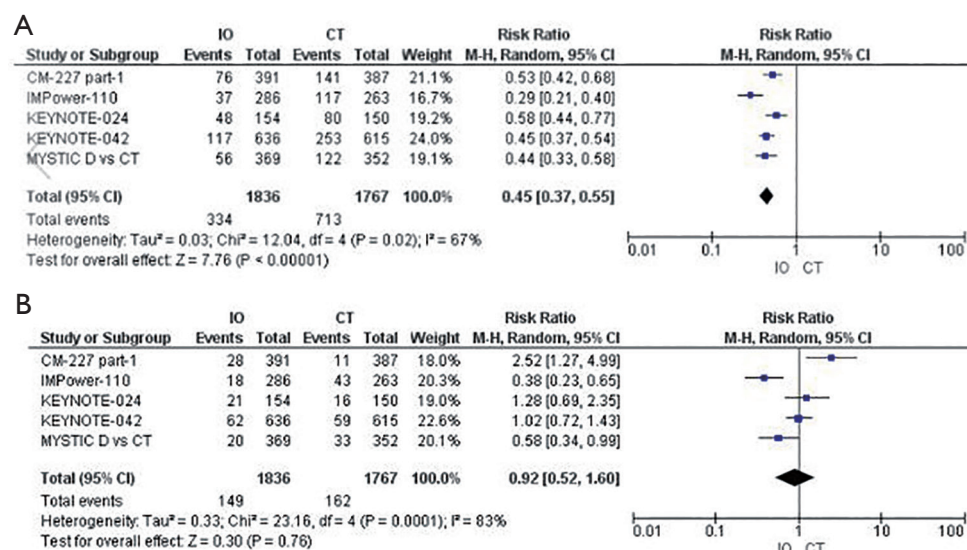
**Figure S2** Flow diagram (CONSORT) of the included studies in the meta-analysis.



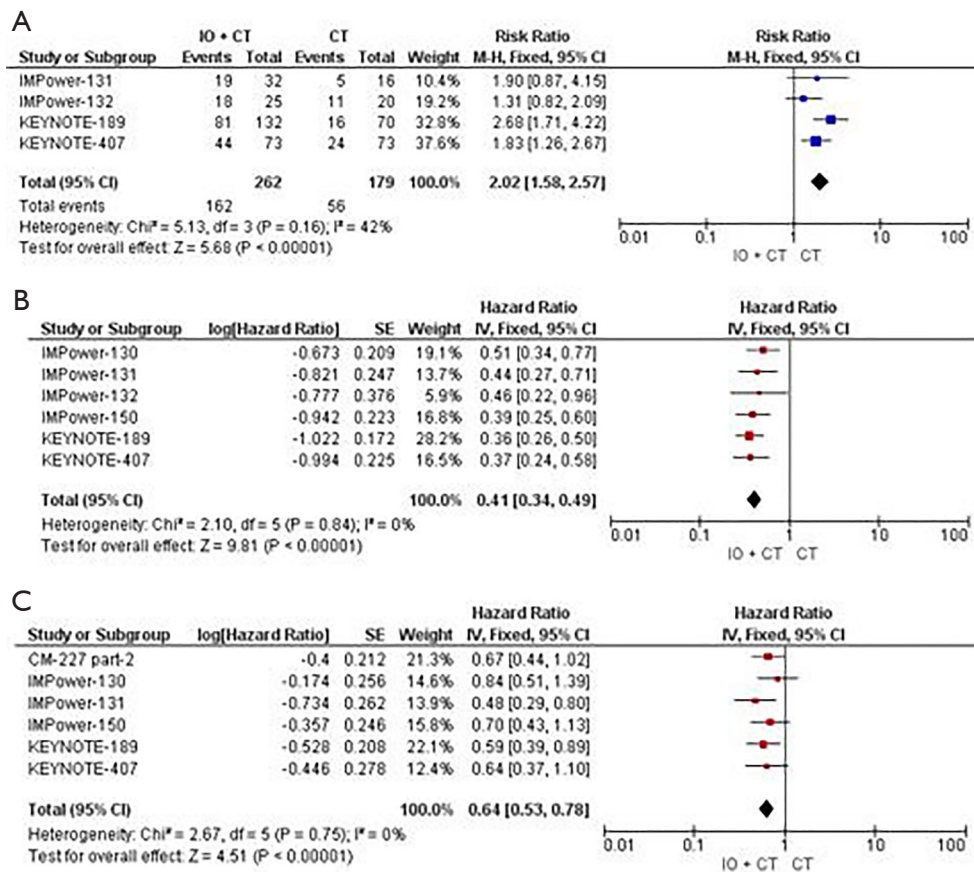
**Figure S3** Forest plots of (A) RR of ORR, (B) HR of PFS and (C) OS of advanced NSCLC patients with tumor PD-L1 expression higher than 50% undergoing IO versus CT alone. RR, risk ratio; ORR, objective response rate; HR, hazard ratio; PFS, progression-free survival; OS, overall survival; IO, single-agent immunotherapy; CT, standard platinum-based chemotherapy.



