Supplementary

Table S1 Search strategy

PubMed	
#1	(non-small-cell lung cancer[title/abstract] OR non-small cell lung cancer[title/abstract] OR non small-cell lung cancer[title/abstract] OR non small cell lung cancer[title/abstract] OR non-small-cell lung carcinoma[title/abstract] OR non-small cell lung carcinoma[title/abstract] OR non small-cell lung carcinoma[title/abstract] OR non small cell lung carcinoma[title/abstract] OR nsclc[title/abstract])
#2	(epidermal growth factor receptor[title/abstract] OR EGFR[title/abstract])
#3	(treatment[title/abstract] OR therapy[title/abstract] OR tyrosine kinase inhibitor[title/abstract] OR TKI[title/abstract] OR osimertinib[title/abstract] OR dacomitinib[title/abstract] OR afatinib[title/abstract] OR erlotinib[title/abstract] OR gefitinib[title/abstract] OR icotinib[title/abstract] OR aumolertinib [title/abstract] OR furmontinib[title/abstract])
#4	((randomized controlled trial [publication type] OR controlled clinical trial [publication type] OR randomized [title/abstract] OR placebo [title/abstract] OR randomly [title/abstract] OR trial [title] OR Randomized Controlled Trials as Topic[mesh]) NOT (animals [mesh] NOT humans [mesh]))
#5	#1 AND #2 AND #3 AND #4
Embase	
#1	'non-small-cell lung cancer':ab,ti OR 'non-small cell lung cancer':ab,ti OR 'non small-cell lung cancer':ab,ti OR 'non small cell lung cancer':ab,ti OR 'non-small-cell lung carcinoma':ab,ti OR 'non-small cell lung carcinoma':ab,ti OR 'non small-cell lung carcinoma':ab,ti OR 'non small cell lung carcinoma':ab,ti OR 'nsclc':ab,ti OR 'non small cell lung cancer'/exp
#2	'epidermal growth factor receptor ':ab,ti OR 'EGFR ':ab,ti
#3	'treatment':ab,ti OR 'therapy':ab,ti OR 'tyrosine kinase inhibitor':ab,ti OR 'TKI':ab,ti OR 'osimertinib':ab,ti OR 'dacomitinib':ab,ti OR 'afatinib':ab,ti OR 'erlotinib':ab,ti OR 'gefitinib ':ab,ti OR 'icotinib':ab,ti OR 'aumolertinib':ab,ti OR 'furmontinib':ab,ti
#4	'randomized':ab,ti OR 'placebo':ab,ti OR 'randomly':ab,ti OR 'randomized controlled trial'/exp
#5	#1 AND #2 AND #3 AND #4
Cochrane Central Register of Controlled Trials	
#1	(EGFR):ti,ab,kw OR (epidermal growth factor receptor):ti,ab,kw
#2	(tyrosine kinase inhibitor):ti,ab,kw OR (TKI):ti,ab,kw OR (osimertinib):ti,ab,kw OR (dacomitinib):ti,ab,kw OR (afatinib):ti,ab,kw OR (erlotinib):ti,ab,kw OR (gefitinib):ti,ab,kw OR (icotinib):ti,ab,kw OR (aumolertinib):ti,ab,kw OR (furmontinib):ti,ab,kw
#3	(randomized):ti,ab,kw OR (randomly):ti,ab,kw OR (placebo):ti,ab,kw
#4	#1 AND #2 AND #3
Web of Science	
#1	(TI=(non-small-cell lung cancer OR non-small cell lung cancer OR non small-cell lung cancer OR non small cell lung cancer OR non-small-cell lung carcinoma OR non-small cell lung carcinoma OR non small-cell lung carcinoma OR non small cell lung carcinoma OR nsclc) OR AB=(non-small-cell lung cancer OR non-small cell lung cancer OR non small-cell lung cancer OR non small cell lung cancer OR non-small-cell lung carcinoma OR non-small cell lung carcinoma OR non small-cell lung carcinoma OR non small cell lung carcinoma OR nsclc))
#2	(TI=(epidermal growth factor receptor OR EGFR) OR AB=(epidermal growth factor receptor OR EGFR))
#3	(TI=(tyrosine kinase inhibitor OR TKI OR osimertinib OR dacomitinib OR afatinib OR erlotinib OR gefitinib OR icotinib OR aumolertinib OR furmontinib) OR AB=(tyrosine kinase inhibitor OR TKI OR osimertinib OR dacomitinib OR afatinib OR erlotinib OR gefitinib OR icotinib OR aumolertinib OR furmontinib))
#4	(TI=(compare OR comparison OR comparative OR comparing OR versus OR vs) OR AB=(compare OR comparison OR comparative OR comparing OR versus OR vs)) AND (TI=(randomized OR trial) OR AB=(randomized OR placebo OR randomly))
#5	#1 AND #2 AND #3 AND #4

