Efficacy and Safety of First-line Treatments for Advanced Epidermal Growth Factor Receptor Mutated NSCLC: systematic review and network meta-analysis

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Supplementary materials

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Section/topic	#	Checklist item*	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1-2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: • Background: main objectives; • Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal and *synthesis methods, such as network meta-analysis.* • Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* • Discussion/Conclusions: limitations; conclusions and implications of findings. • Other: primary source of funding; systematic review registration number with registry name.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
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.	7
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. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	7
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.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Materials page 6
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).	7-8
Data	10	Describe method of data extraction from reports (e.g., piloted forms,	8-9

collection process		independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	9
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.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	9-10
Synthesis of results	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	10
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	10-11
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).	9-10
Additional analyses	16	Describe methods of additional analyses, if done, indicating which were pre-specified. This may include, but not be limited to the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	11
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.	11
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network	11
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases	11

		reflected by the network structure.	
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.	11
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).	Supplemental Materials page 21
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study:1) simple summary data for each intervention group, and 2) effect estimates and confidence/credible intervals. *Modified approaches may be needed to deal with information from larger networks.*	11
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	12-14
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14-15
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth [see Item 16]).	15-16
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).	16-19
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). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	19-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
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.	21

Table S1. Checklist of the PRISMA extension for network meta-analysis.

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PICOS = population, intervention, comparators, outcomes, study design.

*Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

((((((((((((non-small-cell lung cancer[title] OR non-small cell lung cancer[title]) OR non small-cell lung cancer[title]) OR non small cell lung cancer[title]) OR non-small-cell lung carcinoma[title]) OR non-small cell lung carcinoma[title]) OR non small-cell lung carcinoma[title]) OR non small cell lung carcinoma[title]) OR nsclc[title]) AND (epidermal growth factor receptor[title/abstract] OR EGFR[title/abstract])) AND ((((((((((((((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 chemotherapy[title/abstract]) OR first-line[title/abstract]) OR first line[title/abstract]) OR treatment-naive[title/abstract]) OR treatment-naïve[title/abstract]) OR untreated[title/abstract])) AND (((((compare[title/abstract] OR comparison[title/abstract]) OR comparative[title/abstract]) OR comparing[title/abstract]) OR versus[title/abstract]) OR vs[title/abstract])) AND ((((((Randomized Controlled Trial[ptyp] OR controlled clinical trial[ptyp]) OR randomized[title/abstract]) OR randomised[title/abstract]) OR randomly[title/abstract]) OR trial[title/abstract]) OR phase[title/abstract])) AND (English[Language])) AND ("0001/01/01"[Date - Publication] : "2019/05/20"[Date - Publication])

Table S2. Literature search criteria.

This search criteria was reviewed and approved by Bingjie Hu (Bingjie_H@gzhmu.edu.cn), clinical librarian of the Research Medical Library at Guangzhou Medical University.

Treatment	Rank of possibility (%)											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Progression-free survival for advanced EGFR-mutated patients												
Osimertinib	**57**	35	8	1	0	0	0	0	0	0	0	0
Dacomitinib	1	4	22	50	21	2	0	0	0	0	0	0
Afatinib	0	0	0	0	8	48	32	9	2	0	0	0
Erlotinib	0	0	0	0	2	21	32	29	13	4	0	0
Gefitinib	0	0	0	0	0	1	8	35	42	15	0	0
Icotinib	0	0	0	0	1	5	7	10	19	57	0	0
Afatinib+Cetuximab	0	0	0	1	5	13	16	15	24	25	0	0
Erlotinib+Bevacizumab	11	18	40	22	9	1	0	0	0	0	0	0
Gefitinib+PbCT	31	41	23	4	0	0	0	0	0	0	0	0
Gefitinib+Pemetrexed	0	1	7	22	54	10	4	2	0	0	0	0
PbCT	0	0	0	0	0	0	0	0	0	1	99	1
PfCT	0	0	0	0	0	0	0	0	0	0	0	**100**
Overall survival for advanced EGFR-mutated patients												
Osimertinib	27	36	22	10	4	1	0	0	0	0	0	0
Dacomitinib	3	10	21	24	18	11	6	3	2	1	1	0
Afatinib	0	1	6	18	29	27	13	4	2	0	0	0
Erlotinib	0	0	0	1	3	7	13	17	19	18	14	9
Gefitinib	0	0	0	0	1	5	14	21	25	20	11	4
Icotinib	0	1	2	4	6	8	9	8	8	13	20	21
Afatinib+Cetuximab	5	4	5	6	7	7	6	5	5	7	8	**34**
Erlotinib+Bevacizumab	7	8	13	15	14	11	8	5	5	4	4	5
Gefitinib+PbCT	**49**	29	14	5	2	0	0	0	0	0	0	0
Gefitinib+Pemetrexed	10	12	16	17	13	9	6	4	3	3	3	3
PbCT	0	0	0	0	1	4	7	9	11	19	30	19
PfCT	0	0	0	1	3	11	19	22	20	14	8	3
Objective response rate for advanced EGFR-mutated patients												
Osimertinib	2	8	15	20	19	15	11	9	0	0	-	-
Dacomitinib	3	10	15	17	15	13	11	15	1	0	-	-
Afatinib	5	32	29	17	8	4	2	1	0	0	-	-
Erlotinib	0	0	2	6	12	19	27	34	1	0	-	-
Gefitinib	0	0	2	8	19	29	28	15	0	0	-	-
Erlotinib+Bevacizumab	4	11	15	17	15	13	13	10	1	0	-	-
Gefitinib+PbCT	**75**	16	5	2	1	0	0	0	0	0	-	-
Gefitinib+Pemetrexed	11	21	17	14	10	8	7	12	1	0	-	-
PbCT	0	0	0	0	0	0	1	2	71	26	-	-
PfCT	0	0	0	0	0	0	0	1	26	**74**	-	-
Grade ≥3 adverse events for advanced EGFR-mutated patients												
Osimertinib	0	0	0	1	2	3	5	9	19	48	12	-
Dacomitinib	2	6	10	18	25	13	11	7	4	3	1	-
Afatinib	0	1	3	8	17	30	24	10	5	2	0	-
Erlotinib	0	0	1	4	8	16	21	31	14	4	1	-
Gefitinib	0	0	0	0	1	3	8	21	42	22	3	-
Icotinib	0	0	0	1	1	1	2	3	4	8	**80**	-
Erlotinib+Bevacizumab	**80**	12	5	2	1	1	0	0	0	0	0	-

Gefitinib+PbCT	8	25	24	18	10	6	4	2	1	1	1	-
Gefitinib+Pemetrexed	6	16	17	21	15	9	7	4	3	2	1	-
PbCT	2	4	6	9	13	17	17	12	9	11	0	-
PfCT	3	36	33	19	7	2	1	0	0	0	0	-
Progression-free survival for exon 19 deletion subpopulation												
Osimertinib	**56**	35	8	1	0	0	0	0	0	0	0	-
Dacomitinib	3	13	33	35	13	3	0	0	0	0	0	-
Afatinib	0	0	1	7	26	44	19	2	0	0	0	-
Erlotinib	0	0	0	2	10	26	45	15	1	0	0	-
Gefitinib	0	0	0	0	0	2	20	75	4	0	0	-
Icotinib	0	0	0	0	0	1	1	3	86	6	2	-
Erlotinib+Bevacizumab	23	32	23	14	6	2	0	0	0	0	0	-
Gefitinib+PbCT	16	16	23	20	13	6	3	2	0	0	0	-
Gefitinib+Pemetrexed	1	4	11	21	30	18	10	4	0	0	0	-
PbCT	0	0	0	0	0	0	0	0	5	78	17	-
PfCT	0	0	0	0	0	0	0	0	3	16	**81**	-
Progression-free survival for Leu858Arg subpopulation												
Osimertinib	1	40	36	17	5	1	0	0	0	0	0	-
Dacomitinib	0	11	20	28	24	11	5	2	0	0	0	-
Afatinib	0	0	3	9	23	38	20	6	1	0	0	-
Erlotinib	0	0	0	0	1	6	16	27	25	24	0	-
Gefitinib	0	0	0	0	0	6	25	35	25	9	0	-
Icotinib	0	5	5	7	9	13	15	11	21	13	1	-
Erlotinib+Bevacizumab	0	12	18	21	22	14	8	3	2	0	0	-
Gefitinib+PbCT	**98**	2	0	0	0	0	0	0	0	0	0	-
Gefitinib+Pemetrexed	1	29	18	18	15	9	5	3	1	1	0	-
PbCT	0	0	0	0	1	2	6	14	24	52	0	-
PfCT	0	0	0	0	0	0	0	0	0	1	**99**	-
Overall survival for exon 19 deletion subpopulation												
Dacomitinib	23	26	21	12	7	6	3	2	-	-	-	-
Afatinib	**45**	38	14	3	1	0	0	0	-	-	-	-
Erlotinib	0	3	7	12	20	25	19	14	-	-	-	-
Gefitinib	1	8	28	30	18	10	4	1	-	-	-	-
Icotinib	4	8	10	11	11	11	30	14	-	-	-	-
Erlotinib+Bevacizumab	27	16	13	12	9	9	7	8	-	-	-	-
PbCT	0	0	2	3	7	10	23	**55**	-	-	-	-
PfCT	0	1	5	17	28	29	15	5	-	-	-	-
Overall survival for Leu858Arg subpopulation												
Dacomitinib	**36**	23	17	10	6	4	3	2	-	-	-	-
Afatinib	0	1	5	11	16	22	24	21	-	-	-	-
Erlotinib	2	10	15	16	16	13	14	12	-	-	-	-
Gefitinib	0	3	7	12	18	18	21	21	-	-	-	-
Icotinib	11	15	15	10	8	8	10	**23**	-	-	-	-
Erlotinib+Bevacizumab	31	17	12	10	6	6	6	11	-	-	-	-
PbCT	18	25	18	11	9	8	8	2	-	-	-	-
PfCT	1	5	12	20	22	21	14	6	-	-	-	-

Table S3. Bayesian ranking results of network meta-analysis.

The number in each cell represents the posterior probability of the row-defining treatment being ranked at the column-defining position. The numbers with biggest probability of ranking first and last are in bold and underscored. EGFR=epidermal growth factor receptor; PbCT=pemetrexed-based chemotherapy; PfCT=pemetrexed-free chemotherapy.

	Overall				**Exon 19 deletion subpopulation**		**Leu858Arg subpopulation**	
Model	Progression -free survival	Overall survival	Objective response rate	Grade ≥3 adverse events	Progression -free survival	Overall survival	Progression -free survival	Overall survival
Consistency	47.56	29.26	73.66	67.39	31.10	18.79	28.04	15.45
Inconsistency	46.61	38.63	80.71	70.27	35.04	20.43	31.61	16.53

Table S4. Comparisons of the fit of consistency and inconsistency models using deviance information criteria (DIC).

The DIC is a Bayesian model evaluation criterion that measures model fit adjusted with complexity of the model; smaller DIC values correspond to more preferable models. (Reference: Spiegelhalter, D.J., Best, N.G., Carlin, B.P., Van der Linde, A. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society Series B (Statistical Methodology) 2002; 64(4):583-639).

Nodes	Direct effect	Indirect effect	Overall	P
Progression-free survival for advanced EGFR-mutated patients				
Osimertinib, Erlotinib	0.78 (0.56 to 0.99)	0.64 (0.32 to 0.95)	0.73 (0.55 to 0.91)	0.47
Osimertinib, Gefitinib	0.78 (0.56 to 0.99)	0.92 (0.60 to 1.20)	0.82 (0.64 to 1.00)	0.47
Afatinib, Gefitinib	0.32 (0.06 to 0.57)	-0.01 (-0.32 to 0.29)	0.18 (-0.02 to 0.37)	0.11
Erlotinib, Gefitinib	0.04 (-0.29 to 0.38)	0.11 (-0.11 to 0.33)	0.09 (-0.10 to 0.27)	0.74
Gefitinib, Gefitinib+PbCT	-0.71 (-0.92 to -0.50)	-1.30 (-2.00 to -0.67)	-0.77 (-0.97 to -0.57)	0.08
Afatinib, PbCT	0.54 (0.25 to 0.84)	1.40 (0.93 to 1.80)	0.80 (0.55 to 1.00)	**0.002**
Gefitinib, PbCT	1.00 (0.52 to 1.60)	0.46 (0.15 to 0.78)	0.62 (0.35 to 0.89)	0.06
Gefitinib+PbCT, PbCT	1.80 (1.30 to 2.40)	1.20 (0.85 to 1.60)	1.40 (1.10 to 1.70)	0.08
Afatinib, PfCT	1.30 (0.94 to 1.60)	1.10 (0.83 to 1.40)	1.20 (0.96 to 1.40)	0.50
Erlotinib, PfCT	1.20 (0.93 to 1.40)	0.97 (0.67 to 1.30)	1.10 (0.91 to 1.30)	0.29
Gefitinib, PfCT	0.90 (0.68 to 1.10)	1.20 (0.89 to 1.40)	1.00 (0.84 to 1.20)	0.15
Overall survival for advanced EGFR-mutated patients				
Osimertinib, Erlotinib	0.46 (0.13 to 0.80)	0.47 (0.06 to 0.88)	0.46 (0.21 to 0.72)	0.98
Osimertinib, Gefitinib	0.46 (0.13 to 0.80)	0.46 (0.05 to 0.87)	0.46 (0.20 to 0.72)	0.99
Afatinib, Gefitinib	0.15 (-0.12 to 0.42)	0.21 (-0.08 to 0.50)	0.18 (-0.02 to 0.37)	0.77
Erlotinib, Gefitinib	0.02 (-0.35 to 0.40)	-0.01 (-0.27 to 0.24)	0.00 (-0.22 to 0.21)	0.88
Gefitinib, Gefitinib+PbCT	-0.49 (-0.75 to -0.23)	-0.74 (-1.50 to -0.03)	-0.51 (-0.76 to -0.27)	0.50
Afatinib, PbCT	0.25 (-0.05 to 0.55)	0.28 (-0.21 to 0.77)	0.26 (0.00 to 0.51)	0.91
Gefitinib, PbCT	-0.03 (-0.60 to 0.54)	0.12 (-0.21 to 0.44)	0.08 (-0.20 to 0.37)	0.66
Gefitinib+PbCT, PbCT	0.78 (0.13 to 1.40)	0.52 (0.12 to 0.93)	0.60 (0.25 to 0.94)	0.51
Afatinib, PfCT	0.19 (-0.09 to 0.47)	0.10 (-0.21 to 0.41)	0.15 (-0.06 to 0.35)	0.70
Erlotinib, PfCT	-0.04 (-0.27 to 0.18)	-0.01 (-0.37 to 0.35)	-0.03 (-0.22 to 0.16)	0.88
Gefitinib, PfCT	-0.05 (-0.29 to 0.19)	-0.01 (-0.27 to 0.25)	-0.03 (-0.21 to 0.15)	0.84
Objective response rate for advanced EGFR-mutated patients				
Osimertinib, Erlotinib	-0.20 (-0.91 to 0.50)	-0.32 (-0.97 to 0.32)	-0.27 (-0.74 to 0.20)	0.81
Osimertinib, Gefitinib	-0.23 (-0.73 to 0.27)	-0.11 (-0.93 to 0.70)	-0.20 (-0.62 to 0.22)	0.80
Afatinib, Gefitinib	-0.61 (-1.10 to -0.15)	-0.35 (-0.86 to 0.15)	-0.49 (-0.83 to -0.16)	0.46
Afatinib, PbCT	-1.50 (-2.00 to -0.99)	-2.00 (-2.80 to -1.20)	-1.60 (-2.10 to -1.20)	0.35
Erlotinib, Gefitinib	-0.23 (-0.85 to 0.39)	0.23 (-0.22 to 0.70)	0.07 (-0.30 to 0.43)	0.24
Gefitinib, Gefitinib+PbCT	0.97 (0.51 to 1.50)	1.30 (0.12 to 2.50)	1.00 (0.58 to 1.50)	0.65
Gefitinib, PbCT	-1.40 (-2.40 to -0.51)	-1.00 (-1.60 to -0.48)	-1.10 (-1.60 to -0.66)	0.47
Gefitinib+PbCT, PbCT	-2.30 (-3.50 to -1.30)	-2.10 (-2.80 to -1.40)	-2.10 (-2.70 to -1.60)	0.66
Afatinib, PfCT	-1.90 (-2.40 to -1.40)	-2.00 (-2.50 to -1.40)	-1.90 (-2.30 to -1.60)	0.95
Erlotinib, PfCT	-1.20 (-1.60 to -0.85)	-1.70 (-2.40 to -1.10)	-1.40 (-1.70 to -1.00)	0.19
Gefitinib, PfCT	-1.60 (-2.10 to -1.20)	-1.20 (-1.70 to -0.80)	-1.40 (-1.80 to -1.10)	0.24
Grade ≥3 adverse events for advanced EGFR-mutated patients				
Osimertinib, Erlotinib	0.39 (-0.03 to 0.82)	0.85 (0.06 to 1.70)	0.49 (0.12 to 0.87)	0.32
Osimertinib, Gefitinib	0.43 (-0.16 to 1.00)	-0.03 (-0.70 to 0.65)	0.23 (-0.21 to 0.67)	0.32
Afatinib, Gefitinib	-0.72 (-1.20 to -0.20)	-0.34 (-0.99 to 0.30)	-0.57 (-0.97 to -0.16)	0.38
Erlotinib, Gefitinib	-1.40 (-3.50 to 0.11)	-0.16 (-0.61 to 0.29)	-0.26 (-0.69 to 0.16)	0.12
Afatinib, PfCT	0.99 (0.53 to 1.50)	0.62 (-0.07 to 1.30)	0.88 (0.50 to 1.30)	0.37
Erlotinib, PfCT	1.20 (0.82 to 1.50)	1.20 (0.44 to 2.00)	1.20 (0.86 to 1.50)	0.93
Gefitinib, PfCT	1.30 (0.75 to 1.90)	1.60 (1.10 to 2.10)	1.40 (1.10 to 1.80)	0.47
Progression-free survival for exon 19 deletion subpopulation				
Osimertinib, Erlotinib	0.84 (0.56 to 1.10)	0.50 (-0.03 to 1.00)	0.77 (0.52 to 1.00)	0.25

