References

22. Aerts JG, Codrington H, Lankheet NA, et al. A randomized phase II study comparing erlotinib versus erlotinib with alternating chemotherapy in relapsed non-small-cell lung cancer patients: the NVALT-10 study. Ann Oncol 2013;24:2860-65.
23. Ardizzoni A, Tiseo M, Boni L, et al. Pemetrexed versus pemetrexed and carboplatin as second-line chemotherapy in advanced non-small-cell lung cancer: results of the GOIRC 02-2006 randomized phase II study and pooled analysis with the NVALT7 trial. J Clin Oncol 2012;30:4501-7.
24. Belvedere O, Follador A, Rossetto C, et al. A randomised phase II study of docetaxel/oxaliplatin and docetaxel in patients with previously treated non-small cell lung cancer: an Alpe-Adria Thoracic Oncology Multidisciplinary group trial (ATOM 019). Eur J Cancer 2011;47:1653-9.
25. Bergqvist M, Holgersson G, Bondarenko I, et al. Phase II randomized study of the IGF-1R pathway modulator AXL1717 compared to docetaxel in patients with previously treated, locally advanced or metastatic non-small cell lung cancer. Acta Oncol 2017;56:441-7.
26. Blumenschein GR, Jr., Smit EF, Planchard D, et al. A randomized phase II study of the MEK1/MEK2 inhibitor trametinib (GSK1120212) compared with docetaxel in KRAS-mutant advanced non-small-cell lung cancer (NSCLC)†. Ann Oncol 2015;26:894-901.
27. Bradbury PA, Morris DG, Nicholas G, et al. Canadian Cancer Trials Group (CCTG) IND211: A randomized trial of pelareorep (Reolysin) in patients with previously treated advanced or metastatic non-small cell lung cancer receiving standard salvage therapy. Lung Cancer 2018;120:142-8.
28. Chiappori A, Bepler G, Barlesi F, et al. Phase II, double-blinded, randomized study of enzastaurin plus pemetrexed as second-line therapy in patients with advanced non-small cell lung cancer. J Thorac Oncol 2010;5:369-75.
29. Cortinovis D, Bidoli P, Cullurà D, et al. Is irinotecan plus docetaxel useful as second-line therapy in advanced non-small cell lung cancer? J Thorac Oncol 2008;3:405-411.
30. Cufer T, Vrdoljak E, Gaafar R, Erensoy I, Pemberton K, grp Ss. Phase II, open-label, randomized study (SIGN) of single-agent gefitinib (IRESSA) or docetaxel as second-line therapy in patients with advanced (stage IIIb or IV) non-small-cell lung cancer. Anticancer Drugs 2006;17:401-9.
31. Dittrich C, Papai-Szekely Z, Vinolas N, et al. A randomised phase II study of pemetrexed versus pemetrexed+erlotinib as second-line treatment for locally advanced or metastatic non-squamous non-small cell lung cancer. Eur J Cancer 2014;50:1571-80.
32. Dowlati A, Chapman R, Subbiah S, et al. Randomized phase II trial of different schedules of administration of rebeccamycin analogue as second line therapy in non-small cell lung cancer. Invest New Drugs 2005;23:563-7.
33. Esteban E, González de Sande L, Fernández Y, et al. Prospective randomised phase II study of docetaxel versus paclitaxel administered weekly in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. Ann Oncol 2003;14:1640-7.
34. Fanucchi MP, Fossella FV, Belt R, et al. Randomized phase II study of bortezomib alone and bortezomib in combination with docetaxel in previously treated advanced non-small-cell lung cancer. J Clin Oncol 2006;24:5025-33.
35. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. J Clin Oncol 2003;21:2237-46.
36. Georgoulias V, Kouroussis C, Agelidou A, et al. Irinotecan plus gemcitabine vs irinotecan for the second-line treatment of patients with advanced non-small-cell lung cancer pretreated with docetaxel and cisplatin: a multicentre, randomised, phase II study. Br J Cancer 2004;91:482-8.
37. Georgoulias V, Agelidou A, Syrigos K, et al. Second-line treatment with irinotecan plus cisplatin vs cisplatin of patients with advanced non-small-cell lung cancer pretreated with taxanes and gemcitabine: a multicenter randomised phase II study. Br J Cancer 2005;93:763-9.
38. Gerber DE, Spigel DR, Giorgadze D, et al. Docetaxel Combined With Bavituximab in Previously Treated, Advanced Nonsquamous Non-Small-Cell Lung Cancer. Clin Lung Cancer 2016;17:169-76.
39. Gervais R, Ducolone A, Breton JL, et al. Phase II randomised trial comparing docetaxel given every 3 weeks with weekly schedule as second-line therapy in patients with advanced non-small-cell lung cancer (NSCLC). Ann Oncol 2005;16:90-6.
40. Gridelli C, Chella A, Valmadre G, et al. Second-line Erlotinib or Intermittent Erlotinib plus Docetaxel in Male Ex-smokers with Squamous NSCLC: The TALISMAN Randomized Trial. Anticancer Res 2016;36:6535-40.
41. Groen HJ, Socinski MA, Grossi F, et al. A randomized, double-blind, phase II study of erlotinib with or without sunitinib for the second-line treatment of metastatic non-small-cell lung cancer (NSCLC). Ann Oncol

