

# Supplementary Materials: Immune-Related Pneumonitis Was Decreased by Addition of Chemotherapy with PD-1/L1 Inhibitors: Systematic Review and Network Meta-Analysis of Randomized Controlled Trials (RCTs)

**Table S1. Demographic Characteristics of the Patients at Baseline.**

Characteristic	Total (n=11466)	I+C group (n=5406)	I group (n=6060)	p-value
<b>No. of RCT</b>	31 trails	15 trails	19 trails	0.424
<b>Median age</b>	64 years	63 years	65 years	N. R
<b>Sex</b>				
Male	6443(56.2%)	2384(44.1%)	4059(67.0%)	0.152
Female	5023(43.8%)	3022(55.1%)	2001(33.0%)	0.122
<b>History</b>				
NSCLC/SCLC	5616(49.0%)	2467(45.6%)	3149(52.0%)	0.748
TNBC	2269(19.8%)	1960(36.3%)	309(5.1%)	0.573
ES, G/GEJ	1112(9.7%)	250(4.6%)	862(14.2%)	0.401
UC	1419(12.4%)	453(8.4%)	966(15.9%)	0.141
Others	1050(9.1%)	276(5.1%)	774(12.8%)	0.775
<b>PD-1/L1 Inhibitors</b>				
PD-1 inhibitors	7481(65.2%)	2775(51.3%)	4706(77.7%)	0.263
PD-L1 inhibitors	3985(34.8%)	2631(48.7%)	1354(22.3%)	0.840

Abbreviation: I+C group, PD-1/L1 inhibitors plus chemotherapy; I group, PD-1/L1 inhibitors; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; G/GEJ: Gastric and gastroesophageal junction cancer; TNBC: Triple-negative breast cancer; NSCLC: non-small-cell lung cancer; UC: urothelial cancer; HNSCC: Head and neck squamous cell carcinoma; ES: esophagus.

**Table S2. Value of SUCRA and mean rank in overall population. Higher SUCRA scores correlated with a higher risk of IRP.**

Treatment group	Any grade IRP		Grade 3-5 IRP	
	SUCRA	Mean rank	SUCRA	Mean rank
PD-1/L1+chemotherapy	50.7	2	50.5	2
PD-1/L1 monotherapy	99.3	1	99.2	1
Chemotherapy	50.7	3	0.3	3

**Notes:** IRP, Immune-related Pneumonitis; ICIs, immune check inhibitors; SUCRA, surface

under the cumulative ranking curve.

**Table S3. Value of SUCRA and mean rank for different ICIs comparison. Higher SUCRA scores correlated with a higher risk of IRP.**

Treatment group	Any grade IRP		Grade 3-5 IRP	
	SUCRA	Mean rank	SUCRA	Mean rank
PD-1 monotherapy	97.8	1.1	92.5	1.3
PD-1+chemotherapy	52.4	2.9	65.7	2.9
PD-L1 monotherapy	52.4	2.9	52.9	2.4
PD-L1+chemotherapy	47.3	3.1	34.0	3.6
Chemotherapy	0.0	5.0	4.8	4.8

**Notes:** IRP, Immune-related Pneumonitis; ICIs, immune check inhibitors; SUCRA, surface under the cumulative ranking curve.

**Table S4. The value of SCURA for 3 group and mixed RR that I+C group Versus I group based on cancer type**

Immune-related Pneumonitis	Any grade IRP				Grade 3-5 IRP			
	I+C group	I group	C group	RR (I+C VS. I)	I+C group	I group	C group	RR (I+C VS. I)
<b>Cancer type</b>								
NSCLC	51.3	98.7	0.0	0.44 (0.19-1.01)	49.7	98.9	1.4	0.39 (0.15-0.98)
TNBC	58.5	82.7	8.8	0.25 (0.00-14.09)	63.1	78.8	8.2	0.46 (0.02-12.13)
UC	45.1	97.4	7.5	0.23 (0.04-1.33)	N. R	N. R	N. R	N. R
G/GEJ/ES	70.6	79.1	0.1	0.91 (0.36-2.27)	N. R	N. R	N. R	N. R