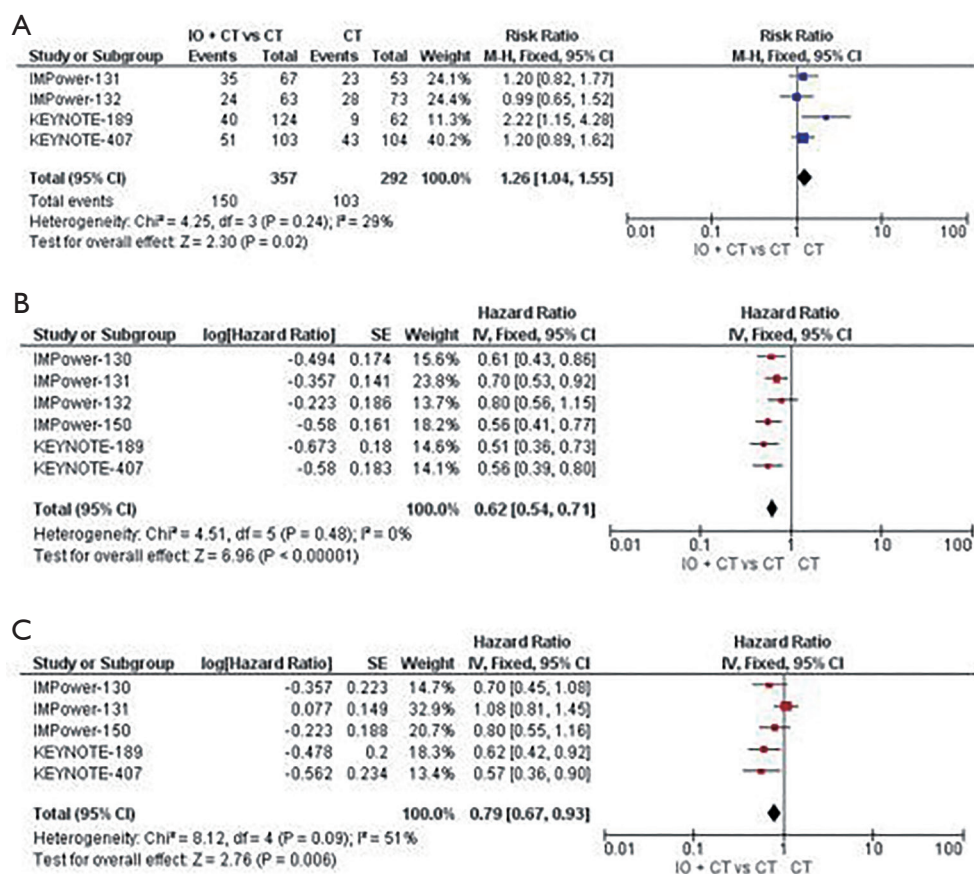
**Figure S4** Forest plots of HR of OS of advanced NSCLC patients with tumor PD-L1 expression 1–49% (A) and <1% (B) undergoing IO versus CT alone. HR, hazard ratio; OS, overall survival; IO, single-agent immunotherapy; CT, standard platinum-based chemotherapy.



**Figure S5** Forest plots of TRAEs (A) and discontinuation rate (B) in advanced NSCLC patients undergoing IO versus CT alone. TRAEs, treatment-related adverse events; IO, single-agent immunotherapy; CT, standard platinum-based chemotherapy.