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2013;24:2382-9.
42. Han B, Li K, Zhao Y, et al. Anlotinib as a third-line therapy in patients with refractory advanced non-small-cell lung cancer: a multicentre, randomised phase II trial (ALTER0302). Br. J. Cancer 2018;118:654-61.
43. Heigener DF, von Pawel J, Eschbach C, et al. Prospective, multicenter, randomized, independent-group, open-label phase II study to investigate the efficacy and safety of three regimens with two doses of sagopilone as second-line therapy in patients with stage IIIB or IV non-small-cell lung cancer. Lung Cancer 2013;80:319-25.
44. Heist RS, Wang X, Hodgson L, et al. CALGB 30704 (Alliance): A randomized phase II study to assess the efficacy of pemetrexed or sunitinib or pemetrexed plus sunitinib in the second-line treatment of advanced non-small-cell lung cancer. J Thorac Oncol 2014;9:214-21.
45. Herbst RS, O'Neill VJ, Fehrenbacher L, et al. Phase II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non-small-cell lung cancer. J Clin Oncol 2007;25:4743-50.
46. Heudobler D, Schulz C, Fischer JR, et al. Pioglitazone and clarithromycin combined with metronomic lowdose chemotherapy versus nivolumab in patients with advanced non-small cell lung cancer treated in 2nd-line and beyond: outcomes from a randomized phase II trial (ModuLung). Ann Oncol 2019;30:v646-v647.
47. Heymach JV, Johnson BE, Prager D, et al. Randomized, placebo-controlled phase II study of vandetanib plus docetaxel in previously treated non-small-cell lung cancer. J Clin Oncol 2007;25:4270-7.
48. Ikezawa Y, Asahina H, Oizumi S, et al. A randomized phase II trial of erlotinib vs. S-1 as a third- or fourth-line therapy for patients with wild-type EGFR non-small cell lung cancer (HOT1002). Cancer Chemother Pharmacol 2017;80:955-63.
49. Jones S, Thompson D, Barton J, et al. A randomized phase II trial of oral topotecan versus docetaxel in the second-line treatment of non-small-cell lung cancer. Clin. Lung Cancer 2008;9:154-9.
50. Juan O, Aparisi F, Sanchez-Hernandez A, et al. Intercalated Dosing Schedule of Erlotinib and Docetaxel as a Therapeutic Strategy to Avoid Antagonism and Optimize Its Benefits in Advanced Non-Small-Cell Lung Cancer. A Randomized Phase II Clinical Trial. Clin Lung Cancer 2015;16:193-9.
51. Kentepozidis N, Economopoulou P, Christofyllakis C, et al. Salvage treatment with irinotecan/cisplatin versus pemetrexed/cisplatin in patients with non-small cell lung cancer pre-treated with a non-platinum-based regimen in the first-line setting: a randomized phase II study of the Hellenic Oncology Research Group (HORG). Clin Transl Oncol 2017;19:317-25.
52. Kim ST, Uhm JE, Lee J, et al. Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small cell lung cancer who failed previous chemotherapy. Lung Cancer 2012;75:82-8.
53. Kim YS, Cho EK, Woo HS, et al. Randomized Phase II Study of Pemetrexed Versus Gefitinib in Previously Treated Patients with Advanced Non-small Cell Lung Cancer. Cancer Res Treat 2016;48:80-7.
54. Kim HR, Jang JS, Sun JM, et al. A randomized, phase II study of gefitinib alone versus nimotuzumab plus gefitinib after platinum-based chemotherapy in advanced non-small cell lung cancer (KCSG LU12-01). Oncotarget 2017;8:15943-51.
55. Lai CL, Tsai CM, Chiu CH, et al. Phase II randomized trial of tri-weekly versus days 1 and 8 weekly docetaxel as a second-line treatment of advanced non-small cell lung cancer. Jpn J Clin Oncol 2005;35:700-6.
56. Lee DH, Lee JS, Kim SW, et al. Three-arm randomised controlled phase 2 study comparing pemetrexed and erlotinib to either pemetrexed or erlotinib alone as second-line treatment for never-smokers with non-squamous non-small cell lung cancer. Eur J Cancer 2013;49:3111-21.
57. Levy BP, Giaccone G, Besse B, et al. Randomised phase 2 study of pembrolizumab plus CC-486 versus pembrolizumab plus placebo in patients with previously treated advanced non-small cell lung cancer. Eur J Cancer 2019;108:120-8.
58. Li N, Ou W, Yang H, et al. A randomized phase 2 trial of erlotinib versus pemetrexed as second-line therapy in the treatment of patients with advanced EGFR wild-type and EGFR FISH-positive lung adenocarcinoma. Cancer 2014;120:1379-86.
59. Lin Q, Meng FJ, Liu YE, et al. Phase II trial of capecitabine combined with docetaxel in previously treated patients with non-small cell lung cancer: A randomized controlled study. Oncol Lett 2012;3:761-6.
60. Liu Z, Wei Z, Hu Y, et al. A phase II open-label clinical study of comparing nab-paclitaxel with pemetrexed as second-line chemotherapy for patients with stage IIIB/IV non-small-cell lung cancer. Med Oncol 2015;32:216.
61. Lu S, Chang J, Liu X, et al. Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase II

