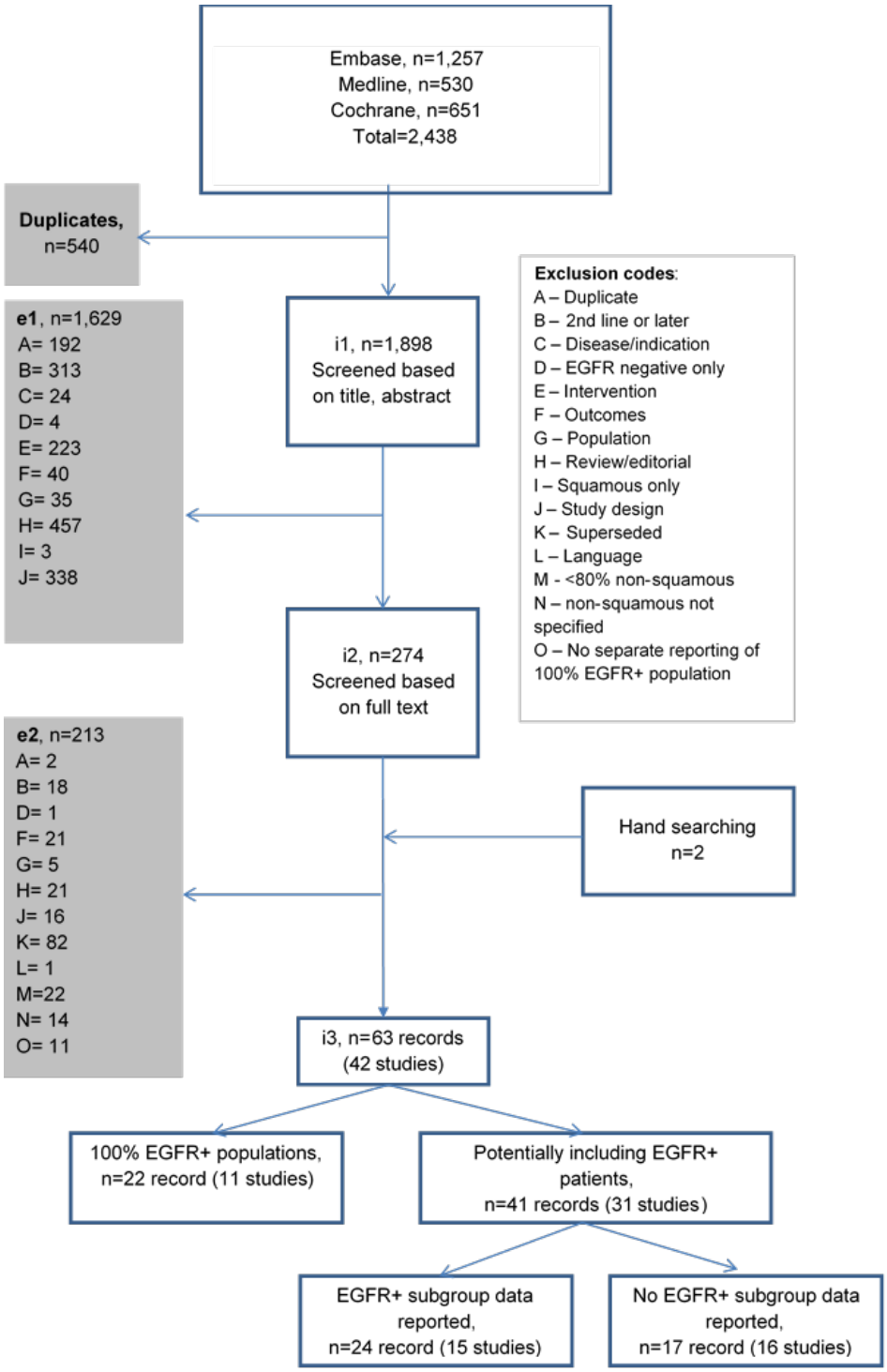
Supplementary materials

Figure S1 PRISMA flow diagram



Abbreviations: EGFR, epidermal growth factor receptor mutation; EGFR+, epidermal growth factor receptor mutation positive.