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Table S2 Evaluating the goodness-of-fit of different models

Model	Dbar	pD	DIC	Data points
Grade ≥3 AEs				
Fixed model consistency	102.94354	33.28819	136.23173	47
Random model consistency	51.79815	44.17975	95.97790	47
Random model inconsistency	49.59127	44.80677	94.39805	47
Discontinuation due to AEs				
Fixed model consistency	68.75005	32.46877	98.21882	47
Random model consistency	47.18005	39.68092	86.86097	47
Random model inconsistency	48.46642	40.35971	88.82613	47

Dbar can evaluate the goodness-of-fit of models. If Dbar value and data points are close, it indicates the model fit is acceptable. The model fit Leverage (pD) can measure the complexity of models. Deviance information criterion (DIC) measures the goodness-of-fit of models. Model with smaller DIC is regarded as the model that can predict the data better and more parsimoniously. AEs, adverse events.

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Table S3 Assessment of local inconsistency

Comparisons	Direct estimate of OR (95% CrI)	Indirect estimate of OR (95% CrI)	Network estimate of OR (95% CrI)	P value
Grade ≥3 AEs				
Gef versus Erl	1.25 (0.41, 6.05)	0.54 (0.12, 3)	0.88 (0.39, 2.41)	0.35525
Osi versus Erl	0.3 (0.03, 2.72)	0.27 (0.01, 8.17)	0.42 (0.09, 2.23)	0.92475
PfCT versus Erl	4.06 (1.57, 13.46)	9.97 (2.56, 54.6)	5.47 (2.53, 13.46)	0.29375
Osi versus Gef	1.02 (0.12, 9.97)	0.25 (0.01, 4.95)	0.49 (0.1, 2.14)	0.39075
PfCT versus Gef	7.39 (2.41, 24.53)	4.48 (1.02, 16.44)	6.05 (1.21, 36.6)	0.49450
PbCT versus Ico	14.88 (1.63, 134.29)	13.46 (0.58, 298.87)	13.46 (2.59, 73.7)	0.95925
PfCT versus Ico	2.66 (0.27, 29.96)	2.27 (0.27, 16.44)	2.46 (0.57, 9.97)	0.95800
Afa versus Gef	0.9 (0.11, 8.17)	1.84 (0.11, 27.11)	1.19 (0.25, 6.05)	0.91325
PbCT versus Afa	3.67 (0.37, 36.6)	1.82 (0.25, 12.18)	2.46 (0.61, 9.97)	0.64625
PfCT versus Afa	8.17 (0.92, 73.7)	3.32 (0.2, 66.69)	6.05 (1.19, 33.12)	0.60525
PbCT versus Osi	1.25 (0.41, 6.05)	0.54 (0.12, 3)	0.88 (0.39, 2.41)	0.60975
Discontinuation due to AEs				
Gef versus Erl	1.48 (0.55, 4.48)	3 (0.7, 14.88)	1.77 (0.88, 4.06)	0.42250
Osi versus Erl	0.76 (0.11, 4.95)	0.9 (0.05, 20.09)	0.95 (0.26, 3.32)	0.90525
PfCT versus Erl	3 (1.05, 9.97)	1.6 (0.44, 5.47)	2.32 (1.05, 5.47)	0.39025
Osi versus Gef	0.72 (0.11, 4.95)	0.45 (0.02, 7.39)	0.54 (0.14, 1.73)	0.74175
PfCT versus Gef	0.82 (0.39, 1.55)	3.32 (1.28, 7.39)	1.31 (0.59, 2.56)	0.02150
PbCT versus Ico	12.18 (1.63, 109.95)	9.03 (0.43, 445.86)	11.02 (2.18, 60.34)	0.88600
PfCT versus Ico	13.46 (1.08, 445.86)	18.17 (1.27, 270.43)	14.88 (2.64, 109.95)	0.88650
Afa versus Gef	1.05 (0.21, 4.95)	0.25 (0.06, 1.01)	0.48 (0.15, 1.48)	0.14625
PbCT versus Afa	1.63 (0.26, 9.97)	2.32 (0.2, 24.53)	1.84 (0.5, 6.69)	0.80025
PfCT versus Afa	6.05 (1.61, 22.2)	1.23 (0.35, 4.48)	2.72 (0.85, 8.17)	0.06650
PbCT versus Osi	1.79 (0.27, 11.02)	1.42 (0.11, 16.44)	1.63 (0.43, 6.69)	0.87050

Node-splitting approach was used to assess the local inconsistency for network meta-analysis of grade ≥3 AEs and discontinuation due to AEs. P value ≤0.05 indicates a significant difference between direct estimate and indirect estimate. AEs, adverse events; Afa, afatinib; Aum, aumolertinib; Dac, dacomitinib; Ico, icotinib; Erl, erlotinib; Osi, osimertinib; Fur, furmonertinib; Gef, gefitinib; PbCT, pemetrexed-based chemotherapy; PfCT, pemetrexed-free chemotherapy; OR, odds ratio; CrI, credible interval.