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Study of Fruquintinib After Two Prior Chemotherapy Regimens in Chinese Patients With Advanced Nonsquamous NonSmall-Cell Lung Cancer. J Clin Oncol 2018;36:1207-17.
62. Manegold C, Vansteenkiste J, Cardenal F, et al. Randomized phase II study of three doses of the integrin inhibitor cilengitide versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer. Invest. New Drugs 2013;31:175-82.
63. Morgensztern D, Cobo M, Aix SP, et al. ABOUND.2L+: A randomized phase 2 study of nanoparticle albumin-bound paclitaxel with or without CC-486 as second-line treatment for advanced nonsquamous non-small cell lung cancer (NSCLC). Cancer 2018;124:4667-75.
64. Natale RB, Bodkin D, Govindan R, et al. Vandetanib versus gefitinib in patients with advanced non-small-cell lung cancer: results from a two-part, double-blind, randomized phase ii study. J Clin Oncol 2009;27:2523-9.
65. Natale R, Blackhall F, Kowalski D, et al. Evaluation of antitumor activity using change in tumor size of the survivin antisense oligonucleotide LY2181308 in combination with docetaxel for second-line treatment of patients with non-small-cell lung cancer: a randomized open-label phase II study. J Thorac Oncol 2014;9:1704-8.
66. Neal JW, Dahlberg SE, Wakelee HA, et al. Erlotinib, cabozantinib, or erlotinib plus cabozantinib as second-line or third-line treatment of patients with EGFR wild-type advanced non-small-cell lung cancer (ECOG-ACRIN 1512): a randomised, controlled, open-label, multicentre, phase 2 trial. Lancet Oncol 2016;17:1661-71.
67. Nishino K, Imamura F, Kumagai T, et al. A randomized phase II study of bevacizumab in combination with docetaxel or S-1 in patients with non-squamous non-small-cell lung cancer previously treated with platinum based chemotherapy (HANSHIN Oncology Group 0110). Lung Cancer 2015;89:146-53.
68. Pallis AG, Syrigos K, Kotsakis A, et al. Second-line paclitaxel/carboplatin versus vinorelbine/carboplatin in patients who have advanced non-small-cell lung cancer pretreated with non-platinum-based chemotherapy: a multicenter randomized phase II study. Clin. Lung Cancer 2011;12:100-5.
69. Parikh PM, Vaid A, Advani SH, et al. Randomized, double-blind, placebo-controlled phase II study of single-agent oral talactoferrin in patients with locally advanced or metastatic non-small-cell lung cancer that progressed after chemotherapy. J Clin Oncol 2011;29:4129-36.
70. Von Pawel J, Papai-Szekely Z, Vinolas N, et al. A randomized phase 2 study of pemetrexed vs. pemetrexed+erlotinib in second-line treatment for locally advanced or metastatic, non-squamous NSCLC. Pneumologie 2012;66.
71. Pectasides D, Pectasides M, Farmakis D, et al. Comparison of docetaxel and docetaxel-irinotecan combination as second-line chemotherapy in advanced non-small-cell lung cancer: a randomized phase II trial. Ann Oncol 2005;16:294-9.
72. Quoix E, Lebeau B, Depierre A, et al. Randomised, multicentre phase II study assessing two doses of docetaxel (75 or 100 mg/m2) as second-line monotherapy for non-small-cell lung cancer. Ann Oncol 2004;15:38-44.
73. Ramalingam SS, Spigel DR, Chen D, et al. Randomized phase II study of erlotinib in combination with placebo or R1507, a monoclonal antibody to insulin-like growth factor-1 receptor, for advanced-stage non-small-cell lung cancer. J Clin Oncol 2011;29:4574-80.
74. Ramalingam SS, Blackhall F, Krzakowski M, et al. Randomized phase II study of dacomitinib (PF-00299804), an irreversible pan-human epidermal growth factor receptor inhibitor, versus erlotinib in patients with advanced non-small-cell lung cancer. J Clin Oncol 2012;30:3337-44.
75. Ready N, Karaseva NA, Orlov SV, et al. Double-blind, placebo-controlled, randomized phase 2 study of the proapoptotic agent AT-101 plus docetaxel, in second-line non-small cell lung cancer. J Thorac Oncol 2011;6:781-5.
76. Reck M, Kaiser R, Eschbach C, et al. A phase II double-blind study to investigate efficacy and safety of two doses of the triple angiokinase inhibitor BIBF 1120 in patients with relapsed advanced non-small-cell lung cancer. Ann Oncol 2011;22:1374-81.
77. Robinet G, Barlesi F, Fournel P, et al. Second-line therapy with gefitinib in combination with docetaxel for advanced non-small cell lung cancer: a phase II randomized study. Target Oncol 2007;2:63-71.
78. Ross HJ, Hart LL, Swanson PM, et al. A randomized, multicenter study to determine the safety and efficacy of the immunoconjugate SGN-15 plus docetaxel for the treatment of non-small cell lung carcinoma. Lung Cancer 2006;54:69-77.
79. Scagliotti GV, Bondarenko I, Ciuleanu TE, et al.A randomized phase 2 study of abemaciclib versus docetaxel in patients with stage IV squamous non-small cell lung cancer (sqNSCLC) previously treated with platinum-based chemotherapy. J Clin Oncol 2018;35:9059.
80. Schiller JH, von Pawel J, Schütt P, et al. Pemetrexed