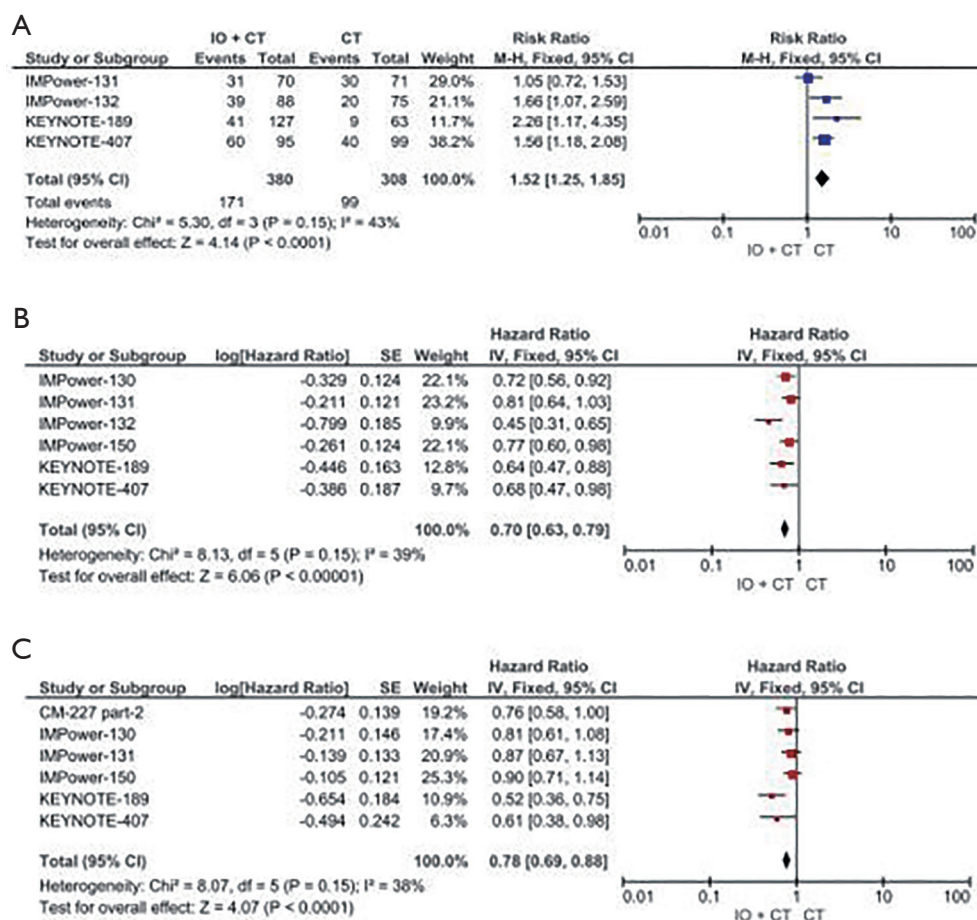


**Figure S6** Forest plots of (A) RR of ORR, (B) HR of PFS and (C) OS of advanced NSCLC patients with tumor PD-L1 expression higher than 50% undergoing IO + CT versus CT alone. RR, risk ratio; ORR, objective response rate; HR, hazard ratio; PFS, progression-free survival; OS, overall survival; IO, single-agent immunotherapy; CT, standard platinum-based chemotherapy.