**Notes:** I+C group, PD-1/L1 inhibitors plus chemotherapy; I group, PD-1/L1 inhibitors; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; G/GEJ: Gastric and gastroesophageal junction cancer; TNBC: Triple-negative breast cancer; NSCLC: non-small-cell lung cancer; UC: urothelial cancer; HNSCC: Head and neck squamous cell carcinoma; ES, G/GEJ: esophageal cancer and gastric or gastroesophageal cancer.



**Table S5. The value of P for inconsistency model test and IF for loop inconsistency in overall population and subgroup analysis.**

Outcomes of Interest	Any grade IRP				Grade 3-5 IRP			
	No. of RCTs	p-value	Loop	95%CI IF	No. of RCTs	p-value	Loop	95%CI IF
<b>Overall population</b>	31	0.3931	0.684	(0.00-1.42)	27	0.9930	0.008	(0.00-1.84)
<b>ICIs</b>	31	0.3545	0.424	(0.00-1.87)	27	0.9616	0.047	(0.00-1.98)
<b>NSCLC</b>	17	N. R	N. R	N. R	16	N. R	N. R	N. R
<b>TNBC</b>	5	N. R	N. R	N. R	5	N. R	N. R	N. R
<b>UC</b>	3	0.1725	1.224	(0.00-3.15)	2	N. R	N. R	N. R
<b>ES, GC/GEJ</b>	3	0.9805	0.030	(0.00-2.65)	2	N. R	N. R	N. R

**Notes:** No.: number; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; G/GEJ: Gastric and gastroesophageal junction cancer; TNBC: Triple-negative breast cancer; NSCLC: non–small-cell lung cancer; UC: urothelial cancer; HNSCC: Head and neck squamous cell carcinoma; ES, G/GEJ: esophageal cancer and gastric or gastroesophageal cancer; N.R, not report.

**Table S6. Results of node-splitting analysis for the assessment inconsistencies for the IRP in cancer type.**

Comparator	Intervention	Overall	NSCLC	TNBC	UC	G, G/GEJ
<b>Any grade IRP</b>						
C group	I group	0.26	N. R	N. R	N. R	N. R
C group	I+C group	0.11	N. R	N. R	0.17	0.98
I group	I+C group	0.12	N. R	N. R	0.17	0.98
<b>Grade 3 -5 IRP</b>						
C group	I group	0.99	N. R	N. R	N. R	N. R
C group	I+C group	0.99	N. R	N. R	N. R	N. R
I group	I+C group	0.99	N. R	N. R	N. R	N. R

**Notes:** IRP, immune-related pneumonitis; C group, chemotherapy group; I group, PD-1/L1 monotherapy; I+C group, PD-1/L1+chemotherapy. N. R, not report.