Osimertinib, Gefitinib	0.84 (0.57 to 1.10)	1.20 (0.67 to 1.70)	0.92 (0.67 to 1.20)	0.25
Afatinib, Gefitinib	0.27 (-0.06 to 0.60)	0.26 (-0.24 to 0.76)	0.27 (0.00 to 0.55)	0.96
Gefitinib, Gefitinib+PbCT	-0.51 (-1.20 to 0.18)	-0.91 (-1.90 to 0.13)	-0.64 (-1.20 to -0.06)	0.53
Afatinib, PbCT	1.30 (0.83 to 1.70)	1.70 (0.50 to 2.80)	1.30 (0.91 to 1.70)	0.53
Gefitinib+PbCT, PbCT	1.90 (1.00 to 2.80)	1.50 (0.63 to 2.40)	1.70 (1.10 to 2.30)	0.53
Afatinib, PfCT	1.60 (1.10 to 2.10)	1.50 (1.10 to 2.00)	1.60 (1.20 to 1.90)	0.79
Erlotinib, PfCT	1.60 (1.20 to 1.90)	1.20 (0.71 to 1.70)	1.40 (1.20 to 1.70)	0.26
Gefitinib, PfCT	1.20 (0.80 to 1.50)	1.50 (1.10 to 1.80)	1.30 (1.00 to 1.50)	0.23
Progression-free survival for Leu858Arg subpopulation				
Osimertinib, Erlotinib	0.67 (0.33 to 1.00)	0.77 (0.18 to 1.40)	0.70 (0.40 to 0.99)	0.79
Osimertinib, Gefitinib	0.68 (0.34 to 1.00)	0.58 (-0.01 to 1.20)	0.65 (0.36 to 0.95)	0.79
Afatinib, Gefitinib	0.34 (-0.06 to 0.74)	0.07 (-0.47 to 0.62)	0.25 (-0.08 to 0.57)	0.44
Gefitinib, Gefitinib+PbCT	-1.20 (-1.90 to -0.41)	-2.20 (-3.30 to -1.10)	-1.50 (-2.10 to -0.86)	0.14
Afatinib, PbCT	0.32 (-0.15 to 0.78)	1.30 (0.09 to 2.60)	0.44 (0.00 to 0.88)	0.13
Gefitinib+PbCT, PbCT	2.20 (1.20 to 3.20)	1.20 (0.25 to 2.10)	1.70 (0.99 to 2.30)	0.14
Afatinib, PfCT	1.10 (0.63 to 1.60)	1.20 (0.66 to 1.60)	1.10 (0.80 to 1.50)	0.96
Erlotinib, PfCT	0.83 (0.47 to 1.20)	0.92 (0.34 to 1.50)	0.86 (0.55 to 1.20)	0.79
Gefitinib, PfCT	0.93 (0.57 to 1.30)	0.86 (0.42 to 1.30)	0.90 (0.62 to 1.20)	0.80
Overall survival for exon 19 deletion subpopulation				
Afatinib, Gefitinib	0.19 (-0.16 to 0.54)	0.39 (-0.15 to 0.92)	0.25 (-0.04 to 0.54)	0.54
Afatinib, PfCT	0.45 (0.06 to 0.82)	0.24 (-0.27 to 0.76)	0.37 (0.07 to 0.68)	0.54
Gefitinib, PfCT	0.06 (-0.32 to 0.43)	0.26 (-0.25 to 0.77)	0.13 (-0.18 to 0.43)	0.54
Overall survival for Leu858Arg subpopulation				
Afatinib, Gefitinib	0.09 (-0.30 to 0.48)	-0.25 (-0.82 to 0.32)	-0.02 (-0.34 to 0.31)	0.33
Afatinib, PfCT	-0.20 (-0.60 to 0.21)	0.15 (-0.42 to 0.71)	-0.08 (-0.41 to 0.25)	0.34
Gefitinib, PfCT	0.05 (-0.35 to 0.45)	-0.29 (-0.86 to 0.27)	-0.06 (-0.39 to 0.26)	0.33

Table S5. Node-splitting analysis of inconsistency.

Significant values ($P \leqslant 0.05$) are in bold and underlined, indicating a significant inconsistency between the direct effect and indirect effects. EGFR=epidermal growth factor receptor; PbCT=pemetrexed-based chemotherapy; PfCT=pemetrexed-free chemotherapy.

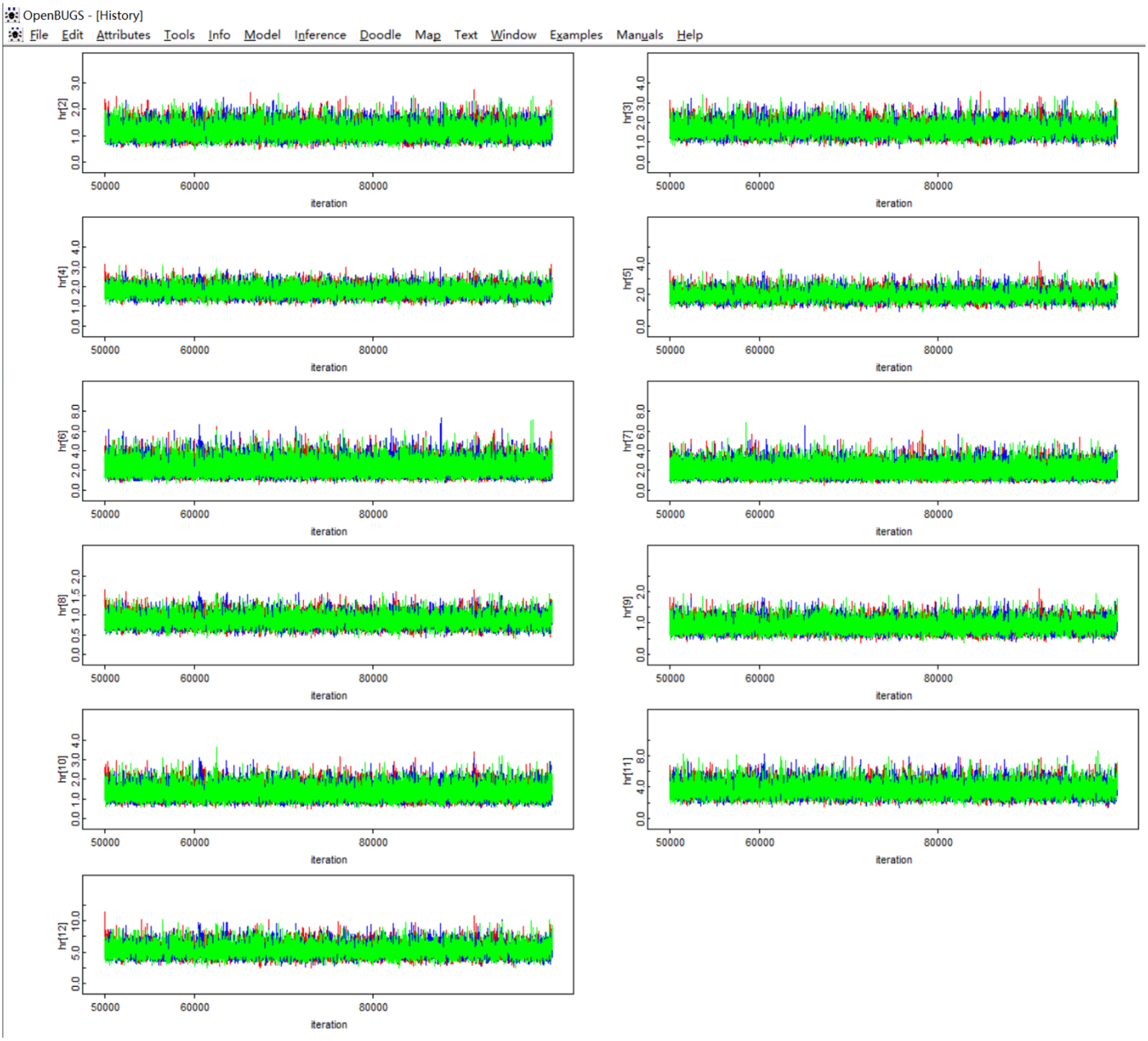
Treatment	Rank of possibility (%) (The first sensitivity analysis)									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Progression-free survival for advanced EGFR-mutated patients										
Osimertinib	**68**	27	5	0	0	0	0	0	0	0
Dacomitinib	1	8	30	45	12	4	0	0	0	0
Afatinib	0	0	1	9	51	36	3	0	0	0
Erlotinib	0	0	0	0	5	25	56	12	2	0
Gefitinib	0	0	0	0	0	3	23	65	9	0
Icotinib	1	3	6	12	23	28	13	15	0	0
Erlotinib+Bevacizumab	13	20	29	24	8	5	0	0	0	0
Gefitinib+PbCT	18	42	29	9	1	0	0	0	0	0
PbCT	0	0	0	0	0	0	4	7	89	0
PfCT	0	0	0	0	0	0	0	0	0	**100**
Overall survival for advanced EGFR-mutated patients										
Osimertinib	**61**	27	9	2	1	0	0	0	0	-
Dacomitinib	10	24	35	16	7	4	2	1	1	-
Afatinib	1	8	25	46	14	5	2	0	0	-
Erlotinib	0	0	1	6	14	18	24	17	19	-
Gefitinib	0	0	0	3	16	23	29	18	12	-
Icotinib	2	3	5	9	12	9	9	21	**30**	-
Gefitinib+PbCT	27	38	21	8	3	2	1	0	0	-
PbCT	0	0	1	4	10	13	12	30	**30**	-
PfCT	0	0	1	7	23	26	23	13	6	-
Objective response rate for advanced EGFR-mutated patients										
Osimertinib	5	12	20	19	16	12	12	4	0	-
Dacomitinib	8	13	16	15	13	12	15	7	2	-
Afatinib	17	34	22	12	7	5	3	0	0	-
Erlotinib	0	2	7	14	21	26	25	5	0	-
Gefitinib	0	1	7	19	27	28	16	2	0	-
Erlotinib+Bevacizumab	12	16	16	13	10	10	14	6	2	-
Gefitinib+PbCT	**57**	20	10	5	3	2	2	1	0	-
PbCT	1	2	3	3	4	5	9	48	26	-
PfCT	0	0	0	0	0	1	3	27	**69**	-
Grade ≥3 adverse events for advanced EGFR-mutated patients										
Osimertinib	0	0	1	2	3	5	9	18	47	15
Dacomitinib	6	11	15	27	13	12	7	4	3	2
Afatinib	0	2	6	16	31	25	10	6	2	0
Erlotinib	0	0	2	6	12	16	28	22	11	3
Gefitinib	0	0	1	2	6	12	27	35	15	3
Icotinib	0	1	1	1	2	2	4	4	9	**76**
Erlotinib+Bevacizumab	**68**	15	7	4	2	2	1	1	0	0
Gefitinib+PbCT	16	28	24	13	7	5	3	2	1	1
PbCT	4	6	9	14	19	18	11	9	12	0
PfCT	5	37	34	16	5	2	1	0	0	0
Progression-free survival for exon 19 deletion subpopulation										
Osimertinib	**86**	13	1	0	0	0	0	0	0	-
Dacomitinib	5	52	37	5	1	0	0	0	0	-

Afatinib	0	3	23	50	22	2	0	0	0	-
Erlotinib	0	0	3	27	54	15	1	0	0	-
Gefitinib	0	0	0	3	16	75	6	0	0	-
Icotinib	0	0	0	1	2	4	83	6	2	-
Erlotinib+Bevacizumab	9	32	35	15	5	3	0	0	0	-
PbCT	0	0	0	0	0	0	6	81	13	-
PfCT	0	0	0	0	0	0	3	12	**85**	-
Progression-free survival for Leu858Arg subpopulation										
Osimertinib	**44**	37	14	4	1	0	0	0	0	-
Dacomitinib	13	23	31	18	10	5	1	0	0	-
Afatinib	1	6	21	39	24	7	1	0	0	-
Erlotinib	0	0	1	4	12	21	27	36	0	-
Gefitinib	0	0	0	3	15	27	35	20	0	-
Icotinib	14	10	13	15	16	9	12	10	0	-
Erlotinib+Bevacizumab	29	22	19	12	8	6	3	1	0	-
PbCT	0	1	2	6	14	24	21	32	0	-
PfCT	0	0	0	0	0	0	0	0	**100**	-
Overall survival for exon 19 deletion subpopulation										
Dacomitinib	30	33	17	9	6	3	2	-	-	-
Afatinib	**62**	31	6	1	0	0	0	-	-	-
Erlotinib	2	7	11	18	27	19	18	-	-	-
Gefitinib	1	15	43	23	12	4	1	-	-	-
Icotinib	6	11	11	14	12	31	15	-	-	-
PbCT	0	0	3	5	10	23	**58**	-	-	-
PfCT	0	3	10	30	32	18	6	-	-	-
Overall survival for Leu858Arg subpopulation										
Dacomitinib	**50**	17	17	7	4	3	2	-	-	-
Afatinib	0	3	8	17	23	26	**24**	-	-	-
Erlotinib	9	16	16	17	13	13	17	-	-	-
Gefitinib	0	6	10	19	20	23	23	-	-	-
Icotinib	14	19	16	9	8	9	**24**	-	-	-
PbCT	25	30	16	9	8	9	3	-	-	-
PfCT	2	10	18	23	22	17	7	-	-	-

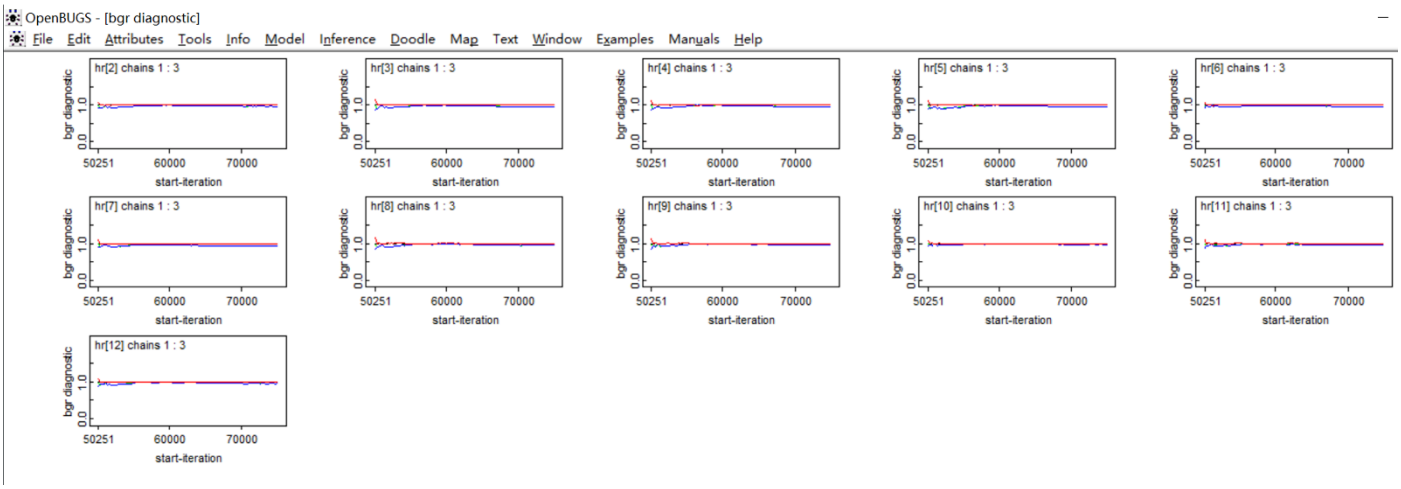
Table S6. Bayesian ranking results of the first sensitivity analysis including only phase III trials.