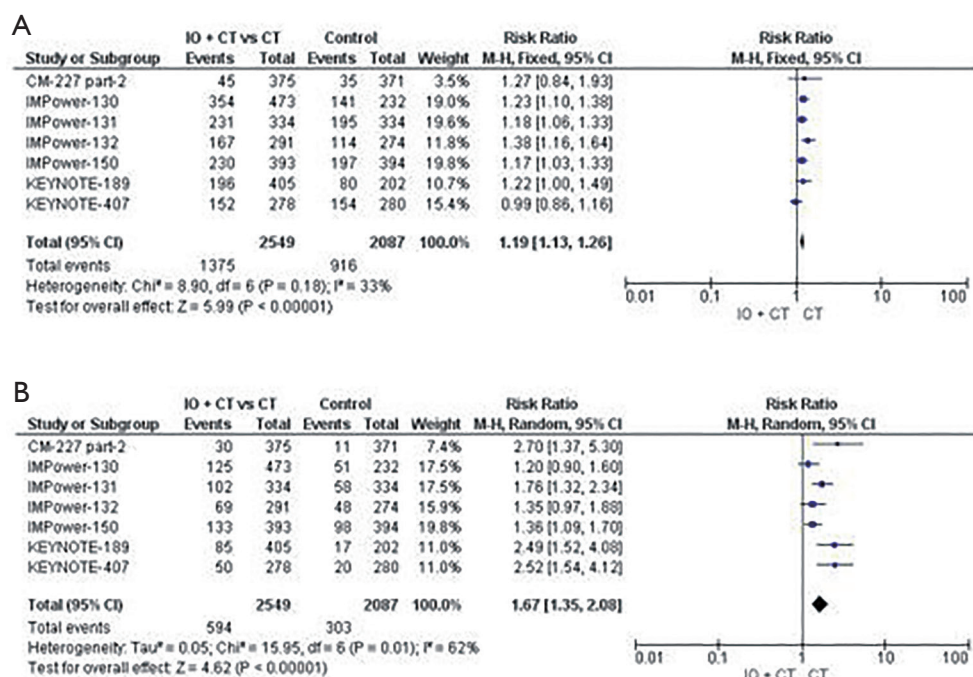


**Figure S7** Forest plots of (A) RR of ORR, (B) HR of PFS and (C) OS of advanced NSCLC patients with tumor PD-L1 expression 1–49% undergoing IO + CT versus CT alone. RR, risk ratio; ORR, objective response rate; HR, hazard ratio; PFS, progression-free survival; OS, overall survival; IO, single-agent immunotherapy; CT, standard platinum-based chemotherapy.

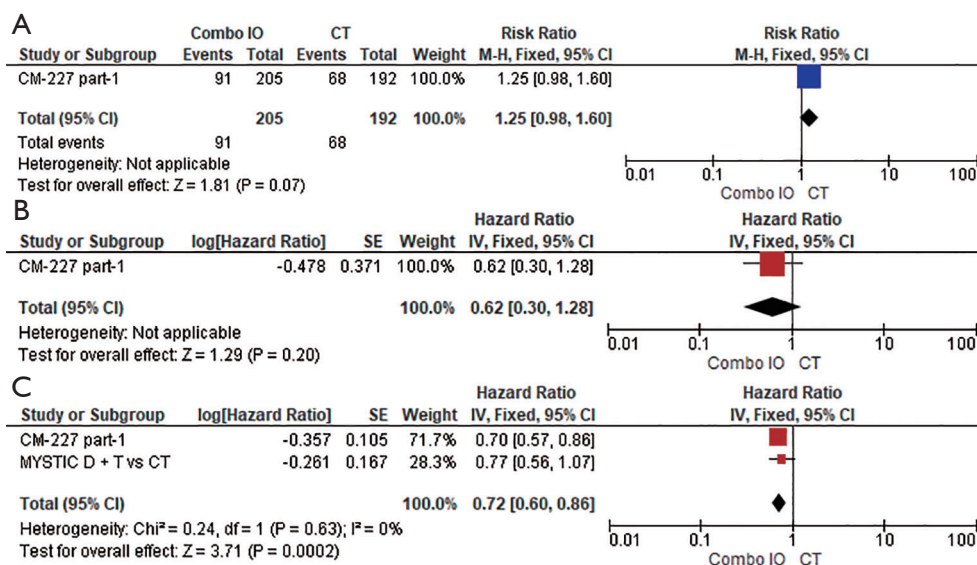




**Figure S8** Forest plots of (A) RR of ORR, (B) HR of PFS and (C) OS of advanced NSCLC patients with tumor PD-L1 expression <1% undergoing IO + CT versus CT alone. RR, risk ratio; ORR, objective response rate; HR, hazard ratio; PFS, progression-free survival; OS, overall survival; IO, single-agent immunotherapy; CT, standard platinum-based chemotherapy.