**Table S7. Results of node-splitting analysis for the assessment inconsistencies for the IRP in different ICIs group.**

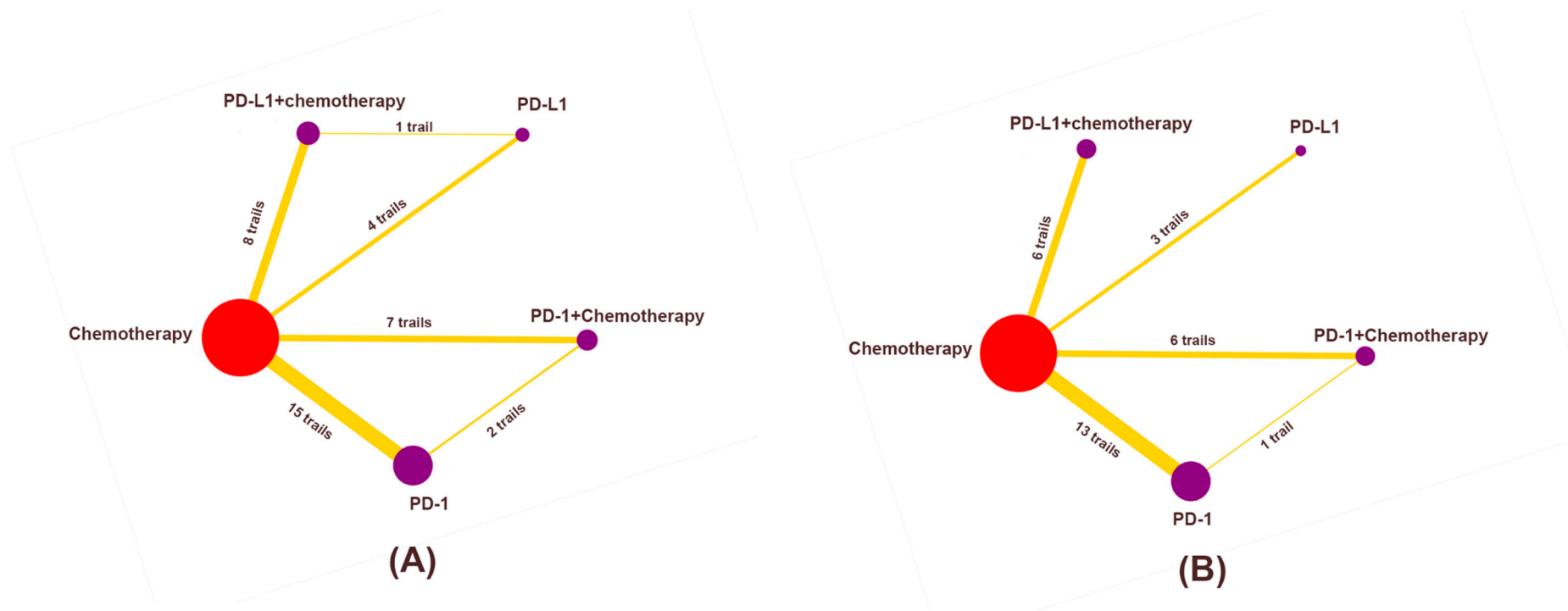
Comparator	Intervention	<i>p</i> -value of any grade	<i>p</i> -value of grade 3-5
<b>IRP in different ICIs</b>			
Chemotherapy	PD-1 monotherapy	0.043	0.96
Chemotherapy	PD-1+chemotherapy	0.064	0.96
Chemotherapy	PD-L1 monotherapy	0.447	N. R
Chemotherapy	PD-L1+chemotherapy	0.970	N. R
PD-1 monotherapy	PD-1+chemotherapy	0.025	0.96
PD-L1 monotherapy	PD-L1+chemotherapy	0.644	N. R