The number in each cell represents the posterior probability of the row-defining treatment being ranked at the column-defining position. The numbers with biggest probability of ranking first and last are in bold and underscored. EGFR=epidermal growth factor receptor.

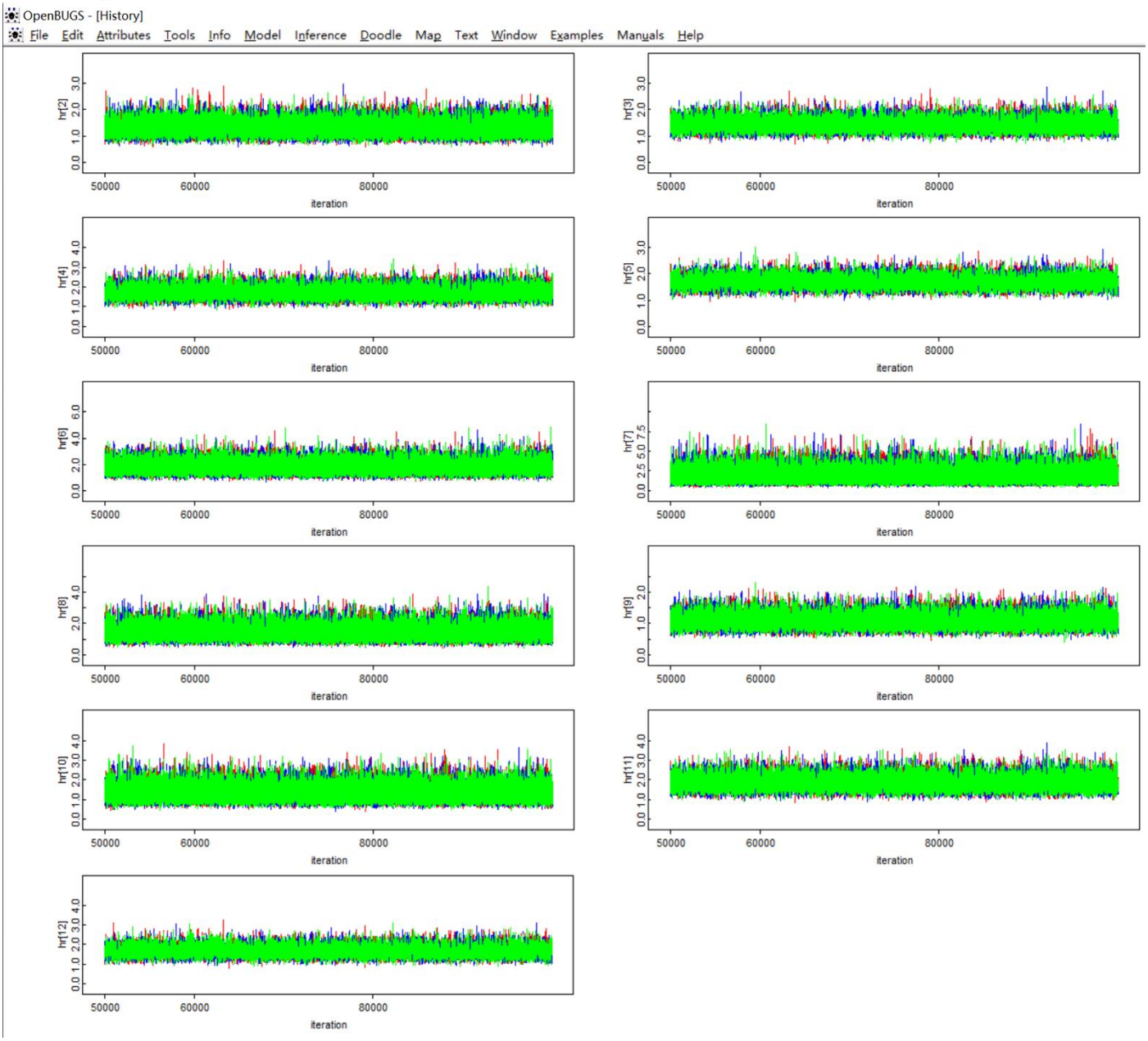
A. History for progression-free survival



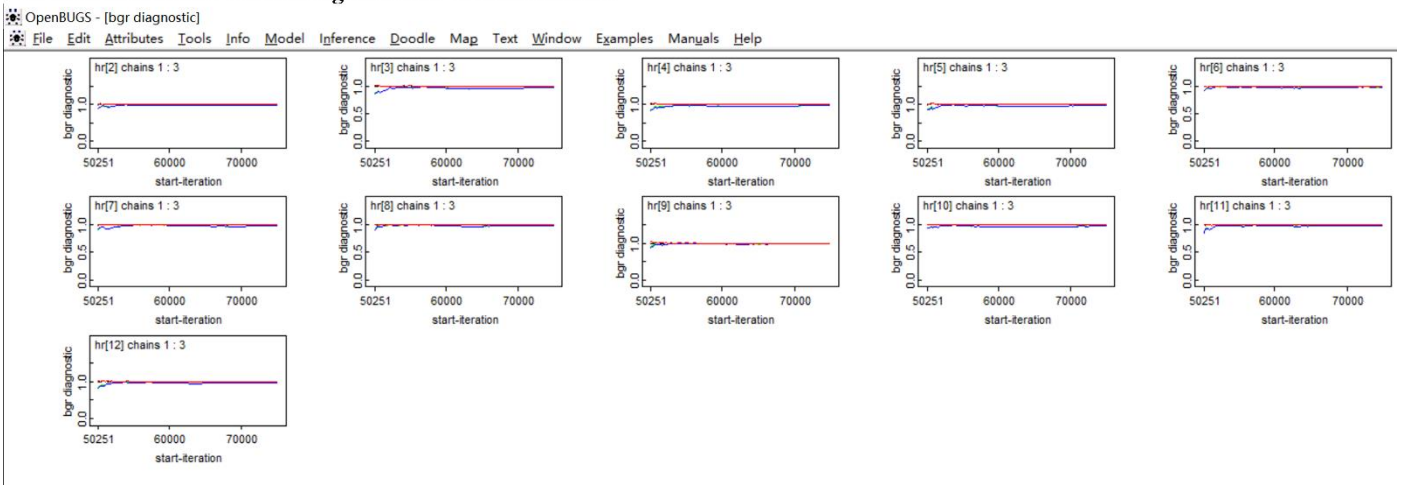
B. Brooks-Gelman-Rubin diagnostic for progression-free survival

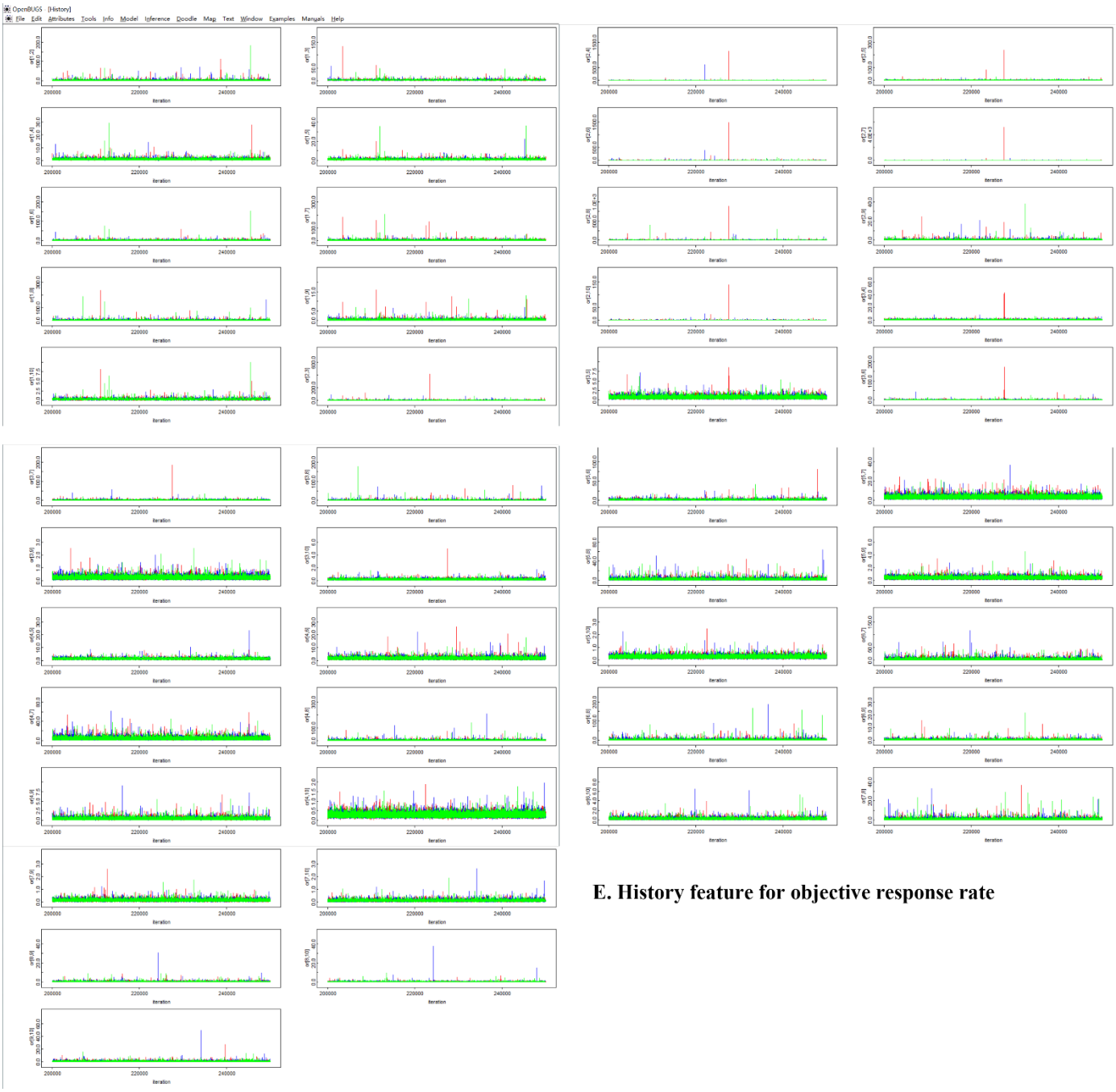


C. History for overall survival



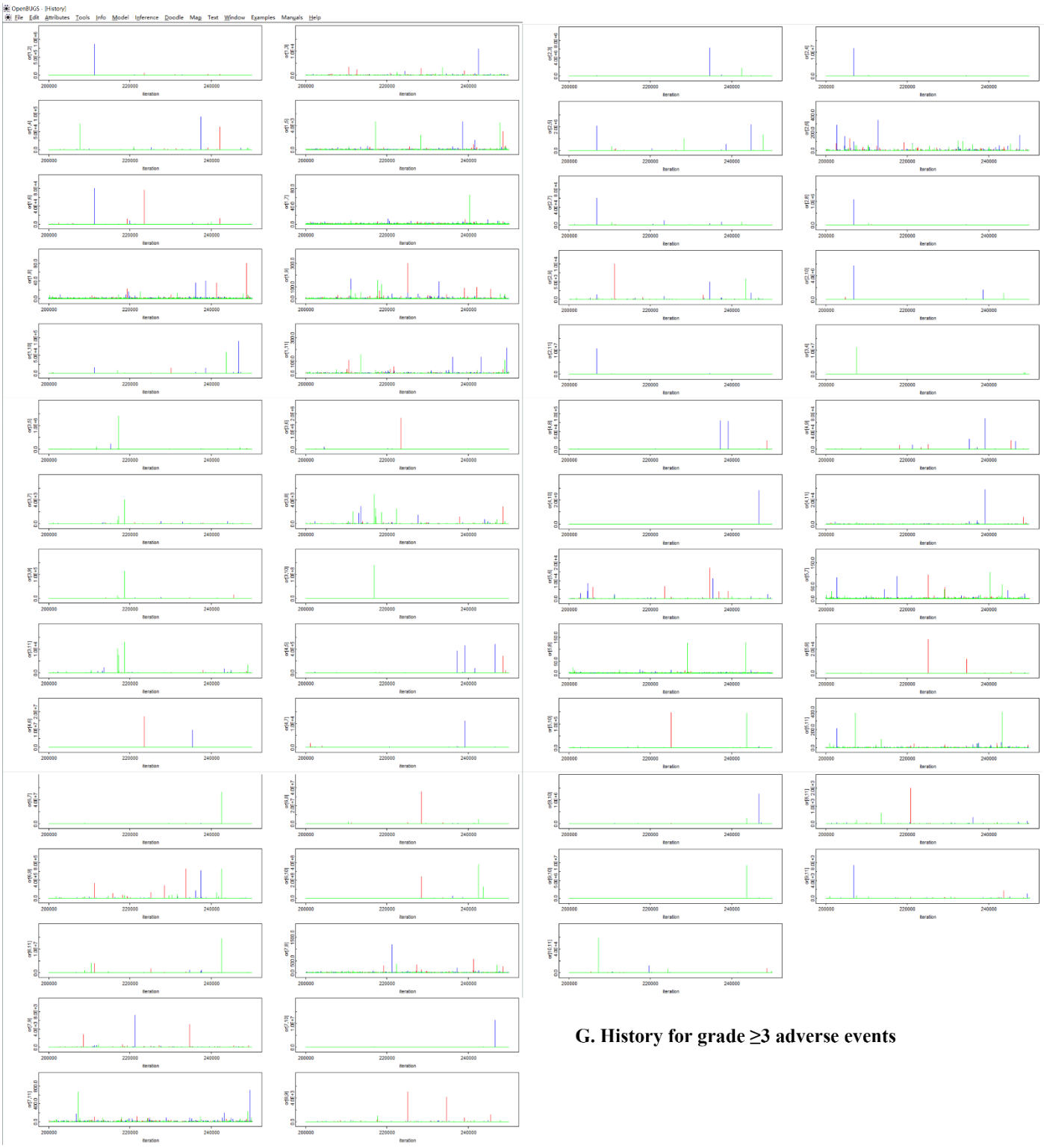
D. Brooks-Gelman-Rubin diagnostic for overall survival





E. History feature for objective response rate

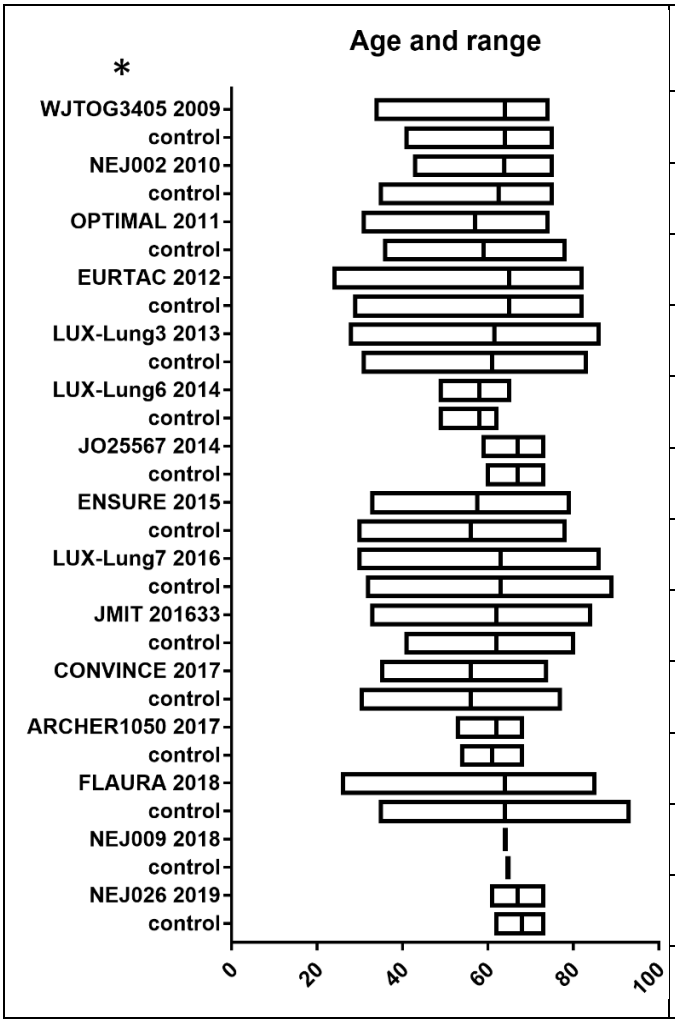
F. Brooks-Gelman-Rubin diagnostic for objective response rate



G. History for grade ≥3 adverse events

H. Brooks-Gelman-Rubin diagnostic for grade ≥3 adverse events

Figure S1. Convergence of the three chains established by inspection of the history feature and the Brooks-Gelman-Rubin diagnostic for progression-free survival (A and B), overall survival (C and D), objective response rate (E and F), and grade ≥3 adverse events (G and H).



