

# Association between ALK tyrosine kinase inhibitor and the risk of interstitial lung disease and pneumonitis in non-small cell lung cancer patients: a systematic review

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## BACKGROUND

Interstitial lung disease (ILD) and pneumonitis are the specific adverse events of anaplastic lymphoma kinase tyrosine kinase inhibitors (ALK-TKIs).

## OBJECTIVE

This study aims to investigate the association between ALK-TKIs and the risks of ILD and pneumonitis in patients with NSCLC and determine which ALK-TKI poses the highest risks.

## METHODS

- We systematically searched PubMed, Embase, Cochrane Central Register of Controlled Trials for randomized controlled trials (RCTs) from inception to April 2024 that reported the event of ILD or pneumonitis.
- We performed pairwise and network meta-analysis with frequentist fixed effects model. Outcomes were overall /serious ILD and pneumonitis.

## RESULTS

- A total of 14 RCTs involving 3859 participants (7 ALK-TKIs and chemotherapy) were included.
- The pairwise meta-analysis results showed that ALK-TKIs significantly increased the risks of both overall ILD (RD=0.01, 95%CI: 0.00 to 0.02, P=0.048) and overall pneumonitis (RD=0.01, 95%CI: 0.00 to 0.02, P=0.039) compared to chemotherapy, while no significant difference existed in the risks of both serious ILD (RD=0.01, 95%CI: -0.00 to 0.02, P=0.130) and serious pneumonitis (RD=0.01, 95%CI: -0.00 to 0.02, P=0.109) between ALK-TKIs and chemotherapy.
- The NMA showed brigatinib with significantly higher risks of both overall ILD and overall pneumonitis than crizotinib (OR=8.87, 95%CI: 1.07 to 73.29; OR=3.43, 95%CI: 1.00 to 11.71, respectively), alectinib (OR=12.78, 95%CI: 1.56 to 104.98; OR=6.09, 95%CI: 1.57 to 23.68, respectively) and ceritinib (OR=32.50, 95%CI: 1.05 to 1005.95; OR=21.88, 95%CI: 1.78 to 268.53, respectively). Further, the NMA showed that brigatinib with a significantly higher risk of serious pneumonitis compared to ceritinib (OR=27.26, 95%CI: 1.33 to 558.33). According to P-score results, brigatinib presented the highest risk ranks of both overall/serious ILD and serious pneumonitis.

## CONCLUSION

ALK-TKIs can increase the risks of both ILD and pneumonitis in NSCLC patients, with brigatinib of highest risks among ALK-TKIs.