**Notes:** IRP, immune-related pneumonitis; ICIs, immune check inhibitors; N. R, not report.

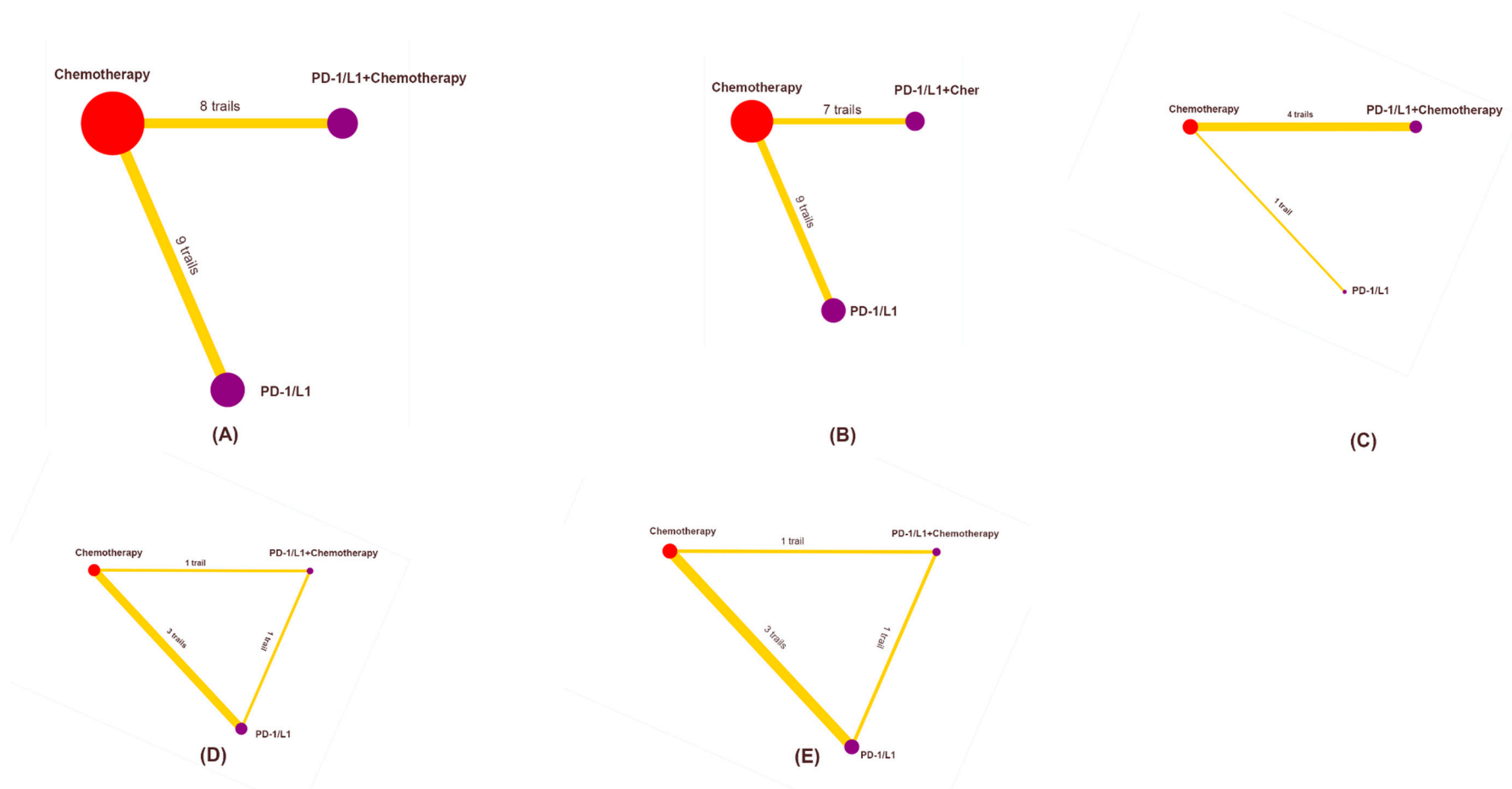
**Table S8: Supplementary basic characteristic for eligible RCTs.**