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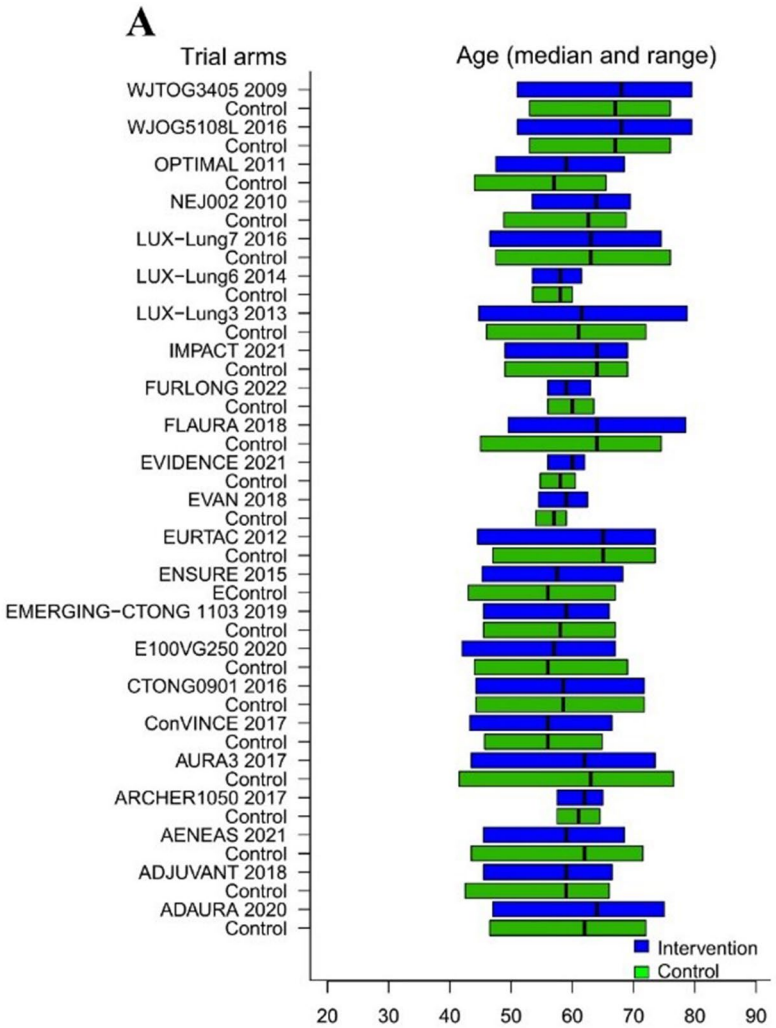

B

Characteristic	Intervention arm	Control arm
Female ratio	0.888	0.849
Smoking status		
Never	0.988	0.486
Former or current	0.448	<0.001
Mutation type		
Exon 19 deletion	0.828	0.932
Exon 21 Leu858Arg	0.646	0.929

Figure S1 Transitivity assumption across included studies. (A) Median age and age range of patients included in Intervention arms and control arms. Age range of trials LUX-LUNG 6, FURLONG, EVIDENCE, EVAN and ARCHER 1050 were instead by interquartile range. Median age of trial NEJ002 was instead by mean age. (B) Difference of main characteristics of population with P value. Trials demonstrated similar characteristics with P value >0.05, except proportion of patients with smoking history across control arms (P<0.001).