identification

screening

included

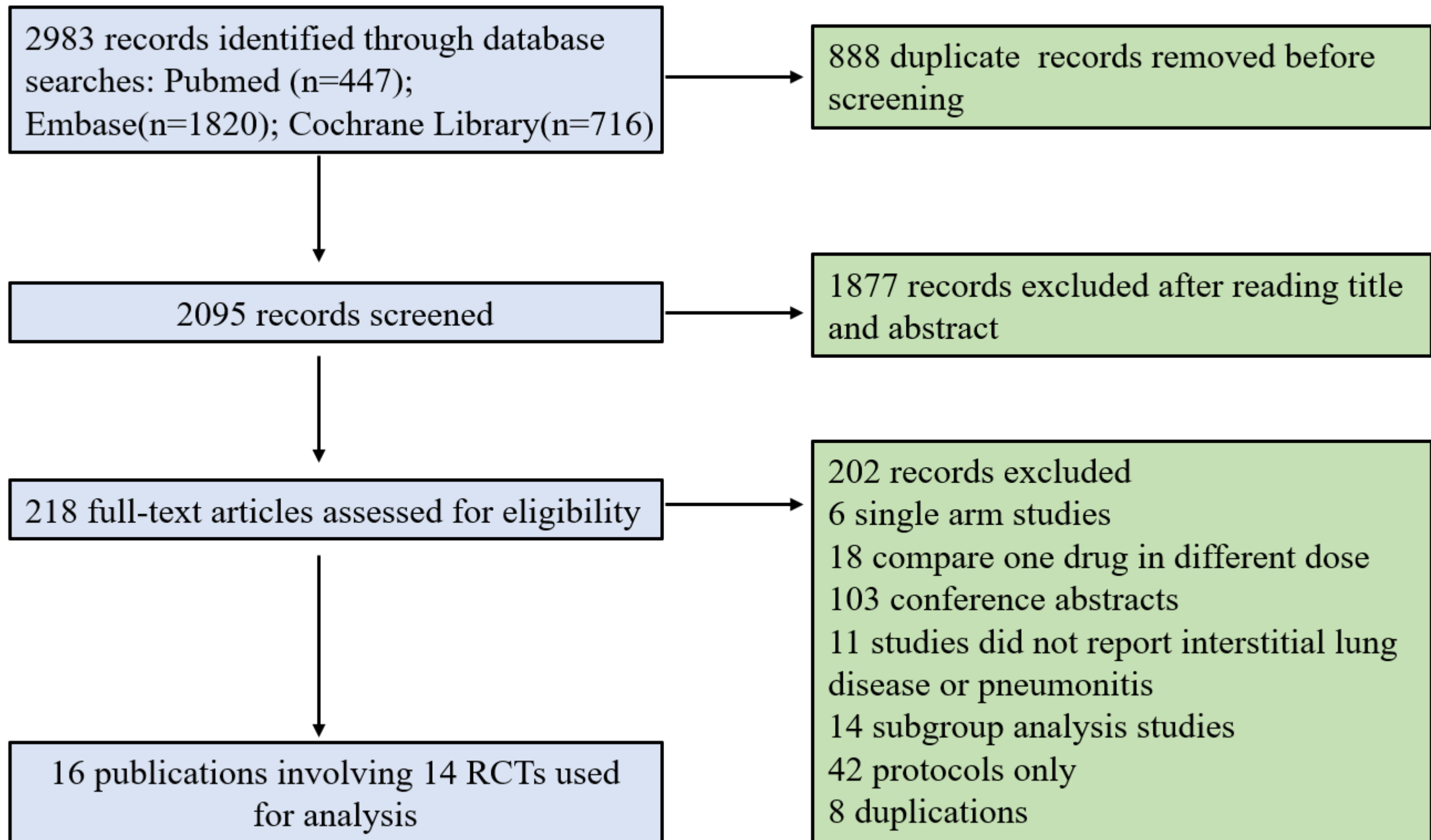
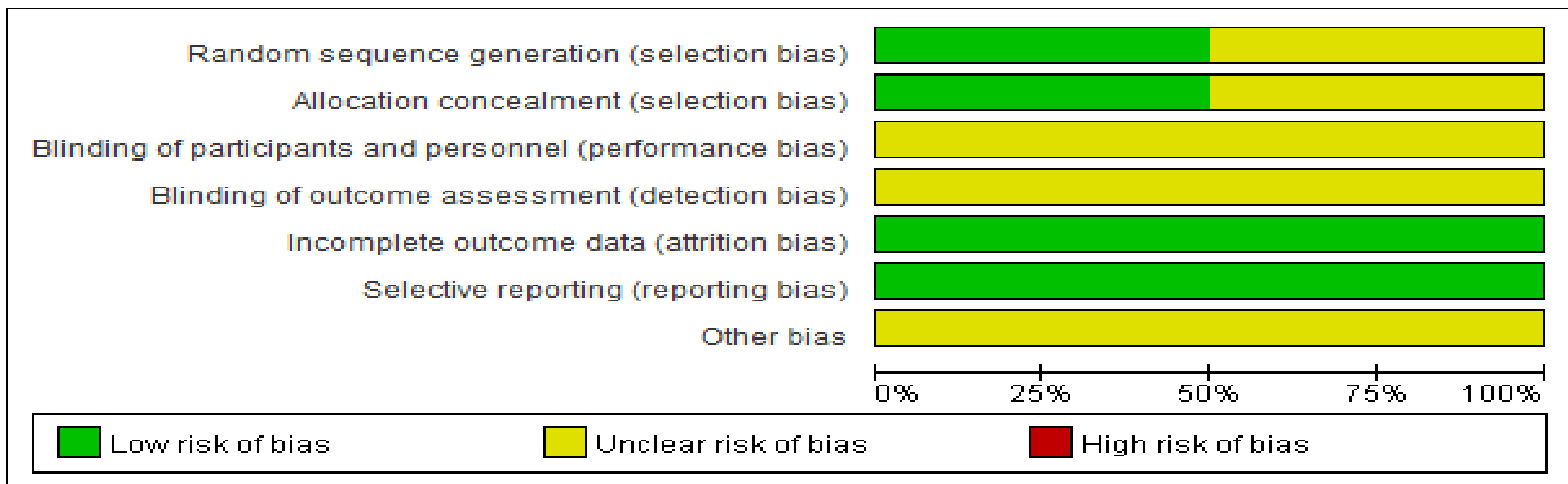