Characteristic	Intervention arm	Control arm
Sample size	0.253	0.247
Female ratio	0.259	0.253
Smoking status		
Never	0.242	0.242
Current	0.248	0.255
Former	0.285	0.285
Clinical stage		
IIIB	0.262	0.269
IV	0.242	0.248
Other	0.303	0.323
Mutation type		
Exon 19 deletion	0.308	0.290
Leu858Arg	0.282	0.260

Figure S2. Assessment of transitivity.

The above characteristics have been evaluated in all trials included in the network. All of the comparisons had similar median age (left) and other main ccharacteristics with P value over 0.05 (right).

* Mean age was given instead of median age in the NEJ002 and NEJ009 studies. Information of age in the CTONG0901 and Han et al. studies were presented as younger or older than a specific age that couldn't be integrated in the figure.

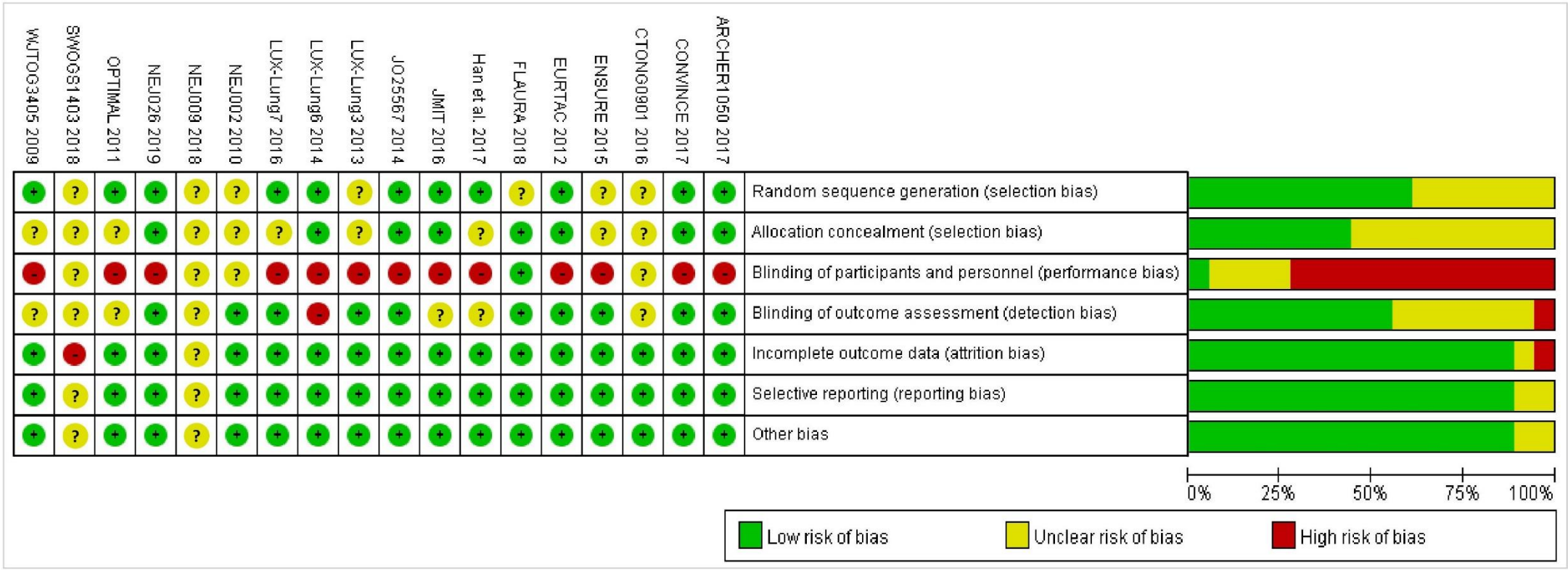


Figure S3. Summary of results from assessment of studies using the Cochrane risk of bias tool.

	Rash	Diarrhea	Stomatitis	Paronychia	Dry skin	Pruritus	Anorexia	Fatigue	Constipation	Nausea	Vomiting	Leucopenia	Neutropenia	Anemia	†Liver dysfunction	ILD
NO. of studies	**16**	**17**	**11**	**12**	**9**	**9**	**14**	**13**	**10**	**11**	**10**	**7**	**14**	**14**	**16**	**15**
Sample size	**4337**	**4528**	**3259**	**3538**	**2655**	**2861**	**4007**	**3309**	**2858**	**3157**	**3016**	**1939**	**3564**	**3801**	**4188**	**4066**
Osimertinib	58	58	29	35	36	17	20	14	15	14	11	NA	NA	12	7	2
Dacomitinib	18	87	44	62	28	20	31	NA	13	19	9	2	1	10	19	1
Afatinib	86	91	62	47	31	17	15	15	2	14	13	3	2	4	16	1
Erlotinib	79	45	23	25	27	19	16	16	9	15	8	6	3	7	23	2
Gefitinib	61	46	20	23	28	19	17	15	13	17	9	6	4	16	39	2
Icotinib	15	7	NA	NA	NA	1	2	NA	NA	3	1	7	3	3	7	0
All EGFR-TKIs	64	61	35	34	29	17	17	15	10	15	9	4	3	10	25	1
***Erlotinib+Bevacizumab**	92	61	37	40	75	45	21	13	23	16	19	NA	1	5	34	1
Gefitinib+PbCT	64	38	31	24	NA	NA	55	32	34	50	NA	20	56	62	58	NA
Gefitinib+Pemetrexed	38	44	36	NA	25	35	NA	28	NA	28	13	NA	17	18	38	2
PbCT	4	11	15	0	2	1	37	42	29	53	35	32	37	22	17	0
PfCT	12	14	7	0	3	3	41	42	22	75	62	63	65	57	21	0

Figure S4. A frequency toxicity profile in relation to the incidence (%) of each specific adverse event based on the population of each treatment we included.

NA=not applicable; EGFR=epidermal growth factor receptor; TKI=tyrosine kinase inhibitor; ILD= interstitial lung disease; PbCT=pemetrexed-based chemotherapy; PfCT=pemetrexed-free chemotherapy.

* Notable incidences of hypertension (58.3%), hemorrhagic events (45.5%) and proteinuria (40.1%) were also associated with erlotinib plus bevacizumab group based on the report of the JO25567 and NEJ026 studies.

† When not reported, liver dysfunction was represented by alanine transaminase increased as it was reported in most studies.

A	Rash	Diarrhea	Stomatitis	Paronychia	Dry skin	†Liver dysfunction	ILD
Comparison	**Vs Osimertinib**						
Dacomitinib	4.18	**4.82**	1.67	5.24	2.06	**3.06**	1.36
Afatinib	**5.75**	**10.27**	2.96	4.90	0.88	**3.15**	0.25
Erlotinib	2.89	1.09	0.79	1.02	0.95	**4.52**	0.51
Gefitinib	2.31	0.87	0.46	0.80	1.09	**8.19**	1.37
Icotinib	1.06	0.30	NA	NA	NA	1.95	0.07
Erlotinib+Bevacizumab	3.01	1.38	1.23	1.32	2.01	**3.68**	0.19
Gefitinib+PbCT	1.64	0.85	1.01	0.57	NA	**10.81**	NA
Gefitinib+ Pemetrexed	1.89	0.77	0.85	NA	0.68	**11.39**	1.42
PbCT	**0.07**	**0.17**	0.20	**0.01**	0.03	**4.41**	0.07
PfCT	**0.11**	**0.19**	0.17	**0.03**	0.05	**2.66**	0.34
	Vs Dac						
Afatinib	1.37	2.12	1.77	0.94	0.43	1.03	0.19
Erlotinib	0.69	**0.22**	0.48	0.19	0.46	1.49	0.37
Gefitinib	0.55	**0.18**	0.28	**0.15**	0.53	**2.67**	1.01
Icotinib	0.25	**0.06**	NA	NA	NA	0.63	0.05
Erlotinib+Bevacizumab	0.72	0.28	0.74	0.25	0.97	1.21	0.14
Gefitinib+PbCT	0.39	**0.18**	0.61	**0.11**	NA	**3.49**	NA
Gefitinib+ Pemetrexed	0.45	**0.16**	0.51	NA	0.33	**3.72**	1.04
PbCT	**0.02**	**0.03**	0.12	**0.01**	0.02	1.42	0.05
PfCT	**0.03**	**0.04**	0.10	**0.01**	0.03	0.87	0.25
	Vs Afatinib						
Erlotinib	0.50	**0.11**	0.27	0.21	1.08	1.45	1.98
Gefitinib	0.40	**0.09**	0.16	**0.16**	1.22	**2.61**	5.39
Icotinib	0.18	**0.03**	NA	NA	NA	0.62	0.27
Erlotinib+Bevacizumab	0.52	**0.13**	0.42	0.27	2.26	1.18	0.76
Gefitinib+PbCT	0.28	**0.08**	0.34	**0.12**	NA	**3.38**	NA
Gefitinib+ Pemetrexed	0.33	**0.07**	0.29	NA	0.77	**3.61**	5.56
PbCT	**0.01**	**0.02**	**0.07**	**0.01**	0.04	1.39	0.29
PfCT	**0.02**	**0.02**	**0.06**	**0.01**	0.06	0.85	1.35
	Vs Erlotinib						
Gefitinib	0.80	0.81	0.58	0.79	1.15	1.81	2.72
Icotinib	0.37	0.28	NA	NA	NA	0.43	0.14
Erlotinib+Bevacizumab	1.04	1.27	1.55	1.29	2.12	0.81	0.38
Gefitinib+PbCT	0.57	0.78	1.28	0.56	NA	**2.36**	NA
Gefitinib+ Pemetrexed	0.65	0.71	1.07	NA	0.71	2.52	2.80
PbCT	**0.02**	**0.16**	0.25	**0.01**	0.03	0.96	0.15
PfCT	**0.04**	**0.17**	0.21	**0.03**	0.06	0.58	0.68
	Vs Gefitinib						
Icotinib	0.46	0.35	NA	NA	NA	**0.24**	0.05
Erlotinib+Bevacizumab	1.30	1.57	2.71	1.64	1.84	0.45	0.14
Gefitinib+PbCT	0.71	0.97	2.20	0.72	NA	1.30	NA
Gefitinib+ Pemetrexed	0.82	0.87	1.86	NA	0.62	1.39	1.03
PbCT	**0.03**	**0.19**	0.44	**0.01**	0.03	0.53	0.05
PfCT	**0.05**	**0.21**	0.37	**0.03**	0.05	**0.32**	0.25

	Vs Icotinib						
Erlotinib+Bevacizumab	2.82	4.51	NA	NA	NA	1.92	2.82
Gefitinib+PbCT	1.56	2.81	NA	NA	NA	**5.52**	NA
Gefitinib+Pemetrexed	1.78	2.52	NA	NA	NA	**5.91**	20.70
PbCT	**0.07**	0.56	NA	NA	NA	2.26	1.08
PfCT	0.11	0.61	NA	NA	NA	1.37	5.01
	Vs Erlotinib+Bevacizumab						
Gefitinib+PbCT	0.55	0.62	0.82	0.43	NA	**2.89**	NA
Gefitinib+Pemetrexed	0.63	0.56	0.69	NA	0.34	3.09	7.35
PbCT	**0.02**	**0.12**	0.16	**0.01**	0.02	1.18	0.38
PfCT	**0.04**	**0.13**	0.14	**0.02**	0.03	0.72	1.78
	Vs Gefitinib+PbCT						
Gefitinib+Pemetrexed	1.15	0.90	0.85	NA	NA	1.07	NA
PbCT	**0.04**	**0.20**	0.20	**0.01**	NA	**0.41**	NA
PfCT	**0.07**	**0.22**	0.17	**0.04**	NA	**0.25**	NA
	Vs Gefitinib+Pemetrexed						
PbCT	**0.04**	0.22	0.24	NA	0.05	0.38	0.05
PfCT	**0.06**	**0.24**	0.20	NA	0.08	**0.23**	0.24
	Vs PbCT						
PfCT	1.57	1.10	0.85	3.56	1.73	0.61	4.64

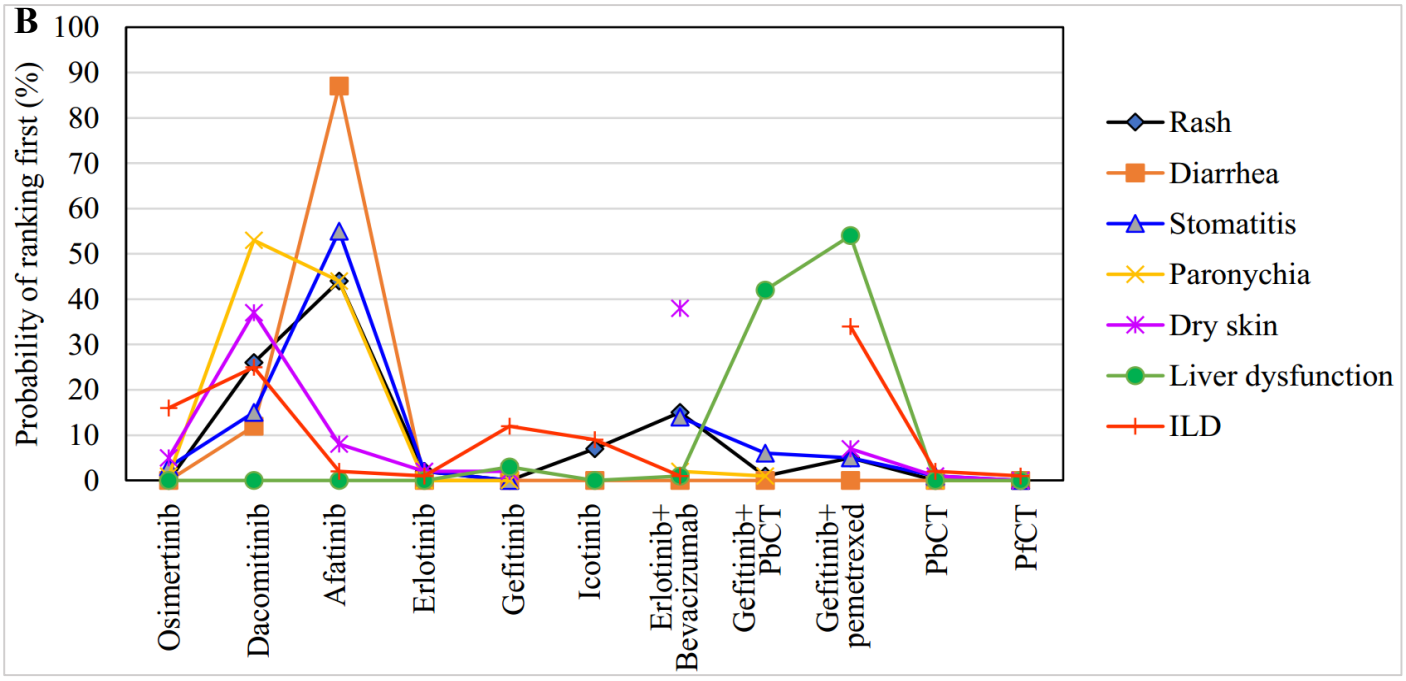
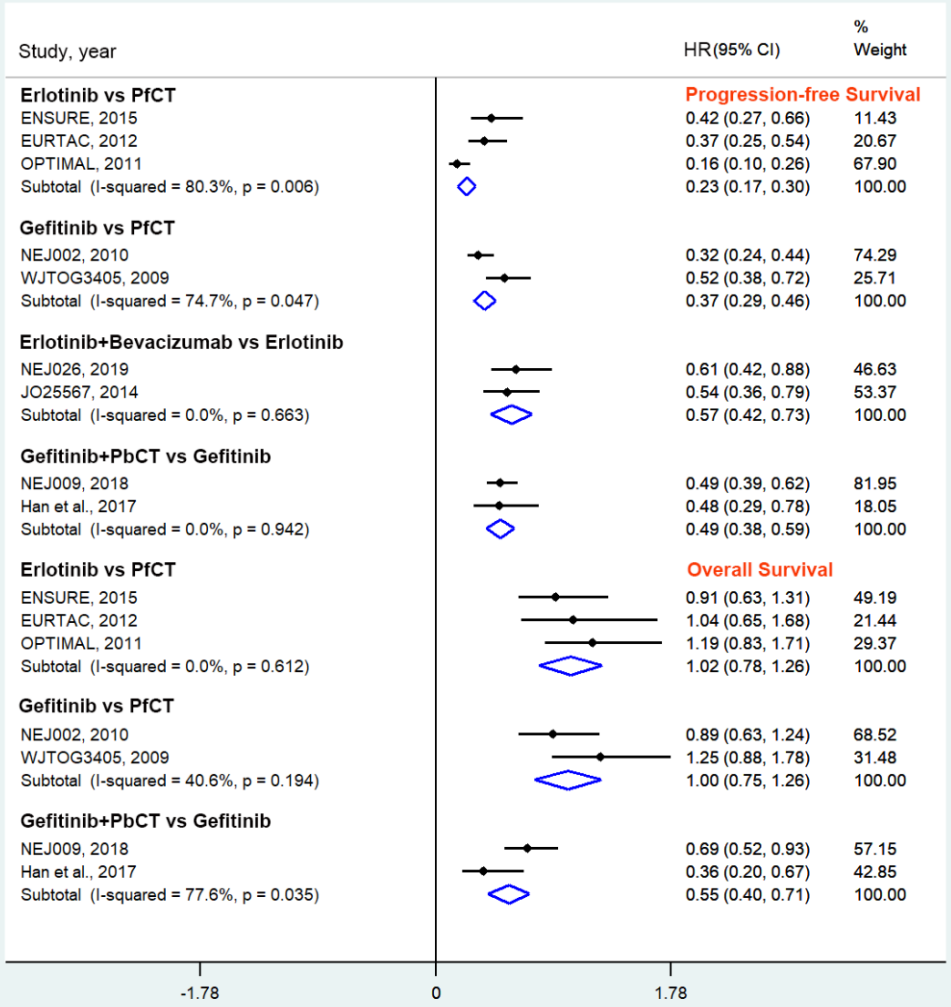
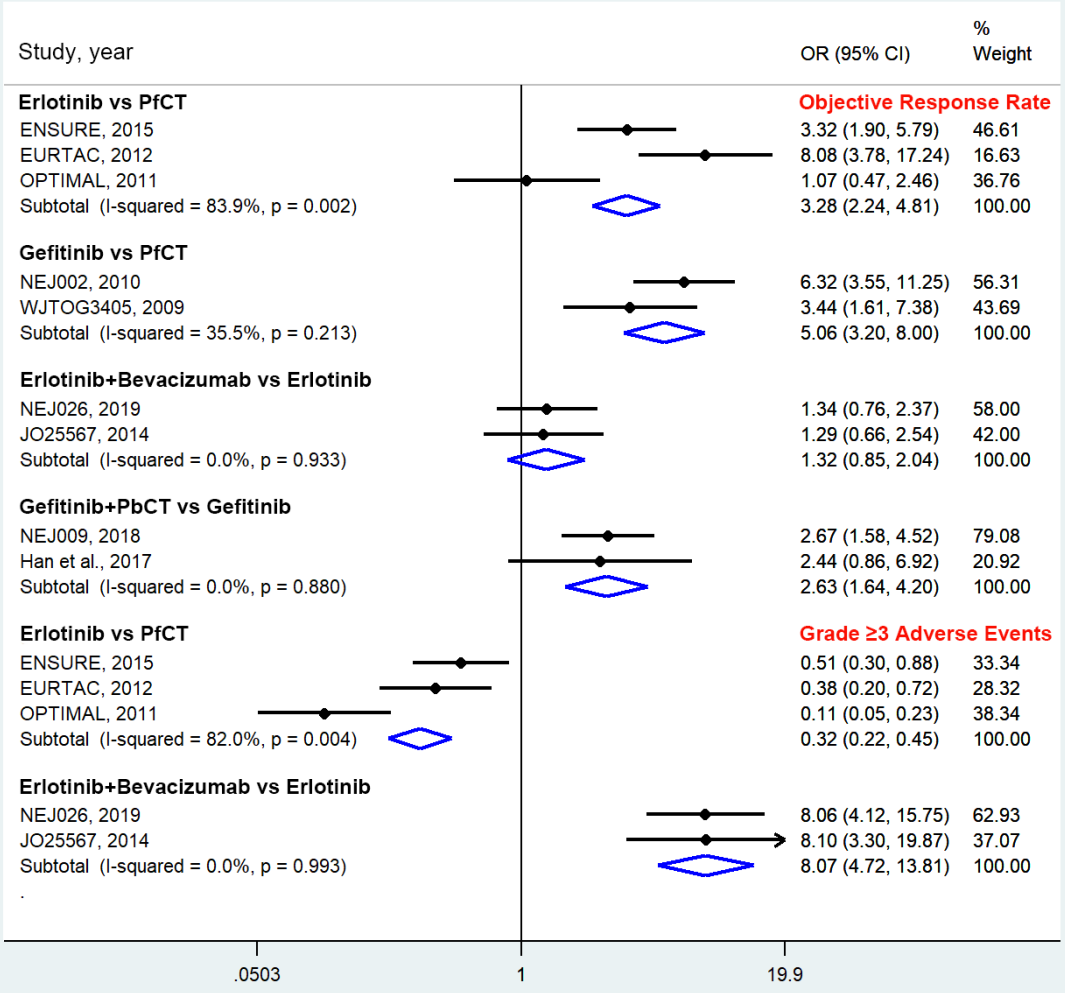