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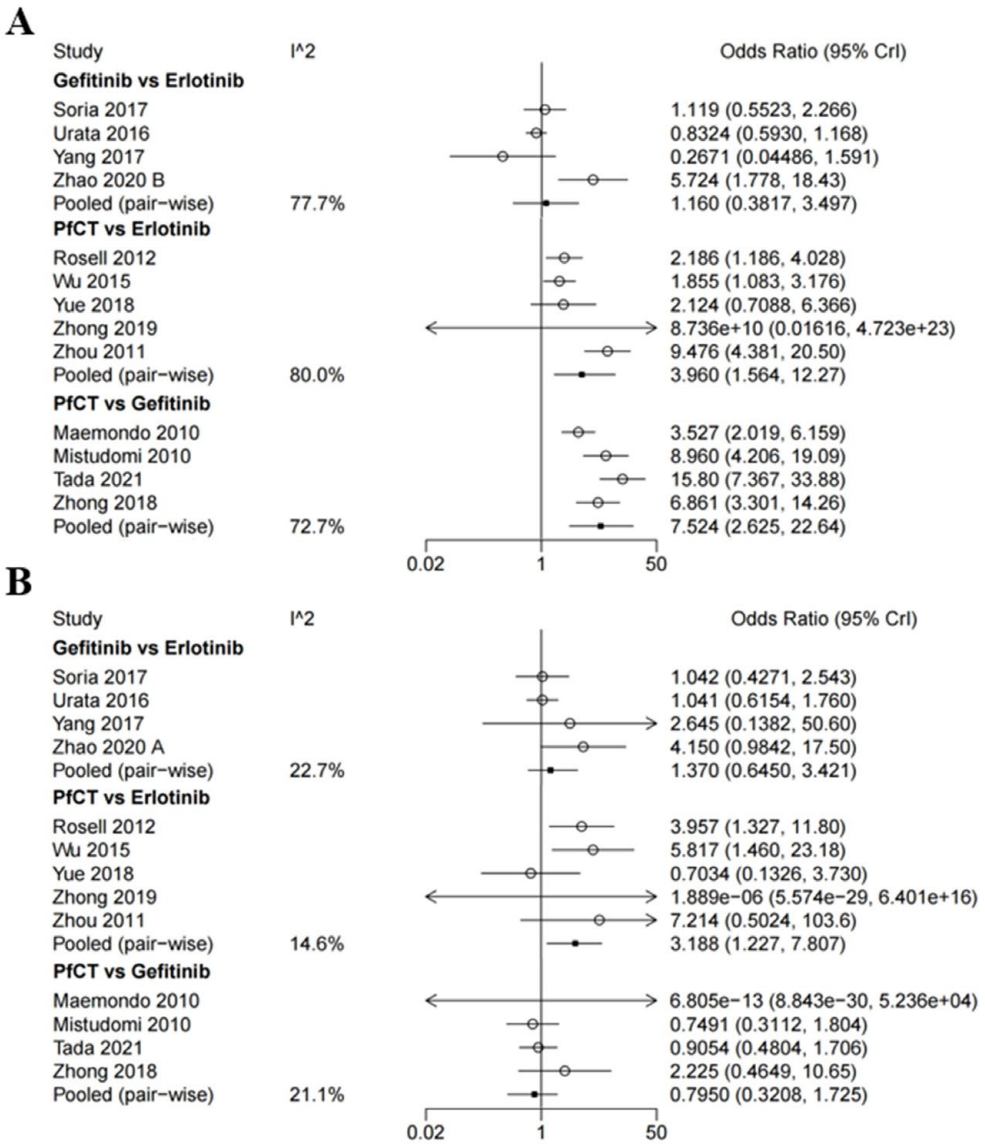

Figure S2 Forest plots depicting the direct estimates for trials assessed same comparison. (A) Heterogeneity in estimate effects for grade ≥3 AEs across trials that assessed same comparison. (B) Heterogeneity in estimate effects for discontinuation due to AEs across trials that assessed same comparison. CrI, credible interval; PbCT, pemetrexed-based chemotherapy; PfCT, pemetrexed-free chemotherapy.

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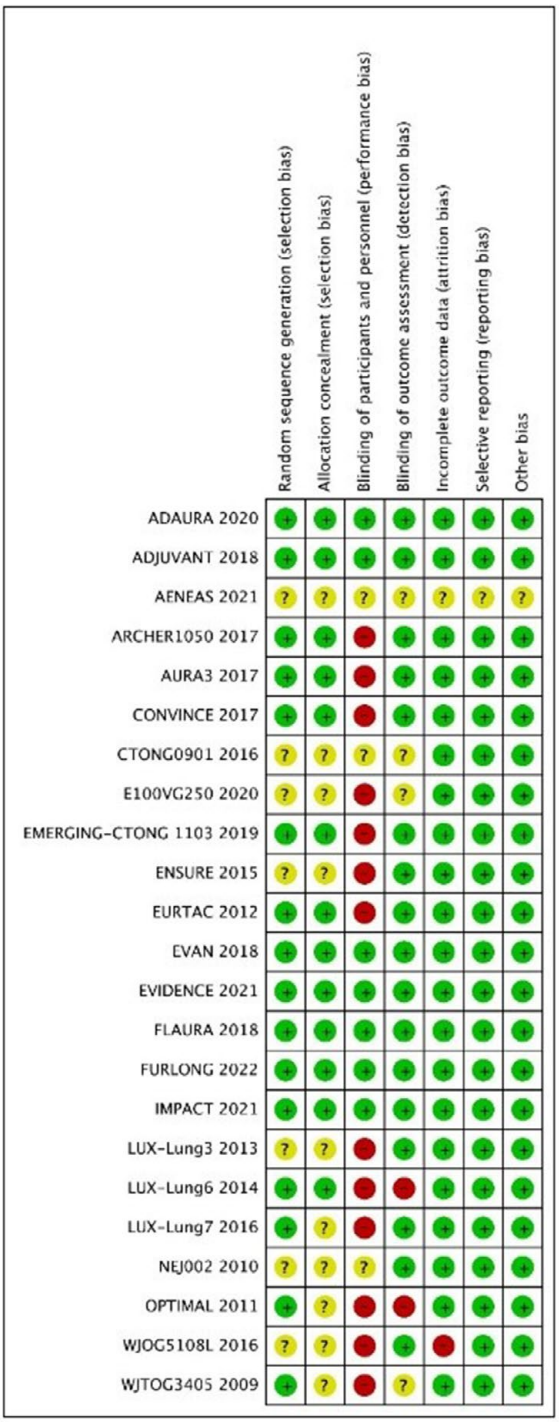