Figure 1. The flow diagram of the network analysis

A



B

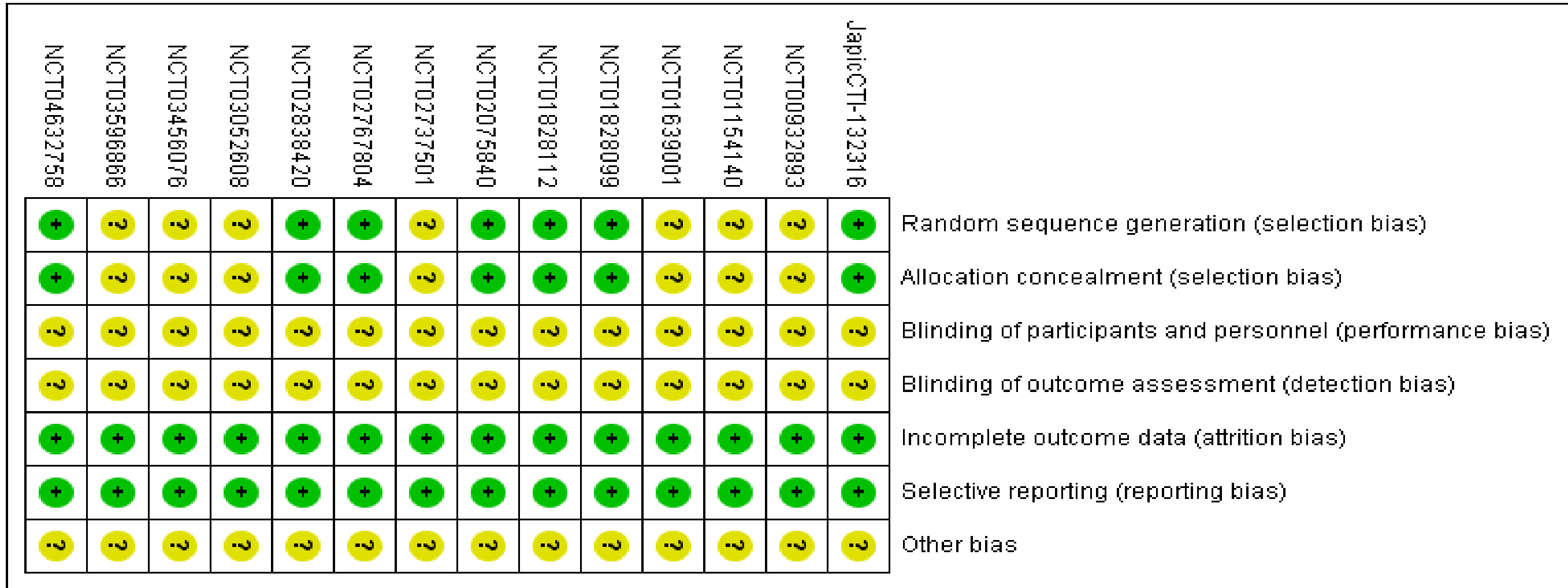


Figure 2. Risk of bias. (A) risk of bias graph. (B) risk of bias summary.