Study name	Study ID	Total, No.		Grade 1-5 IRP, No.		Grade 3-5 IRP, No.	
		Exp	Con	Exp	Con	Exp	Con
CASPIAN	NCT03043872	265	266	7	2	2	1
KEYNOTE-062	NCT02494583	250	254	8	9	N. R	N. R
IMpassion130	NCT02425891	453	437	16	1	2	0
KEYNOTE-522	NCT03036488	781	389	10	5	3	1
KEYNOTE-024	NCT02142738	154	150	12	1	4	1
KEYNOTE-604	NCT03066778	223	223	9	5	3	0
MYSTIC	NCT02453282	369	352	8	5	5	2
KEYNOTE-407	NCT02775435	278	280	23	6	9	3
KEYNOTE-045	NCT02256436	267	245	11	1	6	0
IMpassion031	NCT03197935	164	167	2	2	1	0
IMpower133	NCT02763579	198	196	5	5	N. R	N. R
IMpower110	NCT02409342	286	263	11	1	2	0
KEYNOTE-010	NCT01905657	682	309	40	6	18	2
KEYNOTE-189	NCT02578680	405	202	20	6	12	4
IMvigor130	NCT02807636	453	354	12	12	N. R	N. R
IMpower130	NCT02367781	473	232	31	3	0	1
KEYNOTE-042	NCT02220894	636	615	53	3	22	1
KEYNOTE-061	NCT02370498	294	276	8	0	2	0
KEYNOTE-048	NCT02358031	276	300	15	19	5	2
IMpower132	NCT02657434	291	274	18	6	6	3
IMpower131	NCT02367794	334	334	23	5	4	3
KEYNOTE -355	NCT02819518	562	281	14	0	6	0
KEYNOTE-119	NCT02555657	309	292	6	0	3	0
DANUBE	NCT02516241	345	313	6	1	2	0
KEYNOTE-181	NCT02564263	314	296	15	2	N. R	N. R
CheckMate 017	NCT01642004	131	129	6	0	1	0
CheckMate 057	NCT01673867	287	268	8	1	3	1
CheckMate 078	NCT02613507	337	165	15	0	4	0
CheckMate 026	NCT01927419	267	263	14	1	6	0
CheckMate 066	NCT01721772	206	205	3	0	0	0
CheckMate 037	NCT01721746	268	102	5	0	0	0

**Notes:** Study ID: from ClinicalTrials.gov.; Exp: experimental; Con: control; N.R: not report. No.: the number of patients.