Figure S3 Assessment of risk of bias in included trials.

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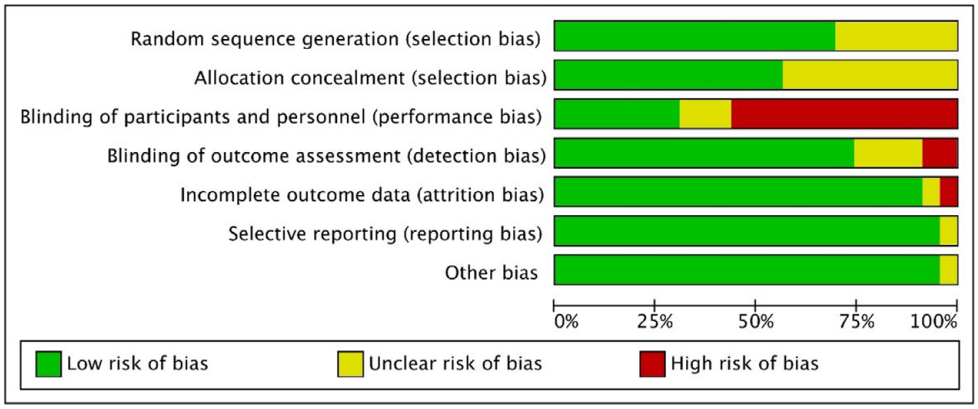
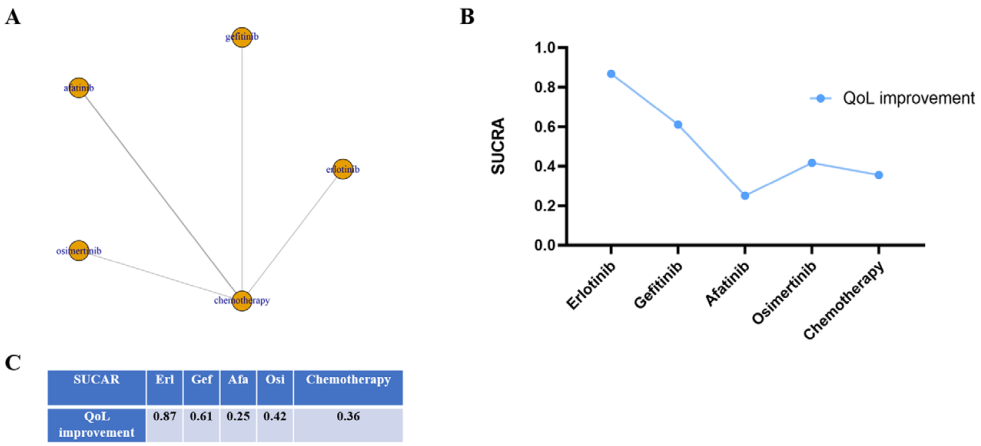


Figure S4 Summary of risk of bias.



C

SUCAR	Erl	Gef	Afa	Osi	Chemotherapy
QoL improvement	0.87	0.61	0.25	0.42	0.36

Figure S5 Network plot and SUCRA estimates for QoL improvement of treatments. (A) Network plot of quality-of-life improvement. (B) Curves demonstrate the SUCRA estimates of treatments. Larger SUCRA indicates more improvement of quality-of-life. (C) SUCRA estimates of treatments. SUCRA, surface under the cumulative ranking curve; Afa, afatinib; Erl, erlotinib; Osi, osimertinib; Gef, gefitinib; QoL, quality of life.