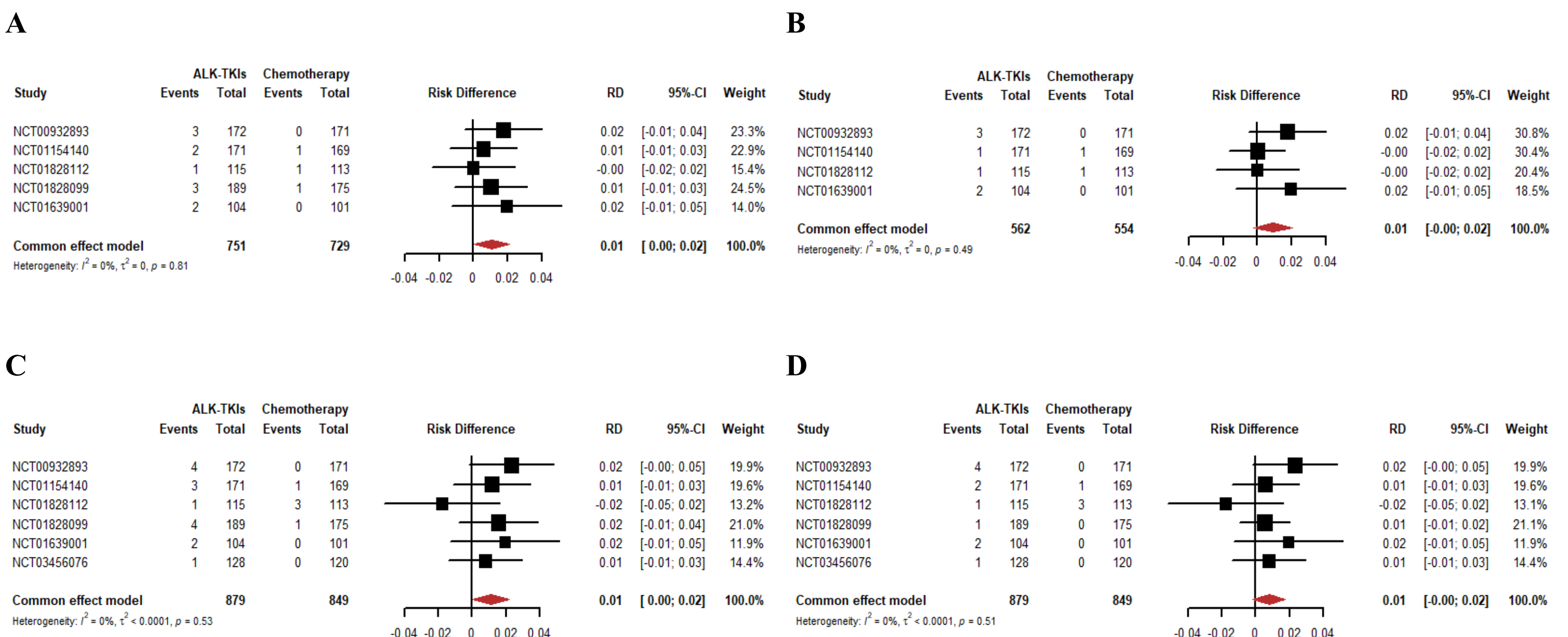


Figure 3. Forest plot of comparison of ALK-TKIs with chemotherapy for ILD and pneumonitis. (A) Forest plot of comparison of ALK-TKIs with chemotherapy for overall ILD. (B) Forest plot of comparison of ALK-TKIs with chemotherapy for serious ILD. (C) Forest plot of comparison of ALK-TKIs with chemotherapy for overall pneumonitis. (D) Forest plot of comparison of ALK-TKIs with chemotherapy for serious pneumonitis.