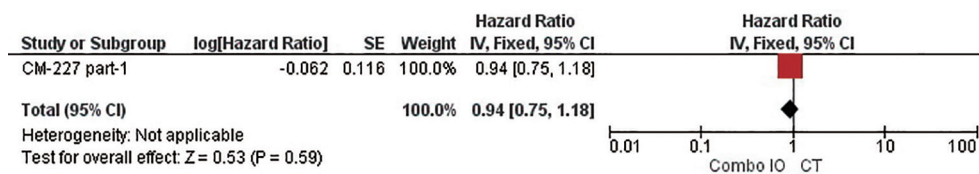


**Figure S9** Forest plots of TRAEs (A) and discontinuation rate (B) in advanced NSCLC patients undergoing IO + CT versus CT alone. TRAEs, treatment-related adverse events; IO, single-agent immunotherapy; CT, standard platinum-based chemotherapy.

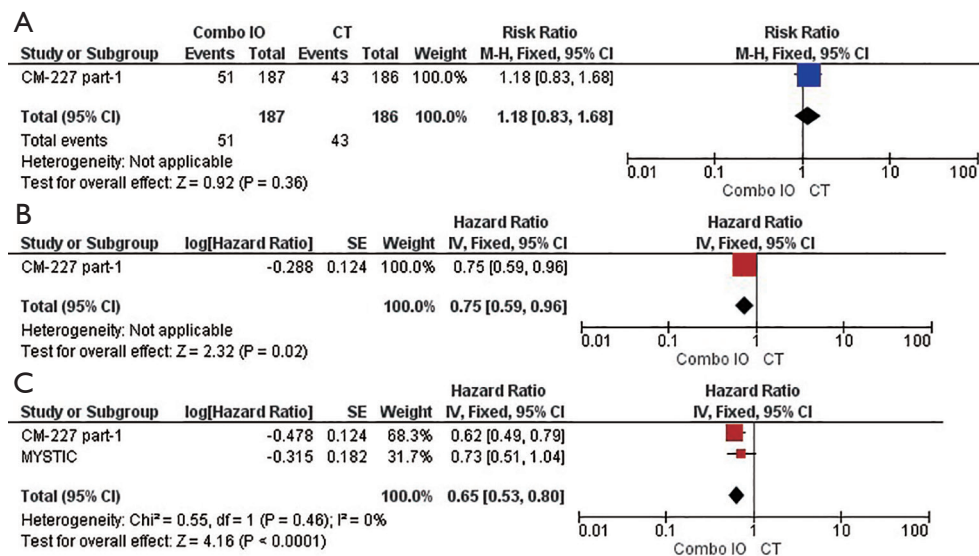


**Figure S10** Forest plots of (A) RR of ORR, (B) HR of PFS and (C) OS of advanced NSCLC patients with tumor PD-L1 expression higher than 50% undergoing Combo IO versus CT alone. RR, risk ratio; ORR, objective response rate; HR, hazard ratio; PFS, progression-free survival; OS, overall survival; Combo IO, immunotherapy combination regimens; CT, standard platinum-based chemotherapy.