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Erlotinib	0.34 (0.01,12.82)	0.11 (0.00,3.00)	0.18 (0.00,8.54)	0.16 (0.01,2.34)
	Gefitinib	0.35 (0.01,6.69)	0.51 (0.01,18.39)	0.47 (0.04,6.32)
		Afatinib	1.49 (0.07,32.58)	1.39 (0.24,8.74)
			Osimertinib	0.92 (0.08,11.67)
				Chemotherapy

Figure S6 Pooled estimates for QoL improvement of treatments. Each cell contains pooled odds ratio and 95% credibility interval which assesses comparison for column treatment versus row treatment. QoL, quality of life.

Erlotinib	0.65 (0.28,1.98)	0.31 (0.06,1.98)	1.7 (0.3,11.35)	1.55 (0.18,16.46)	0.36 (0.08,1.7)	0.65 (0.09,7.5)	0.37 (0.05,4.13)	2.02 (0.38,12.23)	4.27 (1.94,12.38)	0.3 (0.03,3.81)
0.56 (0.2,1.13)	Gefitinib	0.47 (0.08,2.46)	2.61 (0.38,14.36)	2.39 (0.3,17.32)	0.55 (0.11,2.11)	1 (0.15,7.22)	0.57 (0.08,3.76)	3.14 (0.51,14.74)	6.64 (2.67,14.98)	0.44 (0.04,5.17)
8.18 (1.08,61.68)	14.68 (2.26,135.16)	Icotinib	5.37 (0.78,41.96)	4.99 (0.39,79.73)	1.15 (0.18,7.81)	2.08 (0.17,36.02)	1.19 (0.11,20.61)	6.59 (1.37,30.81)	13.94 (3.07,66.98)	0.96 (0.06,13.72)
2.02 (0.39,7.75)	3.57 (0.89,15.7)	0.24 (0.03,1.49)	Afatinib	0.92 (0.06,15.06)	0.21 (0.03,1.63)	0.39 (0.03,6.12)	0.22 (0.02,3.92)	1.23 (0.23,6.03)	2.58 (0.51,13)	0.17 (0.01,2.77)
0.36 (0.05,1.86)	0.64 (0.12,3.18)	0.04 (0,0.48)	0.17 (0.02,1.41)	Dacomitinib	0.24 (0.02,2.58)	0.43 (0.03,7.69)	0.25 (0.02,4.48)	1.35 (0.08,17.16)	2.74 (0.28,24.04)	0.19 (0.01,4.54)
1.15 (0.3,3.77)	2.05 (0.68,7.96)	0.14 (0.02,1)	0.56 (0.13,3.14)	3.2 (0.46,32.3)	Osimertinib	1.89 (0.17,23.82)	1.08 (0.1,12.97)	5.67 (1.11,29.24)	12.06 (2.83,54.53)	0.83 (0.12,5.79)
0.81 (0.08,4.63)	1.43 (0.24,7.82)	0.09 (0.01,1.31)	0.39 (0.04,3.95)	2.27 (0.23,26.58)	0.68 (0.08,4.93)	Aumolertinib	0.56 (0.04,9.12)	3.06 (0.2,36.15)	6.6 (0.7,51.14)	0.46 (0.02,10.85)
0.34 (0.03,2.74)	0.63 (0.08,4.67)	0.04 (0,0.65)	0.17 (0.01,2.13)	1 (0.08,13.8)	0.3 (0.02,3.03)	0.44 (0.03,6.01)	Furmonertinib	5.35 (0.38,59.81)	11.23 (1.27,92.93)	0.77 (0.03,15.1)
0.86 (0.16,3.87)	1.5 (0.35,7.61)	0.11 (0.02,0.51)	0.42 (0.11,1.87)	2.48 (0.28,28.55)	0.75 (0.17,2.9)	1.09 (0.12,10.49)	2.39 (0.22,36.87)	PbCT	2.11 (0.46,10.96)	0.15 (0.01,1.82)
0.45 (0.18,0.96)	0.8 (0.39,1.81)	0.05 (0.01,0.33)	0.22 (0.06,0.84)	1.27 (0.24,8.6)	0.39 (0.1,1.41)	0.55 (0.1,4.75)	1.28 (0.15,12.45)	0.52 (0.11,2.41)	PfCT	0.07 (0.01,0.78)
4.9 (0.55,35.96)	8.55 (1.15,74.39)	0.58 (0.03,6.58)	2.44 (0.25,25.02)	13.93 (1.02,224.87)	4.18 (0.75,20.12)	6.24 (0.33,94.39)	13.84 (0.73,276.89)	5.62 (0.63,45.44)	11.02 (1.21,87.99)	Placebo

Figure S7 Pooled estimates for overall toxicity profile of sensitive analysis only including phase III trials. Each cell contains pooled odds ratio and 95% credibility interval which assesses comparison for column treatment versus row treatment. Upper triangle of table contains results for grade ≥3 AEs, lower triangle contains results for discontinuation due to AEs. PbCT, pemetrexed-based chemotherapy; PfCT, pemetrexed-free chemotherapy; AEs, adverse events.