Table S1 Eligibility criteria for study inclusion in the clinical SR

Criterion	Description
Population	Treatment-naïve adults with locally advanced or metastatic (Stage IIIb or IV) non-squamous epidermal growth factor receptor mutation positive (EGFR+) NSCLC. Publications that do not explicitly state whether the enrolled patients have squamous or non-squamous histology were tagged and details of the citations provided to Roche. Studies where >80% of enrolled patients present with non-squamous histology were eligible for inclusion. Where the study enrolled a mixed population with regard to stage of disease and the results for the metastatic NSCLC population were not reported separately, at least 80% of the enrolled patients had to present with locally advanced or metastatic disease to be eligible for inclusion.
Interventions	Restricted to TKIs only. Studies included at least one study arm examining the following treatments: • Afatinib • Erlotinib • Gefitinib • Dacomitinib [No restriction on dose/treatment regimen and TKI may be administered as monotherapy or in combination with another agent(s)]
Comparators	Included immunotherapy, targeted therapies and chemotherapy
Outcomes	Efficacy • OS • PFS • TTP • Response rates (CR, PR and SD) Safety • All-grade and grade 3/4 AEs Health-related quality of life (HRQoL)
Study design	RCTs with no restriction on study design or phase.
Countries	No restriction
Language	English: English abstracts of foreign publications were considered
Date of publication	No restriction
Publication status	Published studies and unpublished data were considered

Abbreviations: AE, adverse event; CR, complete response; EGFR, epidermal growth factor receptor; EGFR+, epidermal growth factor receptor mutation positive; HRQoL, health-related quality of life; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PR, partial response; RCT, randomized controlled trial; SR, systematic review; SD, stable disease; TKI, tyrosine kinase inhibitors; TTP, time to progression.

Figure S2 Graphical representation of risk of bias assessment of studies included in NMA