Figure S5. Relative toxicity of treatments on seven commonly reported specific adverse events for EGFR-TKIs. **A.** Pooled odds ratios for each available comparison on each specific adverse event (any grade). Significant values are in bold and colored in gray (less toxicity) and light yellow (more toxicity). **B.** Ranking curves indicating the probability of each comparable treatment being ranked first on each specific adverse event. If a study reported zero adverse events in any arm, the classic half integer continuity correction (adding a 0.5 to each cell) was applied for data preparation. NA=not applicable; EGFR=epidermal growth factor receptor; TKI=tyrosine kinase inhibitor; PbCT=pemetrexed-based chemotherapy; PfCT=pemetrexed-free chemotherapy; ILD=interstitial lung disease.

† When not reported, liver dysfunction was represented by alanine transaminase increased as it was reported in most studies.

A


Study, year
HR(95% CI)
% Weight
Erlotinib vs PfCT
Progression-free Survival
ENSURE, 2015 0.42 (0.27, 0.66) 11.43
EURTAC, 2012 0.37 (0.25, 0.54) 20.67
OPTIMAL, 2011 0.16 (0.10, 0.26) 67.90
Subtotal (I-squared = 80.3%, p = 0.006) 0.23 (0.17, 0.30) 100.00
Gefitinib vs PfCT
NEJ002, 2010 0.32 (0.24, 0.44) 74.29
WJTOG3405, 2009 0.52 (0.38, 0.72) 25.71
Subtotal (I-squared = 74.7%, p = 0.047) 0.37 (0.29, 0.46) 100.00
Erlotinib+Bevacizumab vs Erlotinib
NEJ026, 2019 0.61 (0.42, 0.88) 46.63
JO25567, 2014 0.54 (0.36, 0.79) 53.37
Subtotal (I-squared = 0.0%, p = 0.663) 0.57 (0.42, 0.73) 100.00
Gefitinib+PbCT vs Gefitinib
NEJ009, 2018 0.49 (0.39, 0.62) 81.95
Han et al., 2017 0.48 (0.29, 0.78) 18.05
Subtotal (I-squared = 0.0%, p = 0.942) 0.49 (0.38, 0.59) 100.00
Erlotinib vs PfCT
Overall Survival
ENSURE, 2015 0.91 (0.63, 1.31) 49.19
EURTAC, 2012 1.04 (0.65, 1.68) 21.44
OPTIMAL, 2011 1.19 (0.83, 1.71) 29.37
Subtotal (I-squared = 0.0%, p = 0.612) 1.02 (0.78, 1.26) 100.00
Gefitinib vs PfCT
NEJ002, 2010 0.89 (0.63, 1.24) 68.52
WJTOG3405, 2009 1.25 (0.88, 1.78) 31.48
Subtotal (I-squared = 40.6%, p = 0.194) 1.00 (0.75, 1.26) 100.00
Gefitinib+PbCT vs Gefitinib
NEJ009, 2018 0.69 (0.52, 0.93) 57.15
Han et al., 2017 0.36 (0.20, 0.67) 42.85
Subtotal (I-squared = 77.6%, p = 0.035) 0.55 (0.40, 0.71) 100.00
-1.78
0
1.78


Study, year
OR (95% CI)
% Weight
Erlotinib vs PfCT
Objective Response Rate
ENSURE, 2015 3.32 (1.90, 5.79) 46.61
EURTAC, 2012 8.08 (3.78, 17.24) 16.63
OPTIMAL, 2011 1.07 (0.47, 2.46) 36.76
Subtotal (I-squared = 83.9%, p = 0.002) 3.28 (2.24, 4.81) 100.00
Gefitinib vs PfCT
NEJ002, 2010 6.32 (3.55, 11.25) 56.31
WJTOG3405, 2009 3.44 (1.61, 7.38) 43.69
Subtotal (I-squared = 35.5%, p = 0.213) 5.06 (3.20, 8.00) 100.00
Erlotinib+Bevacizumab vs Erlotinib
NEJ026, 2019 1.34 (0.76, 2.37) 58.00
JO25567, 2014 1.29 (0.66, 2.54) 42.00
Subtotal (I-squared = 0.0%, p = 0.933) 1.32 (0.85, 2.04) 100.00
Gefitinib+PbCT vs Gefitinib
NEJ009, 2018 2.67 (1.58, 4.52) 79.08
Han et al., 2017 2.44 (0.86, 6.92) 20.92
Subtotal (I-squared = 0.0%, p = 0.880) 2.63 (1.64, 4.20) 100.00
Erlotinib vs PfCT
Grade ≥3 Adverse Events
ENSURE, 2015 0.51 (0.30, 0.88) 33.34
EURTAC, 2012 0.38 (0.20, 0.72) 28.32
OPTIMAL, 2011 0.11 (0.05, 0.23) 38.34
Subtotal (I-squared = 82.0%, p = 0.004) 0.32 (0.22, 0.45) 100.00
Erlotinib+Bevacizumab vs Erlotinib
NEJ026, 2019 8.06 (4.12, 15.75) 62.93
JO25567, 2014 8.10 (3.30, 19.87) 37.07
Subtotal (I-squared = 0.0%, p = 0.993) 8.07 (4.72, 13.81) 100.00
.0503
1
19.9

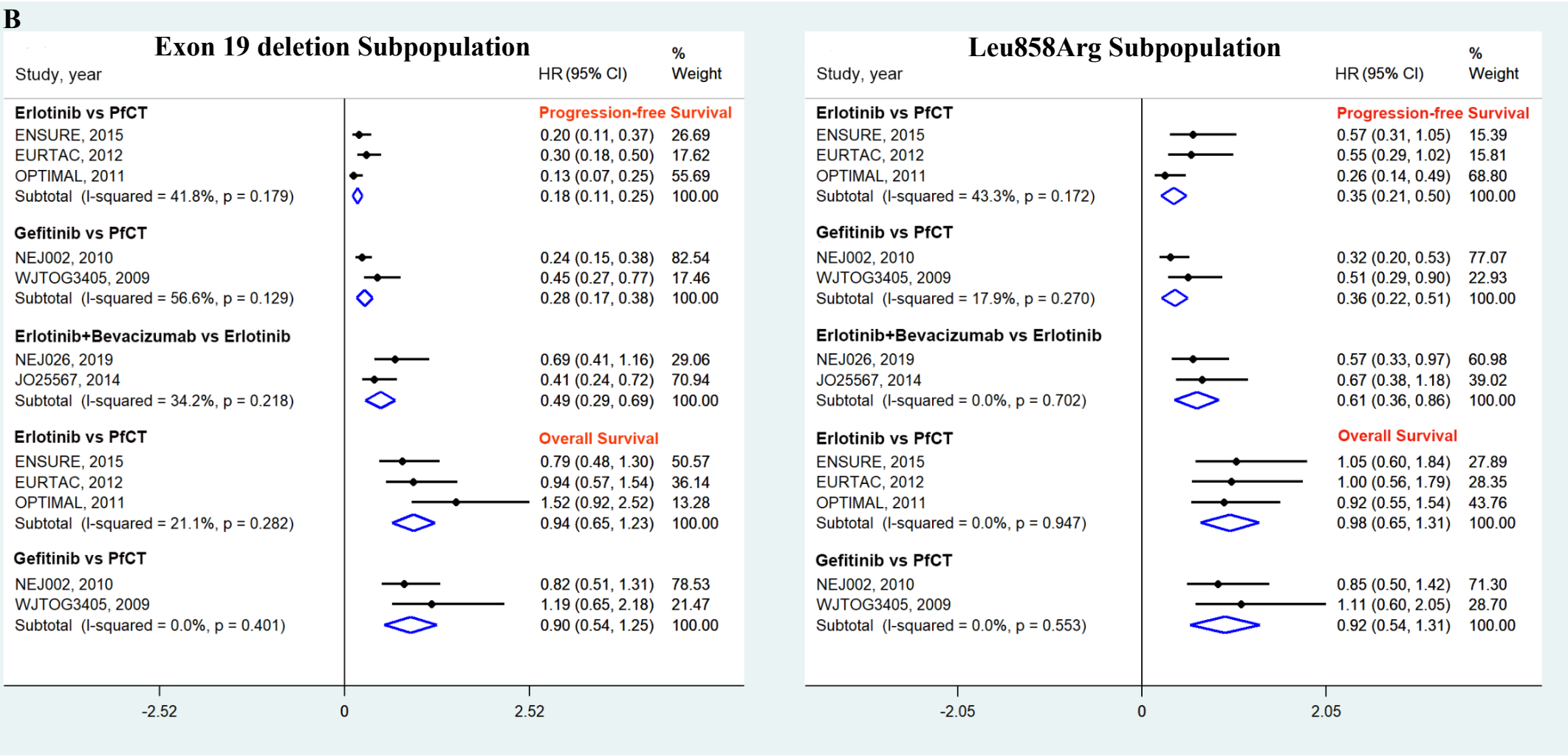


Figure S6. Forest plots depicting results of head-to-head comparisons according to frequentist pairwise meta-analyses on different outcomes in advanced EGFR-mutated patients (A), and exon 19 deletion and Leu858Arg subpopulations (B).

Results were consistent with the corresponding results of the network meta-analysis. Results of heterogeneity assessments are adherently presented. Comparisons assessed in only one trial were not plotted. HR=hazard ratio; OR=odds ratio; CI=confidence interval; EGFR=epidermal growth factor receptor; PbCT=pemetrexed-based chemotherapy; PfCT=pemetrexed-free chemotherapy.