**Figure S1.** Network plots of subgroup analysis based on different ICIs (A) any grade IRP, (B) grade 3-5 IRP

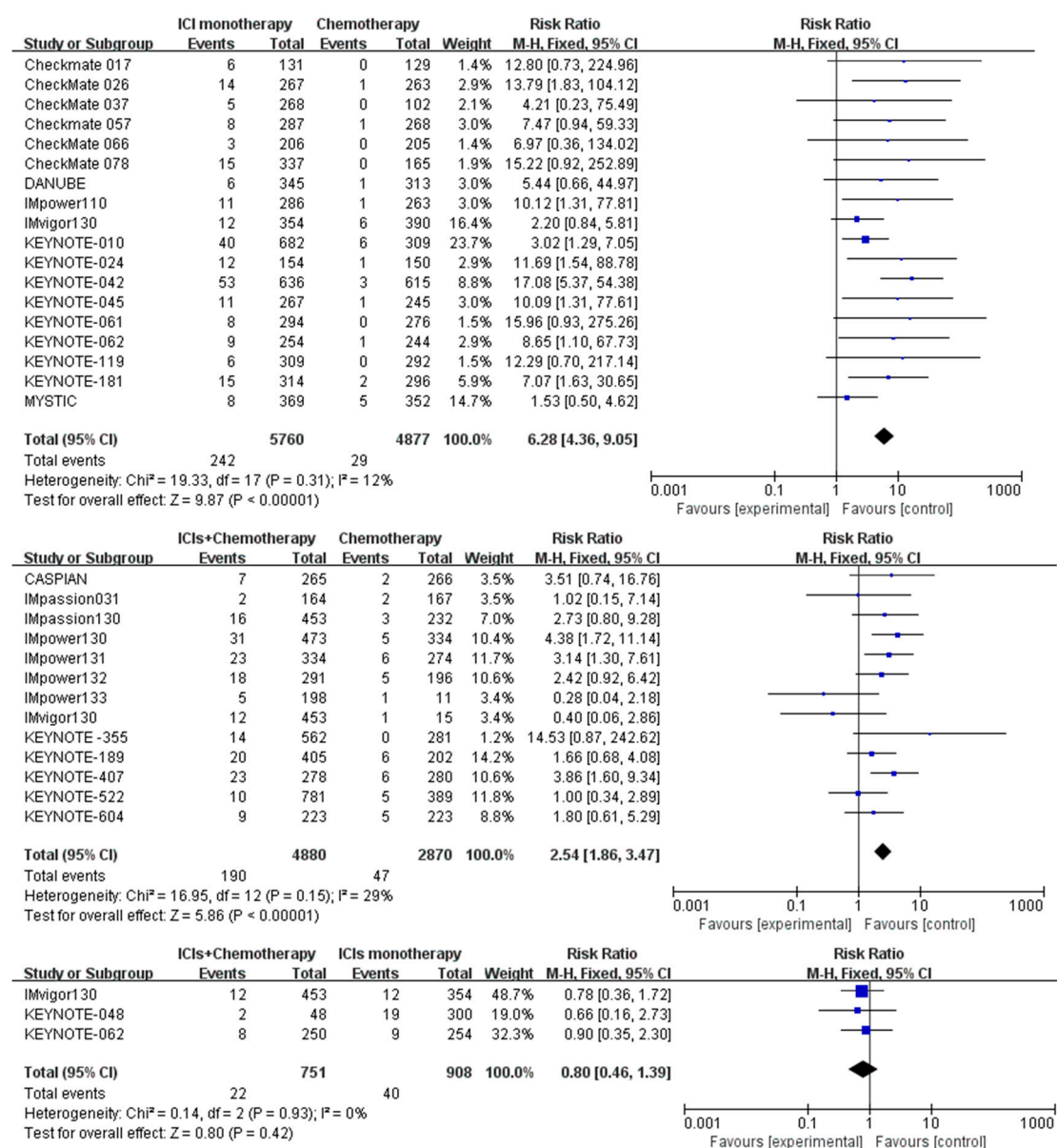


**Figure S2.** Network established for comparisons based on cancer type. (A) any grade IRP and (B) grade 3-5 IRP in NSCLC, (C) any grade IRP and grade 3-5 IRP in TNBC, (D) any grade IRP in UC, (E) any grade IRP in G/GEJ