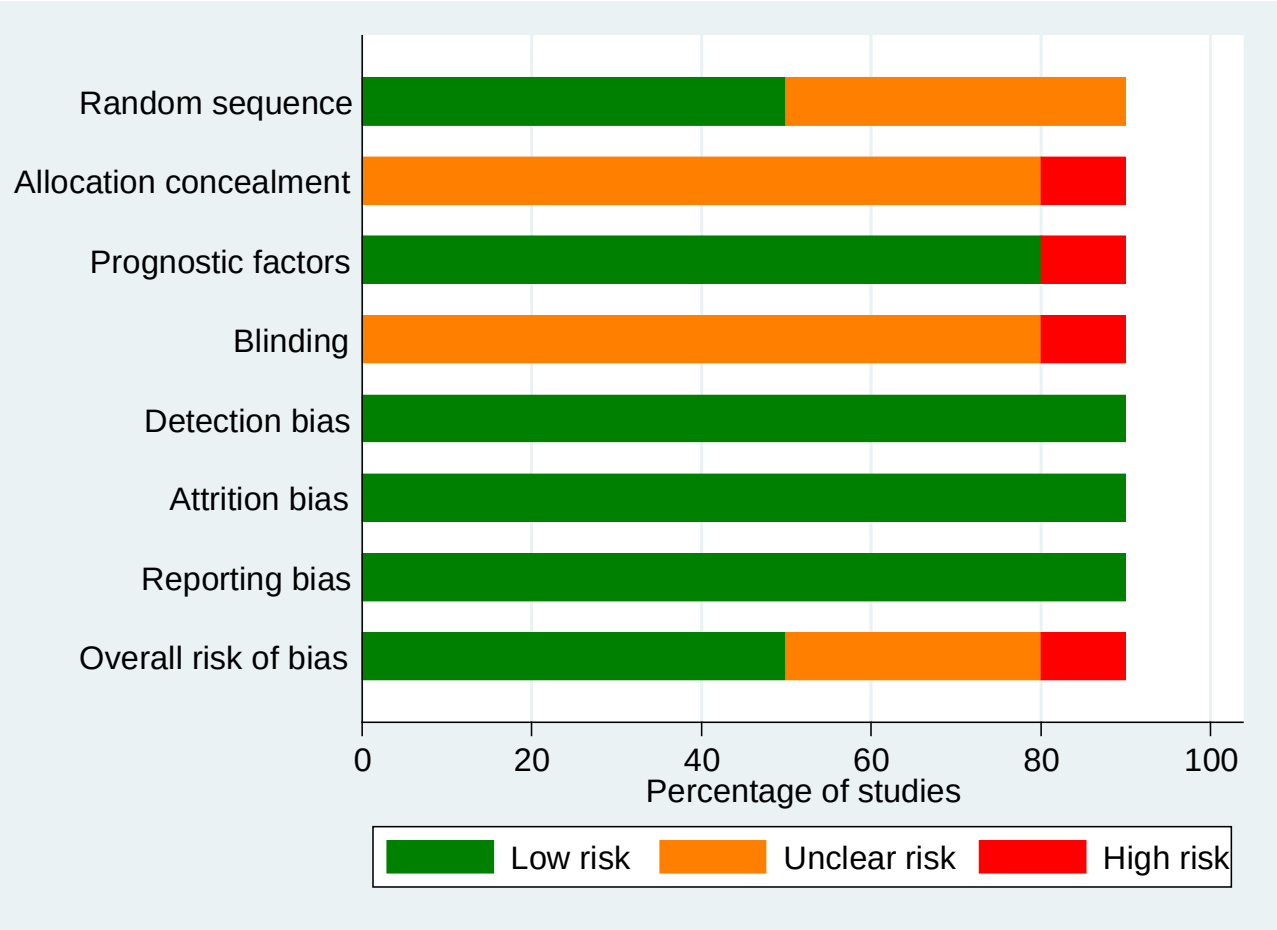


Table S2 Trial-level data reported for PFS and obtained by modeling pseudo-IPD using the PH and AFT models

Trial	Treatment	Published HR (95% CI)	HR (95% CI) modeling IPD	1/AF HR (95% CI)
LUX-Lung 6[12,13,34]	Afatinib	0.28 (0.20, 0.39)	0.27 (0.20, 0.37)	0.44 (0.38, 0.52)
	Chemotherapy	comparator	comparator	comparator
LUX-Lung 3[14,15,34]	Afatinib	0.58 (0.43, 0.78)	0.58 (0.44, 0.78)	0.67 (0.54, 0.83)
	Chemotherapy	comparator	comparator	comparator
LUX-Lung 7[16]	Afatinib	0.73 (0.57, 0.95)	0.73 (0.56, 0.94)	0.79 (0.66, 0.96)
	Gefitinib	comparator	comparator	comparator
EURTAC[5]	Erlotinib	0.37 (0.25, 0.54)	0.38 (0.26, 0.56)	0.49 (0.36, 0.65)
	Chemotherapy	comparator	comparator	comparator
ENSURE[8]	Erlotinib	0.42 (0.27, 0.66)	0.40 (0.26, 0.62)	0.59 (0.47, 0.75)
	Chemotherapy	comparator	comparator	comparator
OPTIMAL[10,11,33]	Erlotinib	0.16 (0.10, 0.26)	0.18 (0.12, 0.28)	0.36 (0.45, 0.29)
	Chemotherapy	comparator	comparator	comparator
JO25567[19]	Erlotinib	comparator	comparator	comparator
	Erlotinib + bevacizumab	0.54 (0.36, 0.79)	0.54 (0.36, 0.80)	0.53 (0.38, 0.72)
WTJOG3405[7,31]	Gefitinib	0.520 (0.378, 0.715)	0.49 (0.35, 0.66)	0.60 (0.47, 0.75)
	Chemotherapy	comparator	comparator	comparator
NEJ002[9,32]	Gefitinib	0.322 (0.236, 0.438)	0.29 (0.22, 0.40)	0.46 (0.39, 0.54)
	Chemotherapy	comparator	comparator	comparator

Abbreviations: AF, acceleration factor; AFT, acceleration failure time; AIC, Akaike information criterion; BIC, Bayesian information criterion; CI, confidence interval; HR, hazard ratio; IPD, individual patient data; PFS, progression-free survival; PH, proportional hazards.