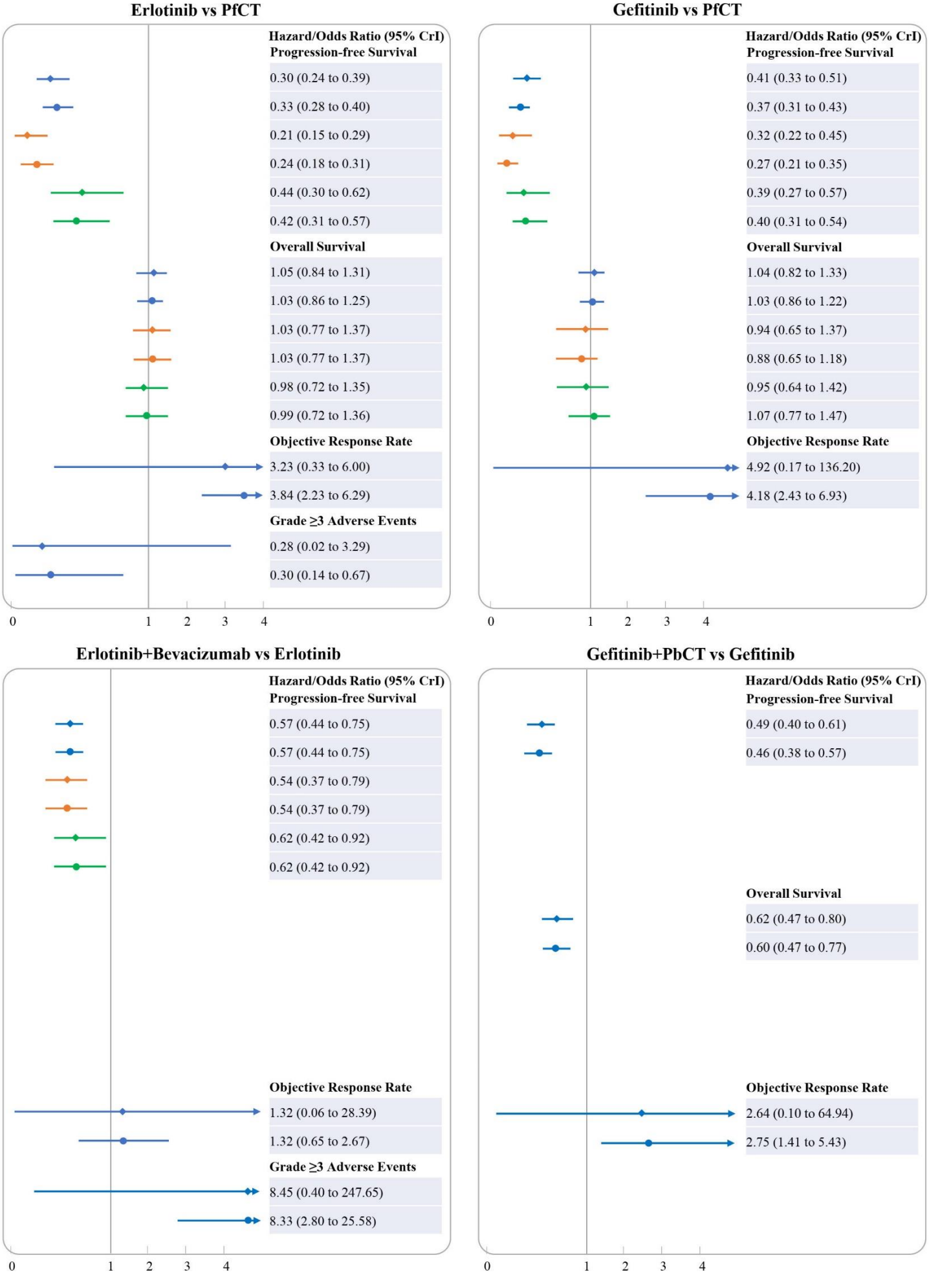

Erlotinib vs PfCT
Hazard/Odds Ratio (95% CrI)
Progression-free Survival
0.30 (0.24 to 0.39)
0.33 (0.28 to 0.40)
0.21 (0.15 to 0.29)
0.24 (0.18 to 0.31)
0.44 (0.30 to 0.62)
0.42 (0.31 to 0.57)
Overall Survival
1.05 (0.84 to 1.31)
1.03 (0.86 to 1.25)
1.03 (0.77 to 1.37)
1.03 (0.77 to 1.37)
0.98 (0.72 to 1.35)
0.99 (0.72 to 1.36)
Objective Response Rate
3.23 (0.33 to 6.00)
3.84 (2.23 to 6.29)
Grade ≥3 Adverse Events
0.28 (0.02 to 3.29)
0.30 (0.14 to 0.67)
0
1
2
3
4
Gefitinib vs PfCT
Hazard/Odds Ratio (95% CrI)
Progression-free Survival
0.41 (0.33 to 0.51)
0.37 (0.31 to 0.43)
0.32 (0.22 to 0.45)
0.27 (0.21 to 0.35)
0.39 (0.27 to 0.57)
0.40 (0.31 to 0.54)
Overall Survival
1.04 (0.82 to 1.33)
1.03 (0.86 to 1.22)
0.94 (0.65 to 1.37)
0.88 (0.65 to 1.18)
0.95 (0.64 to 1.42)
1.07 (0.77 to 1.47)
Objective Response Rate
4.92 (0.17 to 136.20)
4.18 (2.43 to 6.93)
0
1
2
3
4
Erlotinib+Bevacizumab vs Erlotinib
Hazard/Odds Ratio (95% CrI)
Progression-free Survival
0.57 (0.44 to 0.75)
0.57 (0.44 to 0.75)
0.54 (0.37 to 0.79)
0.54 (0.37 to 0.79)
0.62 (0.42 to 0.92)
0.62 (0.42 to 0.92)
Objective Response Rate
1.32 (0.06 to 28.39)
1.32 (0.65 to 2.67)
Grade ≥3 Adverse Events
8.45 (0.40 to 247.65)
8.33 (2.80 to 25.58)
0
1
2
3
4
Gefitinib+PbCT vs Gefitinib
Hazard/Odds Ratio (95% CrI)
Progression-free Survival
0.49 (0.40 to 0.61)
0.46 (0.38 to 0.57)
Overall Survival
0.62 (0.47 to 0.80)
0.60 (0.47 to 0.77)
Objective Response Rate
2.64 (0.10 to 64.94)
2.75 (1.41 to 5.43)
0
1
2
3
4
Overall
Exon 19 deletion
Leu858Arg
Pairwise meta-analysis
Network meta-analysis

Figure S7. Forest plots depicting results of head-to-head comparisons in according to Bayesian pairwise and network meta-analyses.

Results of all comparisons in overall epidermal growth factor receptor mutated (blue) population, and exon 19 deletion (orange) and Leu858Arg (green) subpopulations were consistent between pairwise and network meta-analyses. CrI=credible interval; PbCT=pemetrexed-based chemotherapy; PfCT=pemetrexed-free chemotherapy.

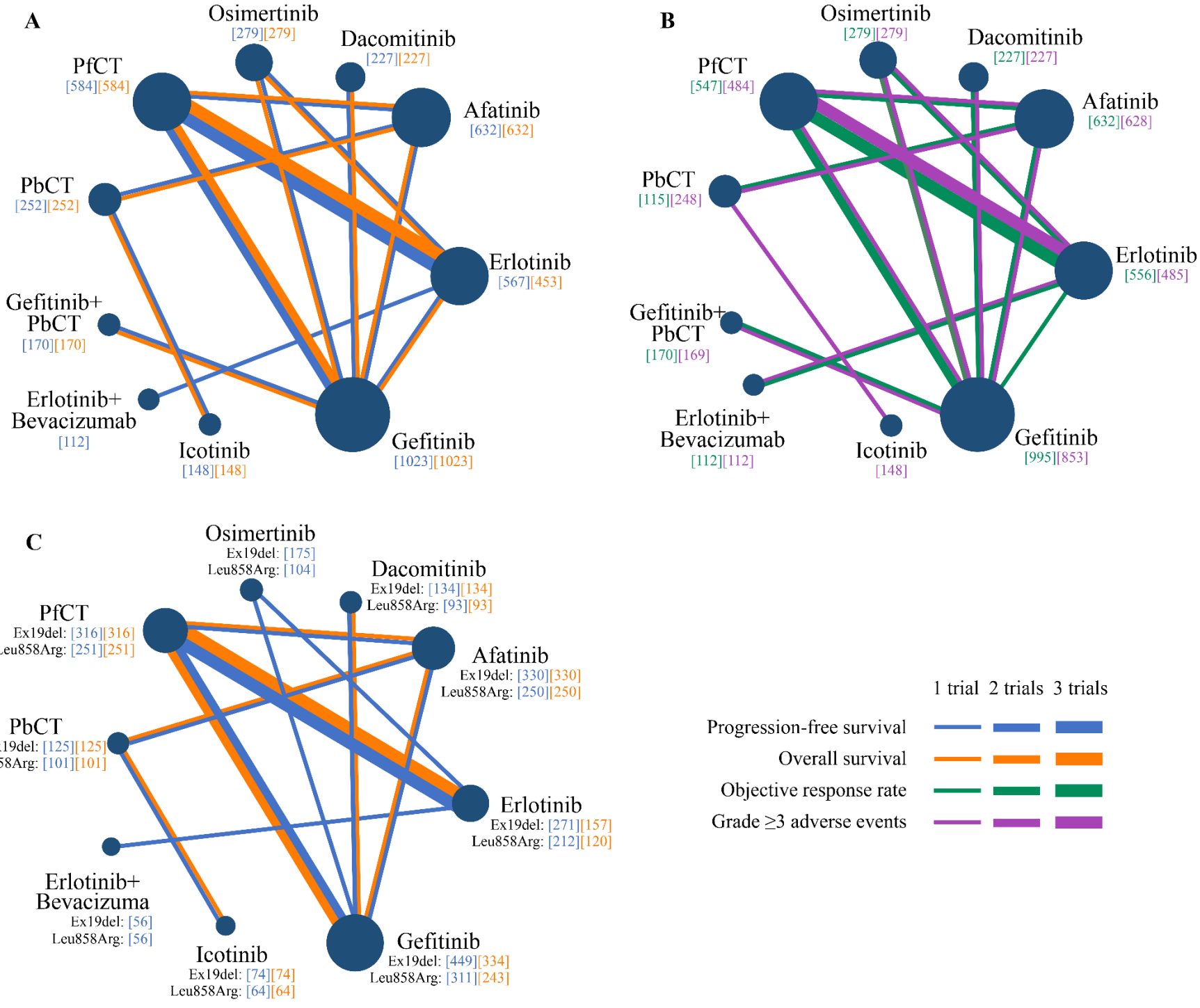

A
Osimertinib
[279][279]
Dacomitinib
[227][227]
PfCT
[584][584]
Afatinib
[632][632]
PbCT
[252][252]
Erlotinib
[567][453]
Gefitinib+
PbCT
[170][170]
Erlotinib+
Bevacizumab
[112]
Icotinib
[148][148]
Gefitinib
[1023][1023]
B
Osimertinib
[279][279]
Dacomitinib
[227][227]
PfCT
[547][484]
Afatinib
[632][628]
PbCT
[115][248]
Erlotinib
[556][485]
Gefitinib+
PbCT
[170][169]
Erlotinib+
Bevacizumab
[112][112]
Icotinib
[148]
Gefitinib
[995][853]
C
Osimertinib
Ex19del: [175]
Leu858Arg: [104]
Dacomitinib
Ex19del: [134][134]
Leu858Arg: [93][93]
PfCT
Ex19del: [316][316]
Leu858Arg: [251][251]
Afatinib
Ex19del: [330][330]
Leu858Arg: [250][250]
PbCT
Ex19del: [125][125]
Leu858Arg: [101][101]
Erlotinib
Ex19del: [271][157]
Leu858Arg: [212][120]
Erlotinib+
Bevacizuma
Ex19del: [56]
Leu858Arg: [56]
Icotinib
Ex19del: [74][74]
Leu858Arg: [64][64]
Gefitinib
Ex19del: [449][334]
Leu858Arg: [311][243]
1 trial
2 trials
3 trials
Progression-free survival
Overall survival
Objective response rate
Grade ≥3 adverse events

Figure S8. Network diagrams for the first sensitivity analysis including only phase III trials.

A. Comparisons on progression-free survival (blue line) and overall survival (orange line) in advanced EGFR-mutated patients. **B.** Comparisons on objective response rate (green line) and grade ≥3 adverse events (purple line) in advanced EGFR-mutated patients. **C.** Comparisons on progression-free survival (blue line) and overall survival (orange line) in exon 19 deletion and Leu858Arg subpopulations. Each circular node represents a type of treatment. The node size is proportional to the total number of patients receiving a treatment (in square brackets). Each line represents a type of head-to-head comparison. The width of lines is proportional to the number of trials comparing the connected treatments. EGFR=epidermal growth factor receptor; PbCT=pemetrexed-based chemotherapy; PfCT=pemetrexed-free chemotherapy.

A

Progression-free Survival

Overall Survival									
Osi	**0.74 (0.55 to 0.99)**	**0.59 (0.45 to 0.77)**	**0.48 (0.40 to 0.58)**	**0.43 (0.36 to 0.52)**	**0.56 (0.33 to 0.96)**	0.80 (0.53 to 1.21)	0.88 (0.66 to 1.19)	**0.34 (0.23 to 0.51)**	**0.16 (0.13 to 0.20)**
1.21 (0.83 to 1.75)	**Dac**	0.80 (0.58 to 1.10)	**0.66 (0.49 to 0.88)**	**0.59 (0.47 to 0.74)**	0.76 (0.44 to 1.34)	1.09 (0.67 to 1.75)	1.20 (0.86 to 1.67)	**0.47 (0.30 to 0.72)**	**0.22 (0.17 to 0.30)**
1.32 (0.97 to 1.81)	1.10 (0.78 to 1.54)	**Afa**	0.82 (0.63 to 1.07)	**0.74 (0.60 to 0.91)**	0.96 (0.61 to 1.52)	1.36 (0.87 to 2.16)	**1.50 (1.10 to 2.06)**	**0.58 (0.44 to 0.78)**	**0.28 (0.22 to 0.35)**
1.59 (1.23 to 2.06)	1.32 (0.94 to 1.87)	1.21 (0.93 to 1.57)	**Erl**	0.90 (0.75 to 1.08)	1.17 (0.69 to 1.99)	**1.66 (1.14 to 2.41)**	**1.83 (1.36 to 2.47)**	0.71 (0.48 to 1.06)	**0.34 (0.28 to 0.41)**
1.58 (1.23 to 2.04)	**1.31 (1.00 to 1.72)**	1.20 (0.98 to 1.47)	0.99 (0.81 to 1.23)	**Gef**	1.30 (0.79 to 2.16)	**1.84 (1.22 to 2.81)**	**2.04 (1.61 to 2.58)**	0.79 (0.55 to 1.14)	**0.38 (0.32 to 0.45)**
1.64 (0.98 to 2.77)	1.37 (0.80 to 2.33)	1.25 (0.82 to 1.88)	1.03 (0.64 to 1.68)	1.04 (0.66 to 1.65)	**Ico**	1.43 (0.75 to 2.74)	1.58 (0.91 to 2.76)	**0.61 (0.43 to 0.87)**	**0.29 (0.18 to 0.49)**
-	-	-	-	-	-	**Erl+Bev**	1.11 (0.69 to 1.79)	**0.43 (0.25 to 0.74)**	**0.21 (0.14 to 0.31)**
1.10 (0.75 to 1.63)	0.92 (0.61 to 1.37)	0.84 (0.59 to 1.20)	**0.69 (0.48 to 0.99)**	**0.70 (0.52 to 0.94)**	0.67 (0.39 to 1.16)	-	**Gef+PbCT**	**0.39 (0.25 to 0.60)**	**0.19 (0.14 to 0.25)**
1.69 (1.11 to 2.60)	1.41 (0.90 to 2.20)	1.28 (0.96 to 1.72)	1.06 (0.72 to 1.57)	1.07 (0.75 to 1.53)	1.03 (0.77 to 1.38)	-	1.54 (0.98 to 2.44)	**PbCT**	**0.48 (0.33 to 0.69)**
1.54 (1.17 to 2.04)	1.28 (0.93 to 1.77)	1.17 (0.95 to 1.44)	0.97 (0.80 to 1.17)	0.97 (0.82 to 1.17)	0.94 (0.59 to 1.49)	-	**1.40 (1.00 to 1.97)**	0.91 (0.64 to 1.31)	**PfCT**

B

Grade ≥3 Adverse Events

Objective Response Rate									
Osi	0.28 (0.03 to 2.64)	0.40 (0.07 to 2.39)	0.61 (0.15 to 2.63)	0.70 (0.17 to 2.92)	2.66 (0.12 to 62.22)	**0.07 (0.01 to 0.76)**	0.17 (0.02 to 1.61)	0.41 (0.03 to 5.09)	**0.17 (0.04 to 0.77)**
0.97 (0.15 to 6.66)	**Dac**	1.40 (0.15 to 13.03)	2.17 (0.24 to 21.17)	2.49 (0.45 to 13.85)	9.61 (0.33 to 276.52)	0.26 (0.02 to 4.76)	0.61 (0.05 to 6.87)	1.47 (0.09 to 24.70)	0.60 (0.07 to 5.09)
1.46 (0.29 to 7.01)	1.51 (0.21 to 9.60)	**Afa**	1.55 (0.31 to 7.84)	1.76 (0.43 to 6.98)	6.75 (0.52 to 90.50)	0.19 (0.02 to 2.15)	0.44 (0.05 to 3.97)	1.04 (0.19 to 6.11)	0.43 (0.11 to 1.67)
0.77 (0.23 to 2.54)	0.79 (0.13 to 4.63)	0.53 (0.14 to 2.04)	**Erl**	1.14 (0.27 to 4.82)	4.34 (0.22 to 91.86)	**0.12 (0.02 to 0.74)**	0.28 (0.03 to 2.63)	0.67 (0.06 to 7.20)	**0.28 (0.10 to 0.72)**
0.81 (0.26 to 2.69)	0.85 (0.18 to 3.69)	0.56 (0.18 to 1.75)	1.06 (0.43 to 2.67)	**Gef**	3.83 (0.22 to 71.23)	0.11 (0.01 to 1.06)	0.25 (0.04 to 1.37)	0.59 (0.07 to 5.57)	**0.24 (0.07 to 0.86)**
-	-	-	-	-	**Ico**	**0.03 (0.00 to 0.93)**	0.06 (0.00 to 1.91)	**0.15 (0.02 to 1.00)**	0.06 (0.00 to 1.11)
1.05 (0.15 to 6.96)	1.07 (0.11 to 10.71)	0.72 (0.10 to 5.51)	1.36 (0.30 to 6.69)	1.27 (0.23 to 7.60)	-	**Erl+Bev**	2.33 (0.13 to 41.14)	5.59 (0.28 to 110.56)	2.31 (0.28 to 17.61)
2.21 (0.35 to 13.69)	2.32 (0.26 to 18.45)	1.52 (0.25 to 10.30)	2.87 (0.54 to 16.56)	2.71 (0.64 to 12.09)	-	2.13 (0.20 to 20.62)	**Gef+PbCT**	0.41 (0.02 to 7.03)	1.01 (0.12 to 8.81)
0.33 (0.04 to 2.85)	0.34 (0.03 to 3.72)	**0.23 (0.05 to 1.00)**	0.42 (0.06 to 3.16)	0.40 (0.06 to 2.65)	-	0.32 (0.02 to 3.71)	0.15 (0.01 to 1.48)	**PbCT**	0.42 (0.04 to 3.70)
0.21 (0.06 to 0.77)	0.21 (0.04 to 1.12)	**0.14 (0.05 to 0.43)**	**0.27 (0.12 to 0.61)**	**0.25 (0.11 to 0.58)**	-	0.20 (0.03 to 1.04)	**0.09 (0.02 to 0.50)**	0.63 (0.10 to 4.17)	**PfCT**