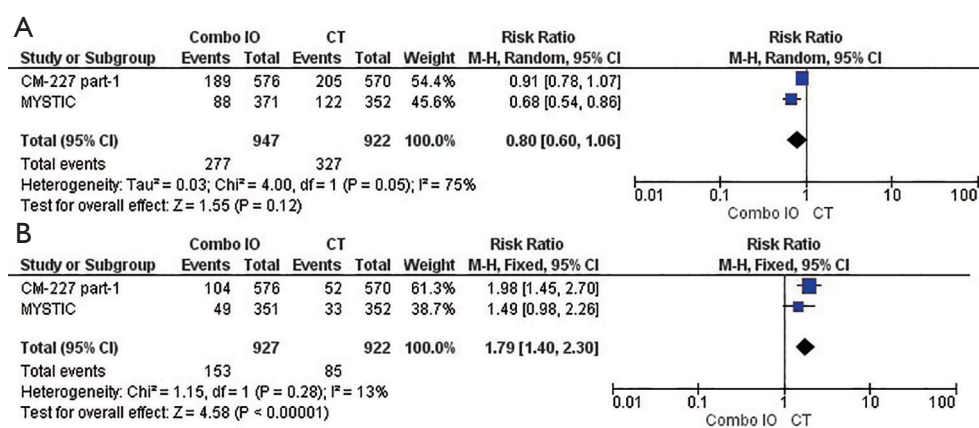




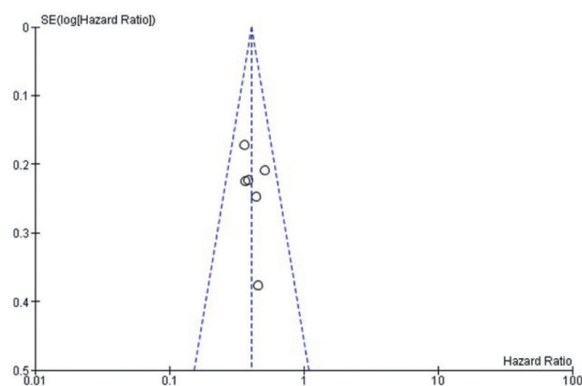
**Figure S11** Forest plots of HR of OS of advanced NSCLC patients with tumor PD-L1 expression 1–49% undergoing Combo IO versus CT alone. RR, risk ratio; ORR, objective response rate; HR, hazard ratio; PFS, progression-free survival; OS, overall survival; Combo IO, immunotherapy combination regimens; CT, standard platinum-based chemotherapy.



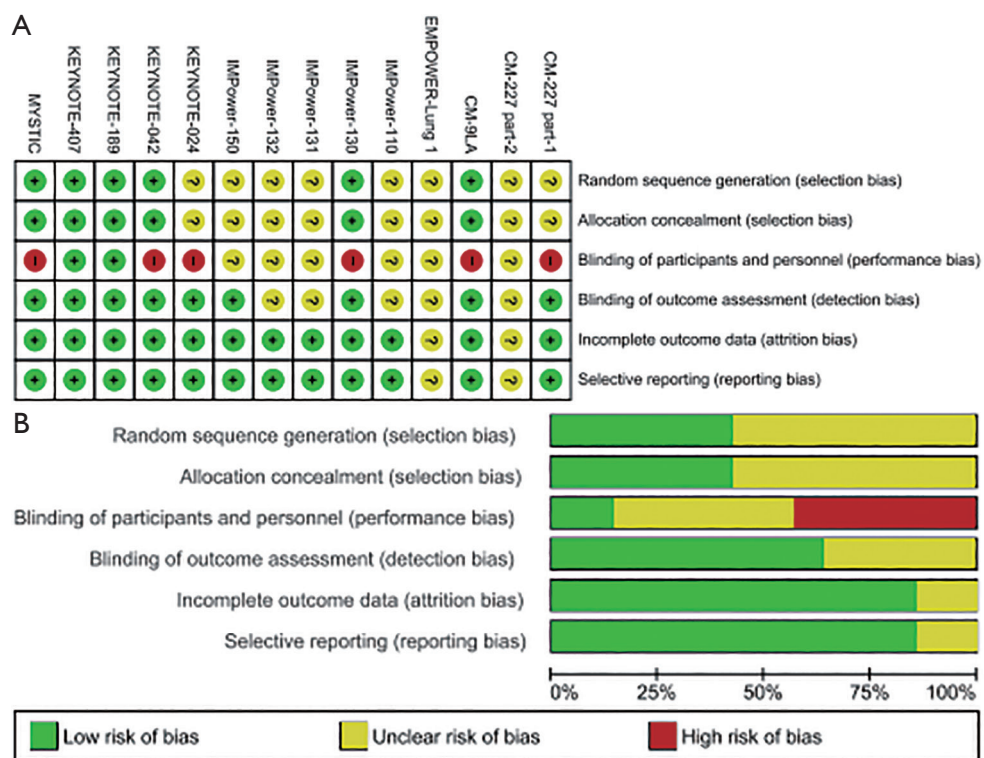
**Figure S12** Forest plots of (A) RR of ORR, (B) HR of PFS and (C) OS of advanced NSCLC patients with tumor PD-L1 expression <1% undergoing Combo IO versus CT alone. RR, risk ratio; ORR, objective response rate; HR, hazard ratio; PFS, progression-free survival; OS, overall survival; Combo IO, immunotherapy combination regimens; CT, standard platinum-based chemotherapy.



**Figure S13** Forest plots of TRAEs (A) and discontinuation rate (B) in advanced NSCLC patients undergoing Combo IO versus CT alone. TRAEs, treatment-related adverse events; IO, single-agent immunotherapy; CT, standard platinum-based chemotherapy.



**Figure S14** Funnel plot assessing the risk of publication bias across the studies.



**Figure S15** Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies (A); Risk of bias summary (B).