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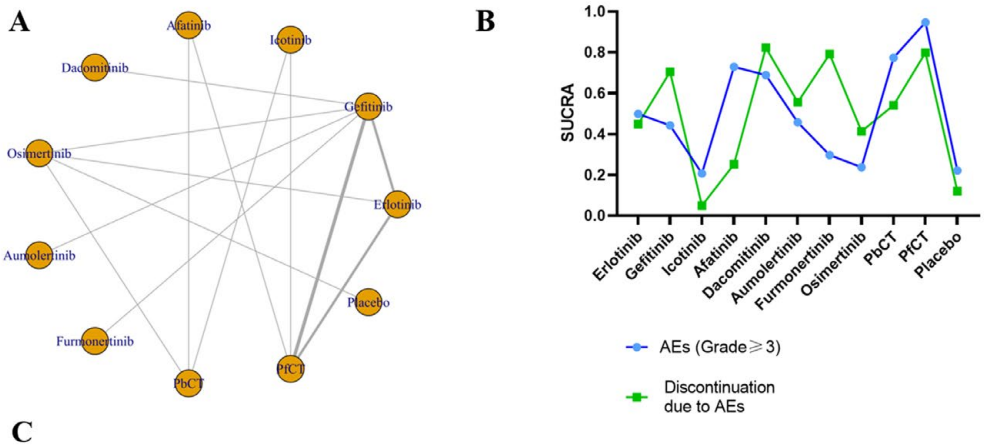

C

SUCAR	Erl	Gef	Ico	Afa	Dac	Osi	Fur	Aum	PbCT	PfCT	Placebo
Grade ≥ 3 AEs	0.57	0.42	0.21	0.71	0.68	0.24	0.27	0.44	0.78	0.95	0.23
Discontinuation	0.45	0.71	0.05	0.25	0.82	0.41	0.79	0.56	0.54	0.80	0.12

Figure S8 Network plot and SUCRA estimates of Sensitive analysis only including phase III trials. (A) Network plot of Sensitive analysis only including phase III trials. Network plot of grade ≥3 and discontinuation of AEs are same. (B) Curves depict the SUCRA estimates of treatments. Larger SUCRA indicates more AEs (grade ≥3) or discontinuation due to AEs. (C) SUCRA estimates of treatments. SUCRA, surface under the cumulative ranking curve; AEs, adverse events; Afa, afatinib; Aum, aumolertinib; Dac, dacomitinib; Erl, erlotinib; Osi, osimertinib; Ico, icotinib; Fur, furmonertinib; Gef, gefitinib; PbCT, pemetrexed-based chemotherapy; PfCT, pemetrexed-free chemotherapy.

Erlotinib	1.04 (0.38,3.89)	0.46 (0.02,13.27)	2.36 (0.4,18.76)	2.51 (0.16,45.47)	0.46 (0.07,3.81)	1.05 (0.09,19.13)	0.61 (0.04,10.57)	2.86 (0.26,32.39)	5.03 (1.87,15.81)
0.63 (0.18,1.39)	Gefitinib	0.43 (0.01,10.88)	2.26 (0.42,12.97)	2.41 (0.18,31.07)	0.44 (0.06,3.1)	1 (0.09,13.65)	0.58 (0.05,6.8)	2.74 (0.25,24.44)	4.73 (1.44,15.17)
7.75 (0.37,158.25)	12.19 (0.7,249.94)	Icotinib	5.15 (0.27,120.15)	5.47 (0.08,439.35)	1.05 (0.04,31.84)	2.44 (0.05,156.04)	1.39 (0.02,98.22)	6.38 (0.56,70.34)	11.08 (0.37,342.41)
1.17 (0.26,4.21)	1.85 (0.56,9.33)	0.15 (0.01,2.45)	Afatinib	1.14 (0.04,21.44)	0.2 (0.02,1.87)	0.46 (0.03,9.2)	0.26 (0.01,5.67)	1.23 (0.15,8.17)	2.1 (0.38,12.15)
0.41 (0.04,3.17)	0.65 (0.08,4.25)	0.05 (0,1.66)	0.35 (0.03,3.24)	Dacomitinib	0.18 (0.01,4.16)	0.42 (0.01,16.42)	0.25 (0.01,10.09)	1.14 (0.03,42.67)	1.96 (0.11,34.83)
1.11 (0.19,4.59)	1.73 (0.41,9.43)	0.14 (0.01,2.22)	0.96 (0.15,4.8)	2.65 (0.27,35.41)	Osimertinib	2.31 (0.12,66.63)	1.31 (0.06,36.28)	6.04 (0.78,53.3)	10.87 (1.32,86.24)
0.9 (0.09,6.79)	1.42 (0.2,12.1)	0.11 (0,3.33)	0.77 (0.06,7.37)	2.2 (0.14,46.04)	0.84 (0.06,8.95)	Aumolertinib	0.58 (0.02,19.22)	2.67 (0.09,68.94)	4.87 (0.28,66.87)
0.4 (0.03,3.79)	0.65 (0.06,5.63)	0.05 (0,2.07)	0.33 (0.02,4.49)	1.04 (0.05,22.36)	0.38 (0.02,4.95)	0.45 (0.02,9.58)	Furmonertinib	4.55 (0.14,124.14)	8.09 (0.57,155.6)
0.68 (0.11,3.84)	1.05 (0.19,7.5)	0.09 (0.01,0.78)	0.58 (0.1,3)	1.63 (0.12,35.56)	0.61 (0.13,3.38)	0.74 (0.06,12.45)	1.66 (0.1,36.2)	PbCT	1.78 (0.17,19.57)
0.37 (0.14,1.22)	0.59 (0.21,3.32)	0.05 (0,0.95)	0.31 (0.09,1.61)	0.92 (0.11,15.49)	0.33 (0.07,2.59)	0.4 (0.05,6.17)	0.92 (0.08,18.83)	0.54 (0.10,4.16)	PfCT