A	Ensartinib	NA	NA	NA	NA	NA	NA
	0.35 (0.01, 16.20)	Brigatinib	NA	7.21 (0.37, 140.92)	10.24 (0.43, 242.00)	43.67 (0.44, 4302.57)	42.90 (1.12, 1650.19)
B	Ensartinib	NA	NA	NA	NA	NA	NA
	2.13 (0.09, 53.05)	Brigatinib	NA	2.58 (0.49, 13.51)	2.71 (0.21, 35.60)	4.20 (0.64, 27.53)	27.26 (1.33, 558.33)
C	Ensartinib	NA	NA	NA	NA	NA	NA
	6.99 (0.30, 161.21)	Brigatinib	NA	6.99 (0.30, 161.21)	6.99 (0.30, 161.21)	6.99 (0.30, 161.21)	6.99 (0.30, 161.21)
D	Ensartinib	NA	NA	NA	NA	NA	NA
	7.30 (0.37, 142.59)	Brigatinib	NA	7.30 (0.37, 142.59)	7.30 (0.37, 142.59)	7.30 (0.37, 142.59)	7.30 (0.37, 142.59)
E	Ensartinib	NA	NA	NA	NA	NA	NA
	7.66 (0.22, 271.59)	Brigatinib	NA	7.66 (0.22, 271.59)	7.66 (0.22, 271.59)	7.66 (0.22, 271.59)	7.66 (0.22, 271.59)
F	Ensartinib	NA	NA	NA	NA	NA	NA
	12.96 (0.61, 276.29)	Brigatinib	NA	12.96 (0.61, 276.29)	12.96 (0.61, 276.29)	12.96 (0.61, 276.29)	12.96 (0.61, 276.29)
G	Ensartinib	NA	NA	NA	NA	NA	NA
	46.56 (1.15, 1877.99)	Brigatinib	NA	46.56 (1.15, 1877.99)	46.56 (1.15, 1877.99)	46.56 (1.15, 1877.99)	46.56 (1.15, 1877.99)
H	Ensartinib	NA	NA	NA	NA	NA	NA
	55.52 (1.76, 1749.95)	Brigatinib	NA	55.52 (1.76, 1749.95)	55.52 (1.76, 1749.95)	55.52 (1.76, 1749.95)	55.52 (1.76, 1749.95)

Figure 5. The ILD and pneumonitis risk profiles of ALK-TKIs in patients with ALK-positive NSCLC by MH-NMA methods with continuity correction. (A) Odds ratio and 95%CI for overall ILD (lower triangle in blue) and serious ILD (upper triangle in green). (B) Odds ratio and 95%CI for overall pneumonitis (lower triangle in blue) and serious pneumonitis (upper triangle in green). NA: no data available.