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with or without matuzumab as second-line treatment for patients with stage IIIB/IV non-small cell lung cancer. J Thorac Oncol 2010;5:1977-85.
81. Segawa Y, Kiura K, Hotta K, et al. A randomized phase II study of a combination of docetaxel and S-1 versus docetaxel monotherapy in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy: results of Okayama Lung Cancer Study Group (OLCSG) Trial 0503. J Thorac Oncol 2010;5:1430-4.
82. Smit EF, Burgers SA, Biesma B, et al. Randomized phase II and pharmacogenetic study of pemetrexed compared with pemetrexed plus carboplatin in pretreated patients with advanced non-small-cell lung cancer. J Clin Oncol 2009;27:2038-45.
83. Soria JC, Fülöp A, Maciel C, et al. SELECT-2: A phase II, double-blind, randomized, placebo-controlled study to assess the efficacy of selumetinib plus docetaxel as a second-line treatment of patients with advanced or metastatic non-small-cell lung cancer. Ann Oncol 2017;28:3028-36.
84. Spigel DR, Burris HA, 3rd, Greco FA, et al. Erlotinib plus either pazopanib or placebo in patients with previously treated advanced non-small cell lung cancer: A randomized, placebo-controlled phase 2 trial with correlated serum proteomic signatures. Cancer 2018;124:2355-64.
85. Spigel DR, Burris HA 3rd, Greco FA, et al. Randomized, double-blind, placebo-controlled, phase II trial of sorafenib and erlotinib or erlotinib alone in previously treated advanced non-small-cell lung cancer. J Clin Oncol 2011;29:2582-9.
86. Talbot DC, Von Pawel J, Cattell E, et al. A randomized phase II pharmacokinetic and pharmacodynamic study of indisulamas second-line therapy in patients with advanced non-small cell lung cancer. Clin Cancer Res 2007;13:1816-22.
87. Tan EH, Goss GD, Salgia R, et al. Phase 2 Trial of Linifanib (ABT-869) in Patients with Advanced Non-small Cell Lung Cancer. J Thorac Oncol 2011;6:1418-25.
88. Wachters FM, Groen HJM, Biesma B, et al. A randomised phase II trial of docetaxel vs docetaxel and irinotecan in patients with stage IIIb-IV non-small-cell lung cancer who failed first-line treatment. Br J Cancer 2005;92:15-20.
89. Waller CF, Vynnychenko I, Bondarenko I, et al. An open-label, multicenter, randomized phase Ib/II study of eribulin mesylate administered in combination with pemetrexed versus pemetrexed alone as second-line therapy in patients with advanced nonsquamous non-small-cell lung cancer. Clin Lung Cancer 2015;16:92-9.
90. Wu Y, Feng J, Hu W, Luo Q. A randomized placebo-controlled clinical study of nab-paclitaxel as second-line chemotherapy for patients with advanced non-small cell lung cancer in China. Biosci Rep 2017;37:BSR20170020.
91. Yoh K, Hosomi Y, Kasahara K, et al. A randomized, double-blind, phase II study of ramucirumab plus docetaxel vs placebo plus docetaxel in Japanese patients with stage IV non-small cell lung cancer after disease progression on platinum-based therapy. Lung Cancer 2016;99:186-93.
92. Zhang Y, Gao C, Qu W, et al. A Randomized Phase II Study of Erlotinib Plus Nab-Paclitaxel Versus Erlotinib Alone as Second-Line Therapy for Chinese Patients with Advanced EGFR Wild-Type Non-Small-Cell Lung Cancer. Cancer Invest 2015;33:241-5.
93. Zhou Q, Cheng Y, Yang JJ, et al. Pemetrexed versus gefitinib as a second-line treatment in advanced nonsquamous nonsmall-cell lung cancer patients harboring wild-type EGFR (CTONG0806): a multicenter randomized trial. Ann Oncol 2014;25:2385-91.