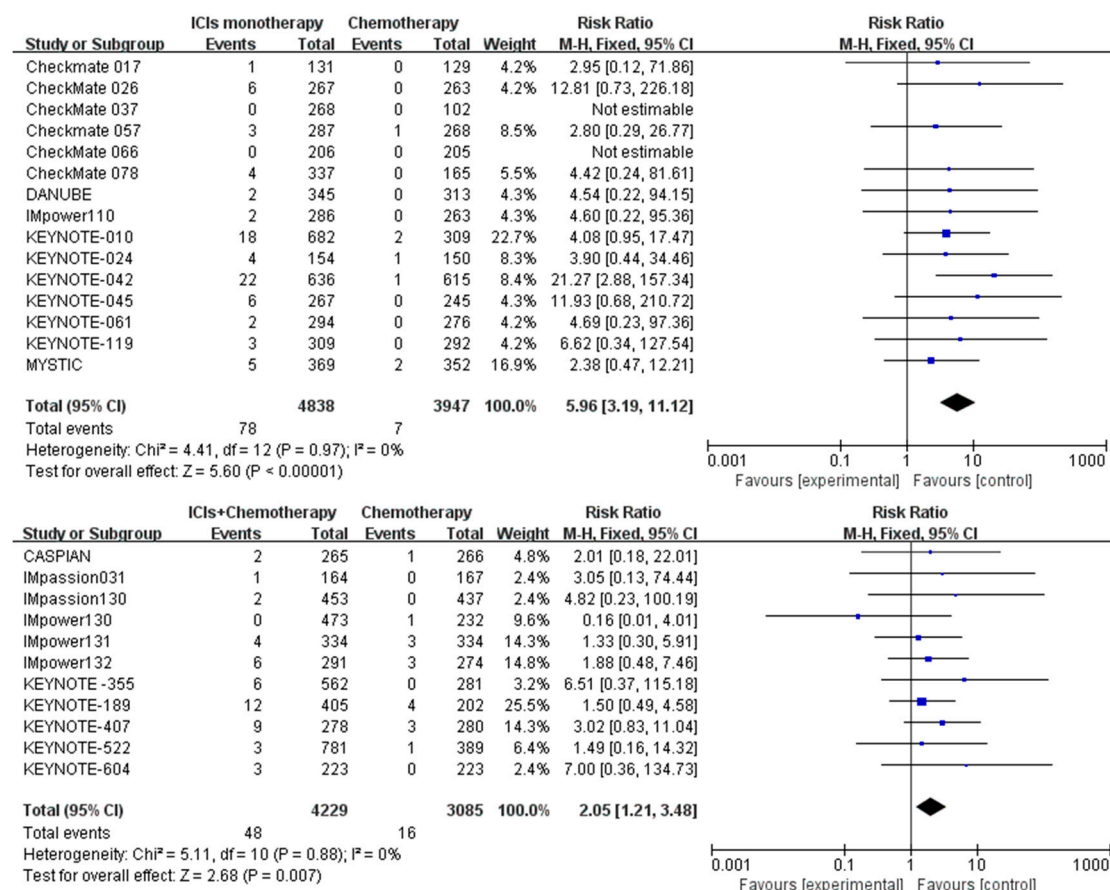


	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
CASPIAN	+	+	+	+	+	+	+
Checkmate 017	?	?	-	+	+	+	+
CheckMate 026	?	?	-	+	+	+	+
CheckMate 037	+	+	-	+	+	+	+
Checkmate 057	?	?	-	+	+	+	+
CheckMate 066	?	?	+	+	+	+	+
CheckMate 078	+	+	-	+	+	+	+
DANUBE	+	+	-	+	+	+	+
IMpassion031	+	+	+	+	+	+	+
IMpassion130	+	+	+	+	+	+	+
IMpower110	?	+	?	+	+	+	+
IMpower130	+	?	-	+	+	+	+
IMpower131	?	?	-	+	+	+	+
IMpower132	+	+	+	?	+	+	+
IMpower133	?	+	+	+	-	+	+
IMvigor130	+	+	?	+	-	+	+
KEYNOTE-010	+	+	-	+	+	+	+
KEYNOTE-024	+	+	?	+	+	+	+
KEYNOTE-042	+	?	-	+	+	+	+
KEYNOTE-045	?	-	?	+	+	+	+
KEYNOTE-048	+	+	?	+	+	+	+
KEYNOTE-061	+	+	+	+	+	+	+
KEYNOTE-062	+	+	?	+	-	+	+
KEYNOTE-119	+	+	-	+	+	+	+
KEYNOTE-181	?	?	-	+	-	+	+
KEYNOTE-189	+	+	+	+	+	+	+
KEYNOTE -355	+	+	+	+	+	+	+
KEYNOTE-407	+	+	+	+	+	+	+
KEYNOTE-522	+	+	+	+	+	+	+
KEYNOTE-604	+	+	+	+	+	+	+
MYSTIC	+	?	?	+	+	+	+