Figure S9 Pooled estimates for overall toxicity profile of sensitive analysis only including trials with advanced NSCLC patients. Each cell contains pooled odds ratio and 95% credibility interval which assesses comparison for column treatment versus row treatment. Upper triangle of table contains results for grade ≥3 AEs, lower triangle contains results for discontinuation due to AEs. PbCT, pemetrexed-based chemotherapy; PfCT, pemetrexed-free chemotherapy; NSCLC, non-small cell lung cancer; AEs, adverse events.

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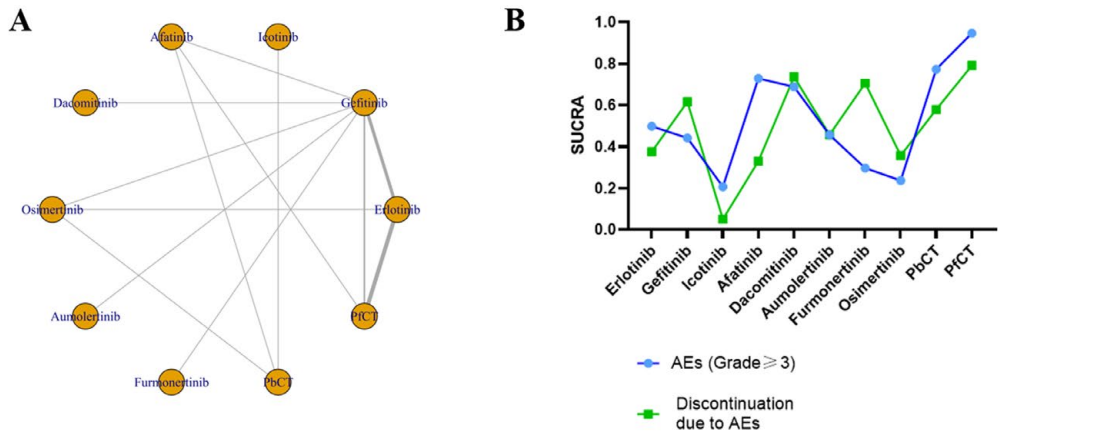

C

SUCAR	Erl	Gef	Ico	Afa	Dac	Osi	Fur	Aum	PbCT	PfCT
Grade ≥ 3 AEs	0.41	0.43	0.24	0.67	0.68	0.20	0.31	0.45	0.72	0.89
Discontinuation	0.38	0.62	0.05	0.33	0.74	0.36	0.71	0.46	0.58	0.79

Figure S10 Network plot and SUCRA estimates of sensitive analysis on trials only including advanced NSCLC patient. (A) Network plot of Sensitive analysis only including trials with advanced NSCLC patients. (B) Curves demonstrate the SUCRA estimates of treatments. Larger SUCRA indicates more AEs (grade ≥3) or discontinuation due to AEs. (C) SUCRA estimates of treatments. Network plot of grade ≥3 and discontinuation of AEs are same. SUCRA, surface under the cumulative ranking curve; AEs, adverse events; Afa, afatinib; Aum, aumolertinib; Dac, dacomitinib; Erl, erlotinib; Ico, icotinib; Osi, osimertinib; Fur, furmonertinib; Gef, gefitinib; PbCT, pemetrexed-based chemotherapy; PfCT, pemetrexed-free chemotherapy; NSCLC, non-small cell lung cancer.

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