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Table S1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist

Section/topic	#	Checklist item	Reported on
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Front page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction, 1st paragraph
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction, 2nd paragraph
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods, Study overview
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods, Study selection
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, Study search
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods, Study search
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods, Data extraction
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods, Data extraction
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods, Assessment of risk of bias
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods, Outcomes
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods, Statistics 1st paragraph
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods, Statistics 1st paragraph
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods, Statistics 2nd paragraph
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results, Study search
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results, Study characteristics
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	*Table S3*
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	*Table S4*
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. [Meta-analysis was not conducted but the data for primary analysis including confidence intervals and consistency within analyses were presented]	*Figure 2*
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	*Figure S1*
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	*Figure 3*
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion 1st paragraph
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion 6th paragraph
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion 7th paragraph
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Footnote

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Table S2 Search strategies

Database and search formula	N
PubMed	340
(Non Small Cell Lung Cancer OR Non Small Cell Lung Carcinoma OR NSCLC OR Adenocarcinoma of Lung OR Squamous carcinoma of lung) AND (Recurrent OR Recurrence OR relapsed OR Advanced OR Advance OR Metastatic OR Metastasis OR Stage IV OR Stage III OR Stage four OR Stage three) AND (Phase II OR Phase two OR Phase 2) AND (Randomized OR Randomised OR Randomly OR RCT) AND (2nd line OR Second line OR 3rd line OR Third line OR later line)	
Limit English	
Web of Science	432
TS=((Non Small Cell Lung Cancer OR Non Small Cell Lung Carcinoma OR NSCLC OR Adenocarcinoma of Lung OR Squamous carcinoma of lung) AND (Recurrent OR Recurrence OR relapsed OR Advanced OR Advance OR Metastatic OR Metastasis OR Stage IV OR Stage III OR Stage four OR Stage three) AND (Phase II OR Phase two OR Phase 2) AND (Randomized OR Randomised OR Randomly OR RCT) AND (2nd line OR Second line OR 3rd line OR Third line OR later line))	
#2 TI=(Phase II OR Phase two OR Phase 2 OR Randomized OR Randomised OR Randomly OR RCT OR 2nd line OR Second line OR 3rd line OR Third line OR later line) OR TS=(randomly)	
#3 #1 AND #2	
Limit English	
Cochrane	584
#1 (Non Small Cell Lung Cancer OR Non Small Cell Lung Carcinoma OR NSCLC OR Adenocarcinoma of Lung OR Squamous carcinoma of lung) AND (Recurrent OR Recurrence OR relapsed OR Advanced OR Advance OR Metastatic OR Metastasis OR Stage IV OR Stage III OR Stage four OR Stage three) AND (Phase II OR Phase two OR Phase 2) AND (Randomized OR Randomised OR Randomly OR RCT) AND (2nd line OR Second line OR 3rd line OR Third line OR later line)	
#2 Phase II:ti OR Phase two:ti OR Phase 2:ti OR Randomized:ti OR Randomised:ti OR Randomly:ti OR RCT:ti OR 2nd line:ti OR Second line:ti OR 3rd line:ti OR Third line:ti OR later line:ti	
#3 #1 AND #2	
Excluding Cochrane review and Cochrane protocol	
EMBASE	69
('non small cell lung cancer'/exp OR 'non small cell lung cancer' OR (non AND small AND ('cell'/exp OR cell) AND ('lung'/exp OR lung) AND ('cancer'/exp OR cancer)) OR 'non small cell lung carcinoma'/exp OR 'non small cell lung carcinoma' OR (non AND small AND ('cell'/exp OR cell) AND ('lung'/exp OR lung) AND ('carcinoma'/exp OR carcinoma)) OR nsclc OR 'adenocarcinoma of lung'/exp OR 'adenocarcinoma of lung' OR (('adenocarcinoma'/exp OR adenocarcinoma) AND of AND ('lung'/exp OR lung)) OR 'squamous carcinoma of lung' OR (squamous AND ('carcinoma'/exp OR carcinoma) AND of AND ('lung'/exp OR lung))) AND (recurrent OR 'recurrence'/exp OR recurrence OR relapsed OR advancedOR 'advance'/exp OR advance OR metastatic OR 'metastasis'/exp OR metastasis OR 'stage iv' OR (stage AND iv) OR 'stage iii' OR (stage AND iii) OR 'stage four' OR (stage AND four) OR 'stage three' OR (stage AND three)) AND ('phase ii' OR (phase AND ii) OR 'phase two' OR (phase AND two) OR 'phase 2' OR (phase AND 2)) AND (randomized OR randomised OR randomly OR rct) AND ('2nd line' OR (2nd AND ('line'/exp OR line)) OR 'second line' OR (second AND ('line'/exp OR line)) OR '3rd line' OR (3rd AND ('line'/exp OR line)) OR 'third line' OR (third AND ('line'/exp OR line)) OR 'later line' OR (later AND ('line'/exp OR line))) AND ('phase ii':ti OR 'phase two':ti OR 'phase 2':ti) AND (randomized:ti OR randomised:ti OR randomly:ti OR rct:ti) AND ('2nd line':ti OR 'second line':ti OR '3rd line':ti OR 'third line':ti OR 'later line':ti) AND [english]/lim	
Total	1425