C

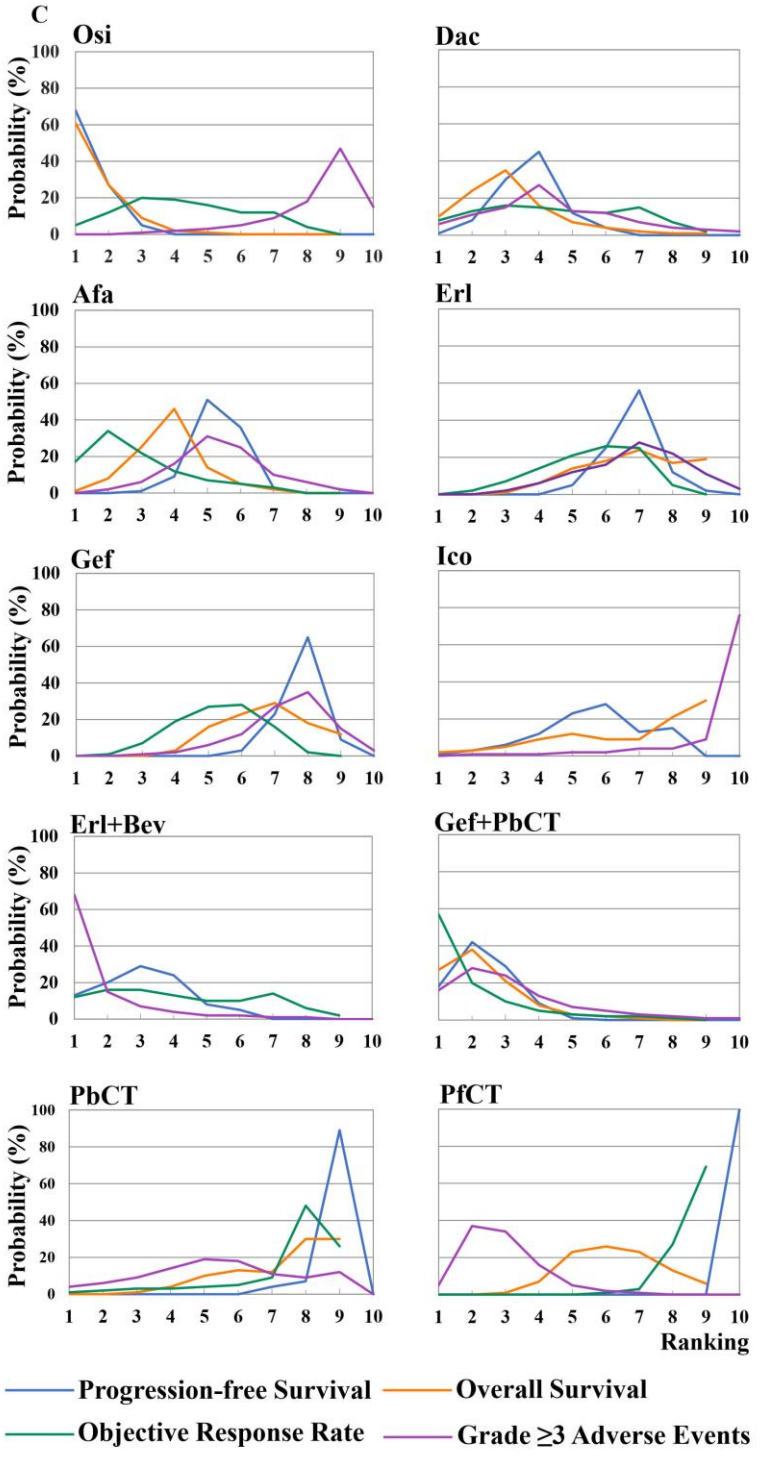


Figure S9: Pooled estimates of the first sensitivity analysis including only phase III trials.

A. Pooled hazard ratios (95% credible intervals) for progression-free survival (upper triangle) and overall survival (lower triangle). **B.** Pooled odds ratios (95% credible intervals) for grade ≥3 adverse events (upper triangle) and objective response rate (lower triangle). Result in each cell is presented as hazard ratio or odds ratio (95% credible interval) for the comparison of row-defining treatment versus column-defining treatment. Hazard ratio <1 and odds ratio >1 favor row-defining treatment. Significant results are in bold and underlined. **C.** Ranking curves indicating the probability of each comparable treatment being ranked from first to last on progression-free survival (blue line), overall survival (orange line), objective response rate (green line) and grade ≥3 adverse events (purple line). Ranking curves are described according to the Bayesian ranking results presented in Supplementary Table 4. Osi=osimertinib; Dac=dacomitinib; Afa=afatinib; Erl=erlotinib; Gef=gefitinib; Ico=icotinib; Bev=bevacizumab; PbCT=pemetrexed-based chemotherapy; PfCT=pemetrexed-free chemotherapy.

A

Progression-free Survival (exon 19 deletion)

Progression-free Survival (Leu858Arg)								
Osi	0.73 (0.50 to 1.07)	**0.53 (0.37 to 0.76)**	**0.47 (0.36 to 0.59)**	**0.40 (0.31 to 0.51)**	**0.23 (0.10 to 0.51)**	0.68 (0.38 to 1.21)	**0.15 (0.08 to 0.27)**	**0.11 (0.08 to 0.15)**
1.21 (0.77 to 1.92)	**Dac**	0.73 (0.48 to 1.10)	**0.64 (0.42 to 0.97)**	**0.55 (0.41 to 0.74)**	**0.31 (0.14 to 0.71)**	0.93 (0.47 to 1.82)	**0.21 (0.11 to 0.38)**	**0.15 (0.10 to 0.22)**
1.41 (0.93 to 2.14)	1.17 (0.72 to 1.89)	**Afa**	0.88 (0.60 to 1.28)	**0.75 (0.56 to 1.00)**	**0.43 (0.21 to 0.87)**	1.27 (0.66 to 2.42)	**0.28 (0.18 to 0.44)**	**0.21 (0.15 to 0.28)**
1.99 (1.49 to 2.66)	**1.64 (1.01 to 2.68)**	1.41 (0.92 to 2.17)	**Erl**	0.86 (0.64 to 1.15)	0.49 (0.22 to 1.09)	1.45 (0.85 to 2.45)	**0.32 (0.18 to 0.58)**	**0.24 (0.18 to 0.31)**
1.92 (1.43 to 2.56)	**1.59 (1.11 to 2.26)**	1.36 (0.98 to 1.89)	0.97 (0.69 to 1.35)	**Gef**	0.57 (0.27 to 1.23)	1.70 (0.92 to 3.08)	**0.37 (0.22 to 0.64)**	**0.28 (0.21 to 0.36)**
1.47 (0.63 to 3.46)	1.22 (0.50 to 2.94)	1.04 (0.50 to 2.18)	0.74 (0.32 to 1.75)	0.77 (0.34 to 1.73)	**Ico**	**2.98 (1.14 to 7.81)**	0.66 (0.38 to 1.14)	0.48 (0.22 to 1.06)
1.14 (0.61 to 2.12)	0.94 (0.45 to 1.96)	0.80 (0.40 to 1.62)	**0.57 (0.33 to 0.99)**	0.59 (0.31 to 1.13)	0.78 (0.28 to 2.13)	**Erl+Bev**	**0.22 (0.10 to 0.49)**	**0.16 (0.09 to 0.30)**
1.93 (1.03 to 3.62)	1.59 (0.81 to 3.12)	1.37 (0.85 to 2.18)	0.97 (0.51 to 1.83)	1.01 (0.57 to 1.78)	1.32 (0.74 to 2.32)	1.70 (0.73 to 3.93)	**PbCT**	0.74 (0.42 to 1.28)
4.67 (3.32 to 6.56)	**3.85 (2.44 to 6.06)**	**3.30 (2.31 to 4.73)**	**2.34 (1.73 to 3.18)**	**2.43 (1.83 to 3.23)**	**3.21 (1.41 to 7.23)**	**4.12 (2.18 to 7.67)**	**2.43 (1.33 to 4.36)**	**PfCT**

B

Overall Survival (exon 19 deletion)

Overall Survival (Leu858Arg)						
Dac	1.13 (0.70 to 1.82)	0.75 (0.43 to 1.31)	0.88 (0.61 to 1.27)	0.74 (0.35 to 1.55)	0.61 (0.33 to 1.12)	0.77 (0.48 to 1.25)
1.43 (0.86 to 2.38)	**Afa**	**0.66 (0.44 to 1.00)**	0.78 (0.58 to 1.04)	0.65 (0.37 to 1.15)	**0.54 (0.36 to 0.80)**	**0.68 (0.51 to 0.92)**
1.30 (0.71 to 2.36)	0.91 (0.57 to 1.44)	**Erl**	1.18 (0.78 to 1.78)	0.99 (0.49 to 1.98)	0.82 (0.46 to 1.44)	1.03 (0.77 to 1.37)
1.41 (0.95 to 2.08)	0.98 (0.71 to 1.36)	1.08 (0.69 to 1.71)	**Gef**	0.84 (0.44 to 1.59)	0.69 (0.42 to 1.13)	0.88 (0.65 to 1.19)
1.26 (0.55 to 2.87)	0.88 (0.46 to 1.69)	0.97 (0.44 to 2.15)	0.89 (0.43 to 1.85)	**Ico**	0.83 (0.55 to 1.25)	1.05 (0.55 to 1.99)
1.11 (0.55 to 2.23)	0.77 (0.47 to 1.26)	0.85 (0.44 to 1.66)	0.79 (0.44 to 1.41)	0.88 (0.57 to 1.35)	**PbCT**	1.27 (0.78 to 2.08)
1.32 (0.80 to 2.19)	0.92 (0.66 to 1.29)	1.02 (0.74 to 1.40)	0.94 (0.68 to 1.30)	1.06 (0.51 to 2.18)	1.20 (0.66 to 2.16)	**PfCT**

C

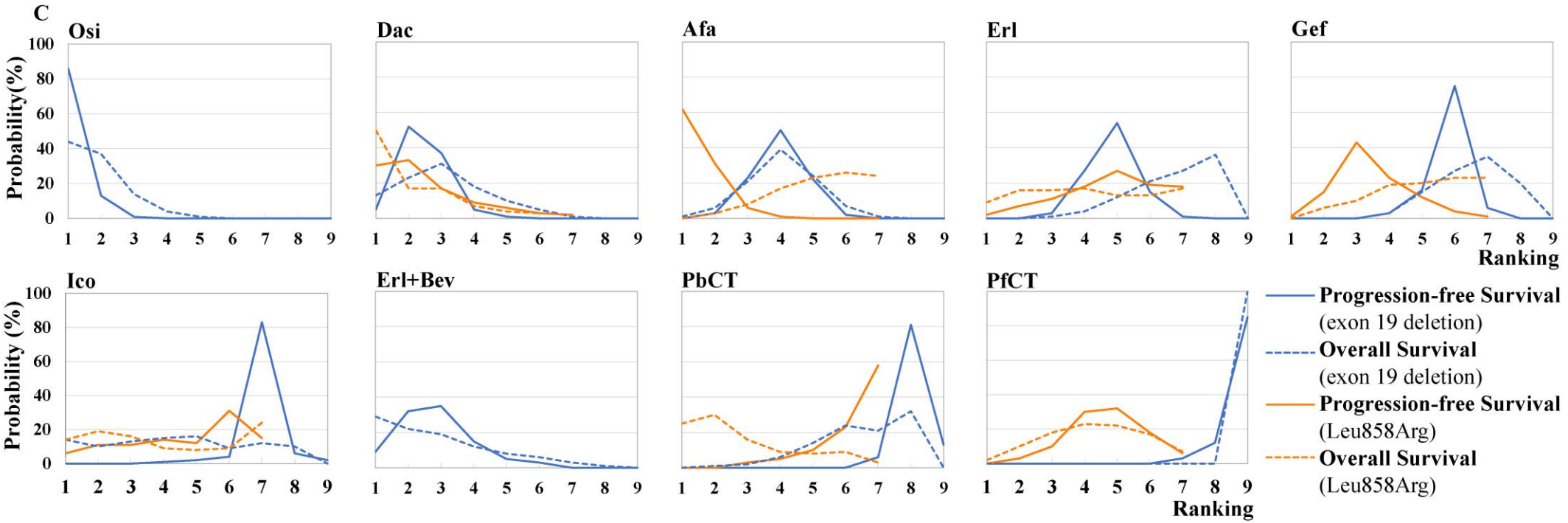
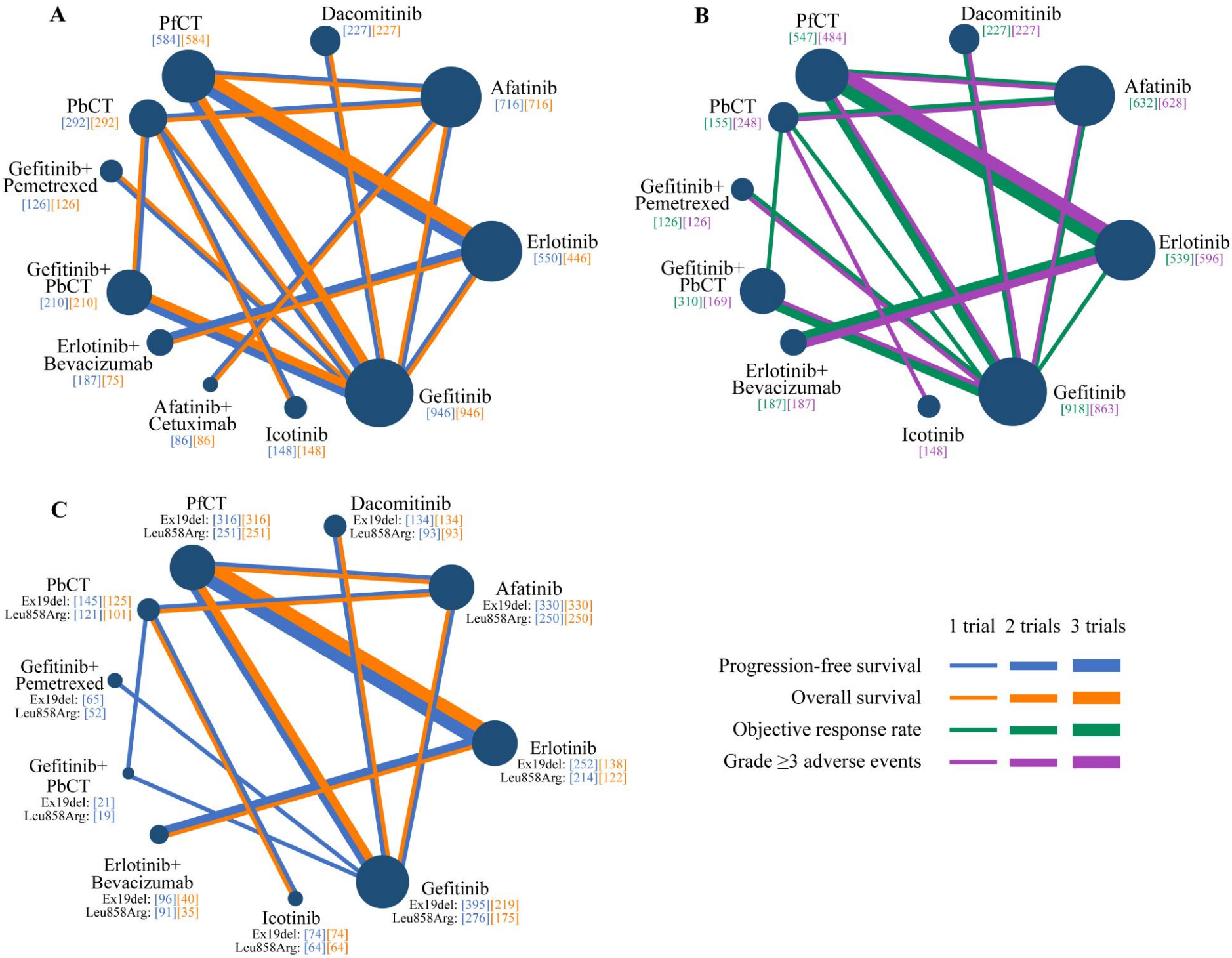


Figure S10: Pooled estimates of first sensitivity analysis (exon 19 deletion and Leu858Arg subpopulation) including only phase III trials.