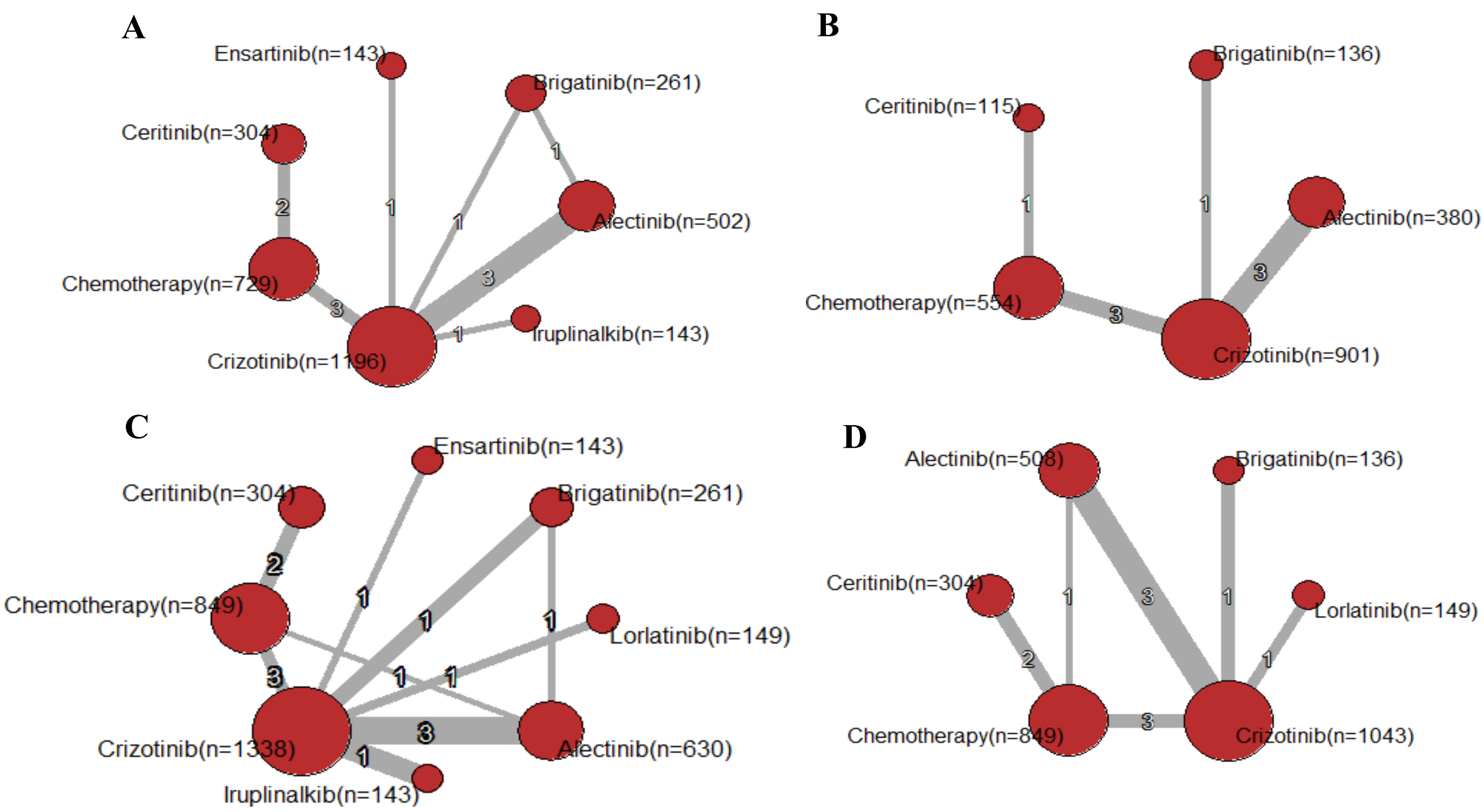


Fig 4. Network plot for ILD and pneumonitis of ALK-TKIs in patients with ALK-positive NSCLC by MH-NMA method with continuity correction. (A) overall ILD, (B) serious ILD, (C) overall pneumonitis, (D) serious pneumonitis.

Table 2. Ranking profiles of ALK-TKIs for ILD and pneumonitis in patients with ALK-positive NSCLC by MH-NMA method with continuity correction. NA, no data available.

Drugs	Overall ILD		Serious ILD		Overall pneumonitis		Serious pneumonitis	
	P-score	Rank	P-score	Rank	P-score	Rank	P-score	Rank
Brigatinib	0.88	1	0.94	1	0.87	2	0.91	1
Irrupinalkib	0.77	2	NA	NA	0.57	3	NA	NA
Ensartinib	0.68	3	NA	NA	0.89	1	NA	NA
Crizotinib	0.50	4	0.66	2	0.57	4	0.69	2
Lorlatinib	NA	NA	NA	NA	0.53	5	0.63	3
Alectinib	0.36	5	0.50	3	0.34	6	0.48	4
Ceritinib	0.24	6	0.23	4	0.14	7	0.10	6
Chemotherapy	0.07	7	0.17	5	0.08	8	0.17	5