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Table S3 Cochrane risk of bias

Author (year)	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 addressed (attrition bias)	Selective reporting (reporting bias)
Aerts (2013) (22)	L	L	H	H	H	L
Ardizzoni (2012) GOIRC02-2006 (23)	L	L	H	H	L	L
Ardizzoni (2012) NVALT7 (23)	L	L	H	H	L	L
Belvedere (2011) (24)	U	U	H	L	L	L
Bergqvist (2017) (25)	L	L	H	L	L	L
Blumenschein (2015) (26)	L	L	H	H	H	L
Bradbury (2018) (27)	L	L	H	H	L	L
Chiappori (2010) (28)	U	U	L	L	H	H
Cortinovis (2008) (29)	L	L	H	H	H	L
Cufer (2006) (30)	U	U	H	H	H	L
Dittrich (2014) (31)	L	L	H	H	H	L
Dowlati (2005) (32)	U	U	H	H	L	H
Esteban (2003) (33)	L	L	H	H	L	L
Fanucchi (2006) (34)	U	U	H	L	H	L
Fehrenbacher (2016) (17)	L	L	H	H	H	L
Fukuoka (2003) (35)	L	L	L	L	L	L
Georgoulias (2004) (36)	L	L	H	L	L	L
Georgoulias (2005) (37)	L	L	H	L	L	L
Gerber (2016) (38)	U	U	L	L	H	L
Gervais (2005) (39)	L	L	H	L	L	L
Gridelli (2016) (40)	L	L	H	H	H	L
Groen (2013) (41)	L	L	L	L	L	L
Han (2018) (42)	L	L	L	L	H	L
Heigener (2013) (43)	U	U	H	H	H	L
Heist (2014) (44)	L	L	H	H	L	L
Herbst (2007) (45)	L	L	L	L	H	L
Heudobler (2019) (46)	L	L	H	H	U	L
Heymach (2007) (47)	U	U	L	L	L	L
Ikezawa (2017) (48)	L	L	H	H	L	L
Jones (2008) (49)	U	U	H	H	L	H
Juan (2015) (50)	L	L	H	H	H	L
Kentepozidis (2017) (51)	L	L	H	H	H	L
Kim (2012) (52)	L	L	H	H	H	L
Kim (2016) (53)	L	L	H	H	L	L
Kim (2017) (54)	U	U	H	L	H	L
Lai (2005) (55)	U	U	H	H	L	H
Lee (2013) (56)	L	L	H	H	H	L
Levy (2019) (57)	L	L	L	L	H	L
Li (2014) (58)	L	L	H	H	L	L
Lin (2012) (59)	U	U	H	H	H	L
Liu (2015) (60)	U	U	H	H	L	L
Lu (2018) (61)	L	L	L	L	L	L
Manegold (2013) (62)	U	U	H	H	H	L
Morgensztern (2018) (63)	L	L	H	H	H	L
Natale (2009) (64)	U	U	L	L	H	L
Natale (2014) (65)	U	U	H	L	H	L
Neal (2016) (66)	L	L	H	H	L	L
Nishino (2015) (67)	L	L	H	L	H	L
Pallis (2011) (68)	U	U	H	L	H	L
Parikh (2011) (69)	L	L	L	L	H	L
Pawel (2012) (70)	U	U	H	H	U	L
Pectasides (2005) (71)	U	U	H	H	L	H
Quoix (2004) (72)	L	L	H	L	H	H
Ramalingam (2011) (73)	U	U	H	H	H	L
Ramalingam (2012) (74)	L	L	H	H	L	L
Ready (2011) (75)	L	L	L	L	H	L
Reck (2011) (76)	U	U	L	L	H	L
Robinet (2007) (77)	U	U	H	L	L	L
Ross (2006) (78)	L	L	H	H	L	L
Scagliotti (2018) (79)	U	U	H	H	U	L
Schiller (2010) (80)	L	L	H	L	H	L
Segawa (2010) (81)	L	L	H	H	H	L
Smit (2009) (82)	L	L	H	H	H	L
Soria (2017) (83)	L	L	L	L	L	L
Spigel (2018) (84)	L	L	L	L	H	L
Spigel (2011) (85)	L	L	L	L	H	L
Talbot (2007) (86)	U	U	H	L	L	L
Tan (2011) (87)	L	L	H	L	H	L
Wachters (2005) (88)	U	U	H	H	L	L
Waller (2015) (89)	U	U	H	H	H	H
Wu (2017) (90)	L	L	L	L	L	L
Yoh (2016) (91)	L	L	L	L	H	L
Zhang (2015) (92)	L	L	H	H	L	L
Zhou (2014) (93)	L	L	H	L	H	L