Table S3 Treatment comparisons for PFS: 1/AF (95% CrI), random-effect model

Treatment A	Treatment B					SUCRA
	Chemotherapy	Afatinib	Erlotinib	Erlotinib + bevacizumab	Gefitinib	
Chemotherapy		***1.99 (1.27, 3.08)***	***2.15 (1.40, 3.26)***	***4.06 (1.70, 9.56)***	***1.81 (1.15, 2.81)***	0.00
Afatinib	***0.50 (0.33, 0.79)***		1.08 (0.59, 1.99)	2.04 (0.77, 5.39)	0.91 (0.55, 1.52)	0.50
Erlotinib	***0.47 (0.31, 0.71)***	0.93 (0.50, 1.70)		1.89 (0.89, 4.01)	0.84 (0.46, 1.56)	0.75
Erlotinib + bevacizumab	***0.25 (0.10, 0.59)***	0.49 (0.19, 1.29)	0.53 (0.25, 1.13)		0.44 (0.17, 1.18)	1.00
Gefitinib	***0.55 (0.36, 0.87)***	1.10 (0.66, 1.83)	1.19 (0.64, 2.19)	2.25 (0.85, 5.93)		0.25

Notes: Results that do not include the null value are bold and italicized. Comparisons of row versus column.
Abbreviations: CrI, credible interval; HR, hazard ratio; PFS, progression-free survival; SUCRA, surface under cumulative ranking curve.

Table S4 Treatment comparisons for PFS: HR (95% CrI), fixed-effect model

Treatment A	Treatment B					SUCRA
	Chemotherapy	Afatinib	Erlotinib	Erlotinib + bevacizumab	Gefitinib	
Chemotherapy		***2.65 (2.20, 3.19)***	***3.26 (2.54, 4.19)***	***6.05 (3.79, 9.62)***	***2.21 (1.84, 2.66)***	0.00
Afatinib	***0.38 (0.31, 0.45)***		1.23 (0.90, 1.68)	***2.28 (1.38, 3.76)***	0.83 (0.69, 1.01)	0.50
Erlotinib	***0.31 (0.24, 0.39)***	0.81 (0.59, 1.11)		***1.85 (1.25, 2.74)***	***0.68 (0.50, 0.93)***	0.75
Erlotinib + bevacizumab	***0.17 (0.10, 0.26)***	***0.44 (0.27, 0.73)***	***0.54 (0.36, 0.80)***		***0.37 (0.22, 0.60)***	1.00
Gefitinib	***0.45 (0.38, 0.54)***	1.20 (0.99, 1.46)	***1.48 (1.08, 2.01)***	***2.73 (1.66, 4.51)***		0.25

Notes: Results that do not include the null value are bold and italicized. Comparisons of row versus column.
Abbreviations: CrI, credible interval; HR, hazard ratio; PFS, progression-free survival; SUCRA, surface under cumulative ranking curve.

Table S5 Treatment comparisons for PFS: 1/AF (95% CrI), fixed-effect model for individual chemotherapy regimens

Treatment A	Treatment B						SUCRA
	Cisplatin + gemcitabine	Afatinib	Erlotinib	Gefitinib	Cisplatin + docetaxel	Erlotinib + bevacizumab	
Cisplatin + gemcitabine		***2.20 (1.88, 2.57)***	***1.79 (1.46, 2.21)***	***1.68 (1.35, 2.1)***	***0.95 (0.74, 1.22)***	***3.39 (2.34, 4.93)***	0.20
Afatinib	***0.45 (0.39, 0.53)***		0.81 (0.64, 1.03)	***0.77 (0.64, 0.91)***	***0.43 (0.34, 0.55)***	***1.54 (1.04, 2.28)***	0.80
Erlotinib	***0.56 (0.45, 0.69)***	1.23 (0.97, 1.55)		0.94 (0.73, 1.21)	***0.53 (0.42, 0.67)***	***1.89 (1.39, 2.57)***	0.60
Gefitinib	***0.59 (0.48, 0.74)***	***1.31 (1.09, 1.56)***	1.06 (0.83, 1.37)		***0.56 (0.46, 0.69)***	***2.01 (1.35, 3.00)***	0.40
Cisplatin + docetaxel	***1.05 (0.82, 1.36)***	***2.32 (1.82, 2.96)***	***1.89 (1.49, 2.41)***	***1.77 (1.44, 2.19)***		***3.57 (2.41, 5.29)***	0.00
Erlotinib + bevacizumab	***0.30 (0.20, 0.43)***	***0.65 (0.44, 0.96)***	***0.53 (0.39, 0.72)***	***0.50 (0.33, 0.74)***	***0.28 (0.19, 0.41)***		1.00