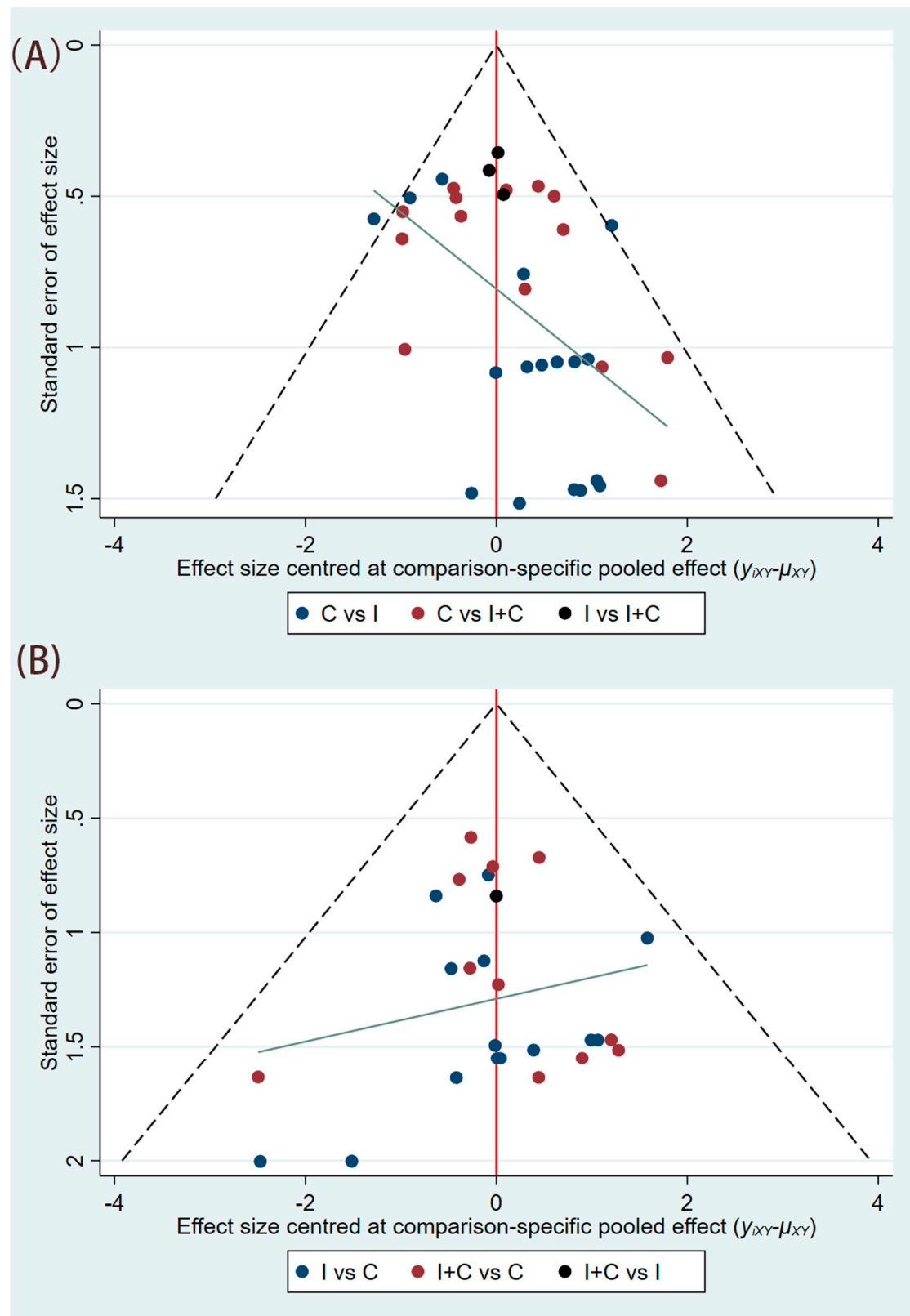
**Figure S3.** Risk of bias summary: review author's judgements about each risk of bias item for each included study.



**Figure S4.** Forest plots and pairwise meta-analysis of direct comparisons for the risk of any grade IRP. ICIs, immune checkpoint inhibitors; IRP, immune-related pneumonitis.



**Figure S5.** Forest plots and pairwise meta-analysis of direct comparisons for the risk of grade 3 or higher IRP. ICIs, immune checkpoint inhibitors; IRP, immune-related pneumonitis.



**Figure S6.** Publication bias for (A) any grade IRP and (B) grade 3-5 IRP in all population.