H/U/L: High/Unclear/Low risk of bias.

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Table S4 Results of individual studies

Author (year)	HRos	ORorr	ΔORR (%)	ORdcr	ΔDCR (%)
Aerts (2013)	1.49	0.50	-6	0.56	-14
Ardizzoni (2012) GOIRC02-2006	1.03	0.99	0	0.77	-6
Ardizzoni (2012) NVALT7	1.19	0.30	-11	0.84	-4
Belvedere (2011)	0.81	2.88	12	3.86	32
Bergqvist (2017)	0.90	0.06	-12	0.55	-12
Blumenschein (2015)	0.97	1.00	0	1.10	2
Bradbury (2018)	0.98	0.97	0	1.10	2
Chiappori (2010)	0.70	1.52	1	1.00	0
Cortinovis (2008)	1.00	0.91	0	2.02	17
Cufer (2006)	0.97	0.96	0	1.20	4
Dittrich (2014)	1.47	0.59	-6	0.87	-3
Dowlati (2005)	1.34	1.00	0	2.20	19
Esteban (2003)	1.21	5.48	11	0.72	-7
Fanucchi (2006)	0.95	0.91	-1	0.36	-24
Fehrenbacher (2016)	0.73	0.99	0	NA	NA
Fukuoka (2003)	0.90	0.96	-1	1.12	3
Georgoulias (2004)	0.91	5.17	14	1.94	15
Georgoulias (2005)	1.02	3.75	15	1.10	2
Gerber (2016)	1.52	0.62	-6	0.82	-5
Gervais (2005)	0.83	1.55	2	1.40	7
Gridelli (2016)	1.24	0.33	-5	1.22	5
Groen (2013)	1.07	1.57	2	NA	NA
Han (2018)	0.78	13.72	10	10.83	52
Heigener (2013)	0.74	0.46	-5	0.95	-1
Heist (2014)	0.71	0.81	-3	1.45	9
Herbst (2007)	1.41	0.97	0	0.58	-13
Heudobler (2019)	0.86	4.73	10	NA	NA
Heymach (2007)	0.71	1.60	8	2.86	20
Ikezawa (2017)	1.32	0.94	-1	0.36	-25
Jones (2008)	0.81	0.97	0	0.86	-4
Juan (2015)	0.70	0.33	-6	1.60	11
Kentepozidis (2017)	1.64	0.77	-4	0.82	-5
Kim (2012)	2.14	1.40	8	1.35	6
Kim (2016)	1.05	1.61	4	1.47	9
Kim (2017)	0.86	0.72	-5	0.66	-10
Lai (2005)	1.00	0.43	-12	1.17	4
Lee (2013)	0.69	3.72	19	0.86	-4
Levy (2019)	1.38	1.46	5	0.54	-13
Li (2014)	1.01	2.79	12	1.10	2
Lin (2012)	0.75	1.10	1	1.14	2
Liu (2015)	1.23	0.71	-4	0.65	-10
Lu (2018)	0.76	9.69	13	34.18	51
Manegold (2013)	1.51	1.03	0	0.39	-11
Morgensztern (2018)	1.70	0.81	-3	0.91	-2
Natale (2009)	0.84	0.13	-7	0.64	-10
Natale (2014)	1.15	3.65	4	NA	NA
Neal (2016)	1.47	0.23	-8	0.15	-42
Nishino (2015)	1.25	11.00	18	1.00	0
Pallis (2011)	0.92	2.75	11	1.67	12
Parikh (2011)	0.68	2.31	2	1.94	14
Pawel (2012)	1.47	0.59	-6	0.88	-3
Pectasides (2005)	1.12	0.62	-9	0.43	-12
Quoix (2004)	1.32	2.93	2	0.77	-6
Ramalingam (2011)	1.19	1.02	0	1.03	1
Ramalingam (2012)	0.80	3.65	12	2.42	15
Ready (2011)	0.82	2.00	2	1.04	1
Reck (2011)	1.44	0.32	-3	0.95	-1
Robinet (2007)	0.83	0.73	-2	2.79	25
Ross (2006)	0.81	0.20	-16	1.14	3
Scagliotti (2018)	1.33	0.11	-18	0.58	-13
Schiller (2010)	1.49	0.22	-12	1.13	3
Segawa (2010)	0.42	1.36	5	1.20	4
Smit (2009)	0.85	3.29	11	1.19	4
Soria (2017)	0.83	2.26	15	NA	NA
Spigel (2018)	0.99	2.36	6	1.54	10
Spigel (2011)	0.89	0.72	-3	1.90	16
Talbot (2007)	1.04	NA	NA	1.71	11
Tan (2011)	0.81	0.44	-4	NA	NA
Wachters (2005)	1.09	1.80	6	1.43	9
Waller (2015)	1.00	1.04	1	1.74	12
Wu (2017)	1.41	0.19	-15	0.16	-37
Yoh (2016)	0.86	1.79	10	1.58	9
Zhang (2015)	0.68	2.19	15	2.39	20
Zhou (2014)	0.72	0.96	0	3.64	31