Notes: Results that do not include the null value are bold and italicized. Comparisons of row versus column.
Abbreviations: AF, acceleration factor; CrI, credible interval; PFS, progression-free survival; SUCRA, surface under cumulative ranking curve.

Table S6 Summary of the PFS NMA results and trial-level data (base case) for the treatment comparisons with trial-level data available

Trial	Treatment comparison	1/AF (95% CI)	FE NMA results based on AFs, 1/AF (95% CrI)	Trial quality assessment-overall risk of bias
LUX-Lung 6[12,13,34]	Afatinib vs chemotherapy	0.44 (0.38, 0.52)	0.48 (0.43, 0.54)	Low
LUX-Lung 3[14,15,34]	Afatinib vs chemotherapy	0.67 (0.54, 0.83)		Low
LUX-Lung 7[16]	Afatinib vs chemotherapy	0.79 (0.66, 0.96)		Unclear
EURTAC[5]	Erlotinib vs chemotherapy	0.49 (0.36, 0.65)	0.46 (0.40, 0.53)	Low
ENSURE[8]	Erlotinib vs chemotherapy	0.59 (0.47, 0.75)		Unclear
OPTIMAL[10,11,33]	Erlotinib vs chemotherapy	0.36 (0.29, 0.45)		Low
WTJOG3405[7,31]	Gefitinib vs chemotherapy	0.60 (0.47, 0.75)	0.53 (0.48, 0.60)	Unclear
NEJ002[9,32]	Gefitinib vs chemotherapy	0.46 (0.39, 0.54)		Low
JO25567[19]	Erlotinib + bevacizumab vs erlotinib	0.53 (0.38, 0.72)	0.53 (0.39, 0.72)	Low

Abbreviations: AF, acceleration factor; CI, confidence interval; CrI, credible interval; FE, fixed-effects; NMA, network meta-analysis.

Table S7 Treatment comparisons of 1/AF (95% CrI) for PFS: fixed-effect model for Asian populations

Treatment A	Treatment B					SUCRA
	Chemotherapy	Afatinib	Erlotinib	Erlotinib + bevacizumab	Gefitinib	
Chemotherapy		***2.26 (1.92, 2.67)***	***2.19 (1.86, 2.58)***	***4.14 (2.92, 5.87)***	***2.00 (1.75, 2.30)***	0.75
Afatinib	***0.44 (0.37, 0.52)***		0.97 (0.77, 1.22)	***1.83 (1.24, 2.7)***	0.89 (0.71, 1.10)	0.50
Erlotinib	***0.46 (0.39, 0.54)***	1.03 (0.82, 1.30)		***1.89 (1.39, 2.57)***	0.91 (0.74, 1.13)	1.00
Erlotinib + bevacizumab	***0.24 (0.17, 0.34)***	***0.55 (0.37, 0.80)***	***0.53 (0.39, 0.72)***		***0.48 (0.33, 0.70)***	0.25
Gefitinib	***0.50 (0.44, 0.57)***	1.13 (0.91, 1.40)	1.10 (0.89, 1.35)	***2.07 (1.42, 3.01)***		0.75

Notes: Results that do not include the null value are bold and italicized. Comparisons of row versus column.
Abbreviations: AF, acceleration factor; CrI, credible interval; PFS, progression-free survival; SUCRA; surface under cumulative ranking curve.