HRos: hazard ratio of overall survival. ORorr: odds ratio of objective response rate. ΔORR: objective response rate difference. ORdcr: odds ratio of disease control rate. ΔDCR: disease control rate difference. NA: not available.

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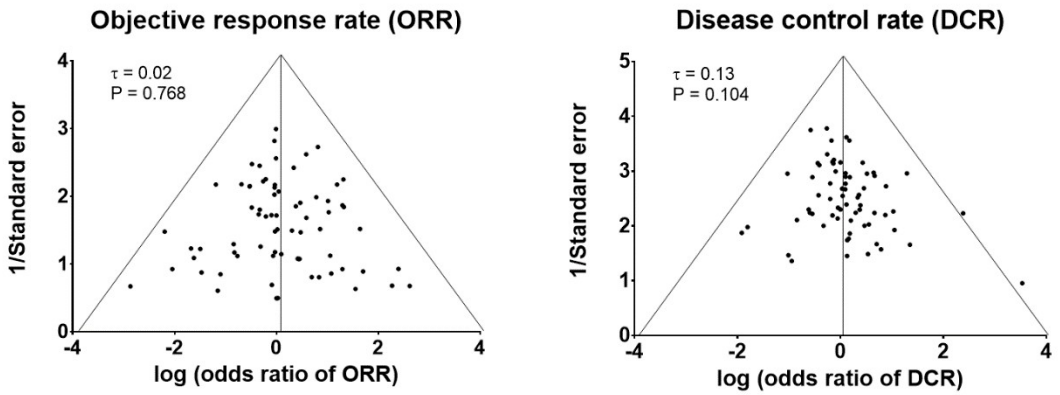

Figure S1 Funnel plots for objective response rate (ORR) and disease control rate (DCR). Begg-Kendall test was applied for publication bias assessment.

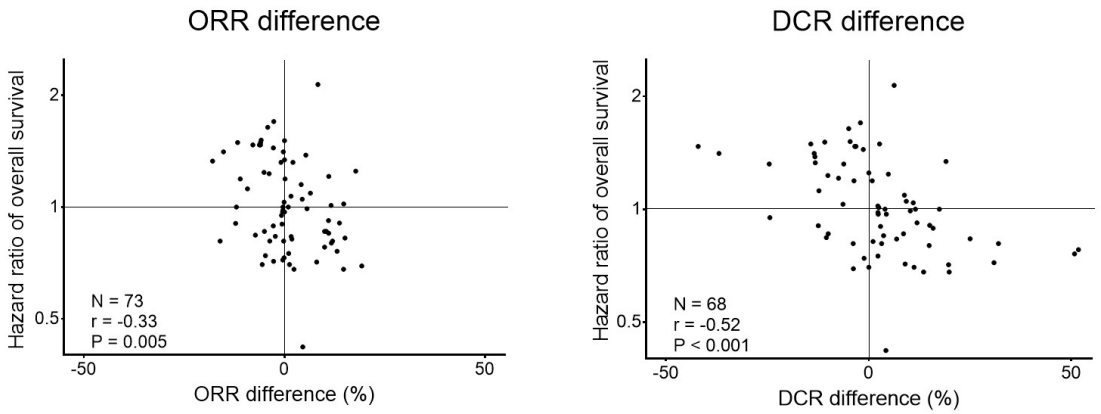

Figure S2 Trial-level surrogacy of objective response rate (ORR) difference and disease control rate (DCR) difference. N: number of trials. r: Spearman's rank correlation coefficient. A correlation coefficient was interpreted as follows: $|r|<0.2$, no correlation; $0.2<|r|<0.4$, weak correlation; $0.4<|r|<0.6$, moderate correlation; $0.6<|r|<0.8$, strong correlation; and $0.8<|r|$, excellent correlation.

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