A. Pooled hazard ratios (95% credible intervals) for progression-free survival of exon 19 deletion (upper triangle) and Leu858Arg (lower triangle) subpopulations. **B.** Pooled hazard ratios (95% credible intervals) for overall survival of exon 19 deletion (upper triangle) and Leu858Arg (lower triangle) subpopulations. Result in each cell is presented as hazard ratio (95% credible interval) for the comparison of row-defining treatment versus column-defining treatment. Hazard ratio <1 favors row-defining treatment. Significant results are in bold and underlined. **C.** Ranking curves indicating the probability of each comparable treatment being ranked from first to last on progression-free survival (solid line) and overall survival (dotted line) of exon 19 deletion (blue line) and Leu858Arg (orange line) subpopulations. Ranking curves are described according to the Bayesian ranking results presented in Supplementary Table 4. Osi=osimertinib; Dac=dacomitinib; Afa=afatinib; Erl=erlotinib; Gef=gefitinib; Ico=icotinib; Bev=bevacizumab; PbCT=pemetrexed-based chemotherapy; PfCT=pemetrexed-free chemotherapy.


A
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Afatinib
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PbCT
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Gefitinib+
Pemetrexed
[126][126]
Erlotinib
[550][446]
Gefitinib+
PbCT
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Erlotinib+
Bevacizumab
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Afatinib+
Cetuximab
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Icotinib
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Afatinib
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PbCT
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Leu858Arg: [251][251]
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PbCT
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PbCT
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Erlotinib+
Bevacizumab
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Gefitinib
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Icotinib
Ex19del: [74][74]
Leu858Arg: [64][64]
1 trial
2 trials
3 trials
Progression-free survival
Overall survival
Objective response rate
Grade ≥3 adverse events

Figure S11. Network diagrams for the second sensitivity analysis excluding the FLAURA study.

A. Comparisons on progression-free survival (blue line) and overall survival (orange line) in advanced EGFR-mutated patients. **B.** Comparisons on objective response rate (green line) and grade ≥3 adverse events (purple line) in advanced EGFR-mutated patients. **C.** Comparisons on progression-free survival (blue line) and overall survival (orange line) in exon 19 deletion and Leu858Arg subpopulations. Each circular node represents a type of treatment. The node size is proportional to the total number of patients receiving a treatment (in square brackets). Each line represents a type of head-to-head comparison. The width of lines is proportional to the number of trials comparing the connected treatments. PbCT=pemetrexed-based chemotherapy; PfCT=pemetrexed-free chemotherapy; EGFR=epidermal growth factor receptor.

A **Progression-free Survival**

Overall Survival

Dac	**0.71 (0.52 to 0.96)**	**0.68 (0.49 to 0.95)**	**0.59 (0.47 to 0.74)**	**0.53 (0.32 to 0.88)**	**0.61 (0.37 to 0.99)**	1.20 (0.78 to 1.83)	1.28 (0.94 to 1.74)	0.87 (0.57 to 1.34)	**0.32 (0.22 to 0.46)**	**0.22 (0.16 to 0.30)**
1.10 (0.78 to 1.54)	**Afa**	0.97 (0.73 to 1.28)	0.83 (0.68 to 1.01)	0.75 (0.49 to 1.15)	0.86 (0.58 to 1.27)	**1.69 (1.15 to 2.49)**	**1.81 (1.38 to 2.37)**	1.24 (0.83 to 1.85)	**0.46 (0.36 to 0.58)**	**0.31 (0.25 to 0.39)**
1.33 (0.92 to 1.91)	1.21 (0.92 to 1.58)	**Erl**	0.86 (0.69 to 1.09)	0.77 (0.47 to 1.27)	0.89 (0.55 to 1.44)	**1.75 (1.34 to 2.29)**	**1.87 (1.38 to 2.54)**	1.28 (0.84 to 1.95)	**0.47 (0.34 to 0.66)**	**0.32 (0.26 to 0.40)**
1.31 (0.99 to 1.73)	1.19 (0.98 to 1.45)	0.99 (0.78 to 1.25)	**Gef**	0.90 (0.57 to 1.41)	1.03 (0.67 to 1.60)	**2.03 (1.43 to 2.89)**	**2.17 (1.77 to 2.65)**	**1.49 (1.04 to 2.11)**	**0.55 (0.42 to 0.71)**	**0.37 (0.31 to 0.45)**
1.38 (0.84 to 2.26)	1.26 (0.85 to 1.85)	1.04 (0.66 to 1.65)	1.05 (0.70 to 1.58)	**Ico**	1.16 (0.65 to 2.08)	**2.28 (1.30 to 4.01)**	**2.44 (1.52 to 3.90)**	1.67 (0.95 to 2.95)	**0.61 (0.43 to 0.87)**	**0.42 (0.26 to 0.67)**
1.36 (0.64 to 2.92)	1.23 (0.62 to 2.45)	1.03 (0.49 to 2.14)	1.03 (0.51 to 2.11)	0.98 (0.45 to 2.17)	**Afa+Cet**	**1.98 (1.14 to 3.43)**	**2.12 (1.32 to 3.40)**	1.45 (0.83 to 2.54)	**0.53 (0.34 to 0.85)**	**0.37 (0.23 to 0.57)**
1.07 (0.62 to 1.86)	0.98 (0.60 to 1.60)	0.81 (0.54 to 1.22)	0.82 (0.51 to 1.31)	0.78 (0.42 to 1.44)	0.80 (0.34 to 1.84)	**Erl+Bev**	1.07 (0.72 to 1.61)	0.74 (0.45 to 1.21)	**0.27 (0.18 to 0.42)**	**0.19 (0.13 to 0.26)**
0.78 (0.54 to 1.14)	**0.71 (0.53 to 0.96)**	**0.59 (0.42 to 0.83)**	**0.60 (0.47 to 0.76)**	**0.57 (0.36 to 0.89)**	0.58 (0.28 to 1.22)	0.73 (0.43 to 1.25)	**Gef+PbCT**	0.69 (0.46 to 1.03)	**0.25 (0.19 to 0.34)**	**0.17 (0.13 to 0.23)**
1.01 (0.60 to 1.68)	0.92 (0.57 to 1.47)	0.76 (0.47 to 1.25)	0.77 (0.50 to 1.19)	0.73 (0.40 to 1.32)	0.75 (0.33 to 1.72)	0.95 (0.49 to 1.79)	1.29 (0.78 to 2.12)	**Gef+P**	**0.37 (0.24 to 0.58)**	**0.25 (0.17 to 0.38)**
1.42 (0.96 to 2.11)	**1.30 (1.01 to 1.67)**	1.08 (0.76 to 1.52)	1.09 (0.82 to 1.44)	1.03 (0.77 to 1.39)	1.06 (0.51 to 2.18)	1.33 (0.77 to 2.27)	**1.82 (1.29 to 2.57)**	1.41 (0.84 to 2.36)	**PbCT**	**0.69 (0.51 to 0.93)**
1.28 (0.92 to 1.79)	1.17 (0.95 to 1.43)	0.97 (0.79 to 1.18)	0.98 (0.81 to 1.17)	0.93 (0.61 to 1.42)	0.95 (0.46 to 1.93)	1.20 (0.75 to 1.89)	**1.64 (1.21 to 2.22)**	1.27 (0.79 to 2.03)	0.90 (0.66 to 1.22)	**PfCT**

B **Grade ≥3 Adverse Events**

Objective Response Rate

Dac	1.25 (0.12 to 10.64)	1.47 (0.13 to 11.76)	2.47 (0.42 to 14.19)	8.41 (0.26 to 240.30)	0.18 (0.01 to 1.99)	0.61 (0.05 to 7.05)	0.75 (0.06 to 9.75)	1.31 (0.07 to 20.79)	0.47 (0.05 to 3.52)
1.35 (0.39 to 4.53)	**Afa**	1.19 (0.22 to 5.46)	1.99 (0.53 to 8.61)	6.74 (0.52 to 93.35)	0.14 (0.02 to 1.02)	0.48 (0.05 to 4.88)	0.61 (0.07 to 6.56)	1.05 (0.18 to 6.16)	0.38 (0.09 to 1.43)
0.75 (0.22 to 2.55)	0.56 (0.23 to 1.34)	**Erl**	1.69 (0.48 to 7.83)	5.69 (0.30 to 133.80)	**0.12 (0.03 to 0.44)**	0.41 (0.05 to 4.47)	0.52 (0.06 to 6.10)	0.88 (0.09 to 10.48)	**0.32 (0.12 to 0.86)**
0.84 (0.31 to 2.31)	0.62 (0.32 to 1.26)	1.12 (0.56 to 2.31)	**Gef**	3.38 (0.17 to 61.40)	**0.07 (0.01 to 0.41)**	0.24 (0.04 to 1.42)	0.31 (0.05 to 1.96)	0.53 (0.05 to 4.69)	**0.19 (0.05 to 0.59)**
-	-	-	-	**Ico**	**0.02 (0.00 to 0.52)**	0.07 (0.00 to 2.29)	0.09 (0.00 to 3.03)	**0.16 (0.02 to 1.00)**	**0.06 (0.00 to 0.98)**
0.99 (0.23 to 4.19)	0.74 (0.23 to 2.38)	1.33 (0.61 to 2.89)	1.18 (0.41 to 3.33)	-	**Erl+Bev**	3.44 (0.30 to 53.57)	4.30 (0.36 to 72.43)	7.38 (0.54 to 124.10)	2.68 (0.54 to 13.94)
2.30 (0.68 to 7.98)	1.71 (0.67 to 4.48)	**3.09 (1.14 to 8.60)**	**2.75 (1.33 to 5.74)**	-	2.33 (0.66 to 8.42)	**Gef+PbCT**	1.25 (0.10 to 16.01)	2.16 (0.12 to 35.36)	0.78 (0.08 to 5.88)
1.20 (0.27 to 5.49)	0.89 (0.24 to 3.43)	1.60 (0.42 to 6.24)	1.43 (0.46 to 4.49)	-	1.20 (0.26 to 5.83)	0.52 (0.13 to 2.02)	**Gef+P**	1.72 (0.09 to 29.32)	0.62 (0.06 to 5.02)
0.26 (0.07 to 0.89)	**0.19 (0.08 to 0.41)**	**0.34 (0.12 to 0.92)**	**0.31 (0.13 to 0.65)**	-	**0.26 (0.07 to 0.90)**	**0.11 (0.04 to 0.27)**	**0.21 (0.05 to 0.83)**	**PbCT**	0.36 (0.04 to 3.24)
0.20 (0.06 to 0.65)	**0.15 (0.07 to 0.32)**	**0.27 (0.15 to 0.49)**	**0.24 (0.13 to 0.44)**	-	**0.20 (0.08 to 0.55)**	**0.09 (0.03 to 0.22)**	**0.17 (0.05 to 0.61)**	0.77 (0.32 to 2.03)	**PfCT**

C

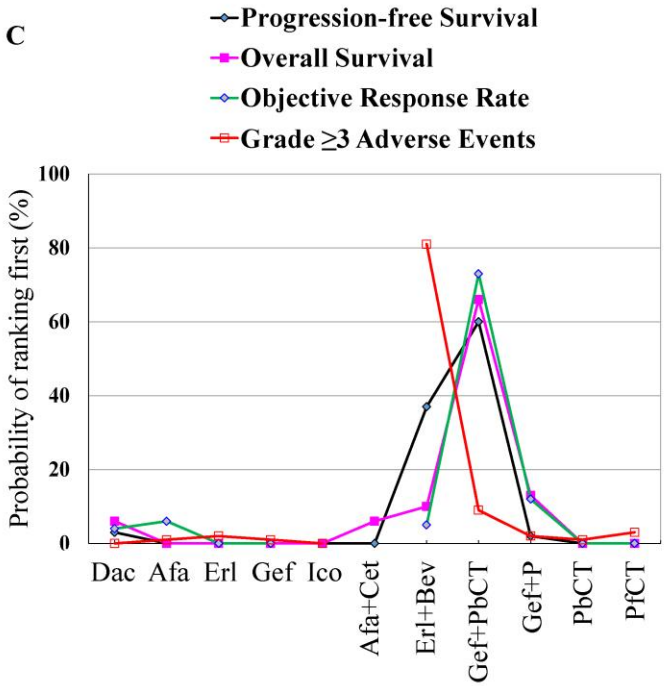


Figure S12: Pooled estimates of the second sensitivity analysis excluding the FLAURA study.

A. Pooled hazard ratios (95% credible intervals) for progression-free survival (upper triangle) and overall survival (lower triangle). **B.** Pooled odds ratios (95% credible intervals) for grade ≥3 adverse events (upper triangle) and objective response rate (lower triangle). Result in each cell is presented as hazard ratio or odds ratio (95% credible interval) for the comparison of row-defining treatment versus column-defining treatment. Hazard ratio <1 and odds ratio >1 favor row-defining treatment. Significant results are in bold and underlined. **C.** Ranking curves indicating the probability of each comparable treatment being ranked first on progression-free survival (black line), overall survival (pink line), objective response rate (green line) and grade ≥3 adverse events (red line). Dac=dacomitinib; Afa=afatinib; Erl=erlotinib; Gef=gefitinib; Ico=icotinib; Cet=cetuximab; Bev=bevacizumab; Gef+P= Gefitinib plus pemetrexed; PbCT=pemetrexed-based chemotherapy; PfCT=pemetrexed-free chemotherapy.

A

Leu858Arg \ Exon 19 deletion	Dac	Afa	Erl	Gef	Ico	Erl+Bev	Gef+PbCT	Gef+P	PbCT	PfCT
Dac	0.74 (0.49 to 1.11)	0.78 (0.46 to 1.33)	**0.55 (0.41 to 0.74)**	**0.30 (0.14 to 0.66)**	1.45 (0.75 to 2.81)	1.05 (0.54 to 2.03)	0.82 (0.48 to 1.41)	**0.20 (0.11 to 0.35)**	**0.16 (0.11 to 0.25)**
1.25 (0.78 to 2.02)	**Afa**	1.06 (0.66 to 1.70)	**0.75 (0.56 to 0.99)**	**0.41 (0.20 to 0.82)**	**1.97 (1.08 to 3.63)**	1.43 (0.78 to 2.63)	1.12 (0.66 to 1.90)	**0.27 (0.17 to 0.41)**	**0.22 (0.16 to 0.31)**
1.75 (0.97 to 3.17)	1.40 (0.84 to 2.34)	**Erl**	0.71 (0.45 to 1.10)	**0.39 (0.17 to 0.89)**	**1.87 (1.27 to 2.73)**	1.36 (0.66 to 2.80)	1.06 (0.56 to 1.99)	**0.25 (0.14 to 0.47)**	**0.21 (0.15 to 0.29)**
1.59 (1.12 to 2.26)	1.27 (0.92 to 1.76)	0.91 (0.56 to 1.48)	**Gef**	0.55 (0.26 to 1.14)	**2.65 (1.47 to 4.78)**	**1.92 (1.06 to 3.45)**	1.50 (0.95 to 2.35)	**0.36 (0.22 to 0.58)**	**0.30 (0.22 to 0.40)**
1.47 (0.63 to 3.45)	1.18 (0.57 to 2.42)	0.85 (0.35 to 2.03)	0.93 (0.43 to 2.01)	**Ico**	**4.88 (1.98 to 12.21)**	**3.54 (1.54 to 8.19)**	**2.76 (1.18 to 6.55)**	0.66 (0.38 to 1.14)	0.55 (0.26 to 1.18)
1.08 (0.53 to 2.20)	0.86 (0.45 to 1.65)	**0.62 (0.41 to 0.92)**	0.68 (0.37 to 1.27)	0.74 (0.28 to 1.93)	**Erl+Bev**	0.73 (0.32 to 1.65)	0.57 (0.27 to 1.19)	**0.14 (0.07 to 0.28)**	**0.11 (0.07 to 0.19)**
0.36 (0.18 to 0.74)	**0.29 (0.15 to 0.56)**	**0.21 (0.10 to 0.45)**	**0.23 (0.12 to 0.43)**	**0.25 (0.10 to 0.60)**	**0.34 (0.14 to 0.80)**	**Gef+PbCT**	0.79 (0.38 to 1.65)	**0.19 (0.10 to 0.35)**	**0.16 (0.08 to 0.30)**
0.93 (0.47 to 1.81)	0.74 (0.38 to 1.43)	0.53 (0.25 to 1.12)	0.58 (0.33 to 1.03)	0.63 (0.24 to 1.66)	0.86 (0.37 to 2.01)	**2.57 (1.10 to 6.00)**	**Gef+P**	**0.24 (0.12 to 0.47)**	**0.20 (0.12 to 0.35)**
1.93 (1.03 to 3.61)	1.55 (0.99 to 2.41)	1.11 (0.57 to 2.15)	1.22 (0.72 to 2.05)	1.32 (0.75 to 2.32)	1.80 (0.84 to 3.90)	**5.36 (2.73 to 10.56)**	2.10 (0.98 to 4.52)	**PbCT**	0.84 (0.50 to 1.42)
4.01 (2.50 to 6.45)	**3.21 (2.22 to 4.64)**	**2.30 (1.61 to 3.29)**	**2.53 (1.84 to 3.48)**	**2.75 (1.23 to 6.11)**	**3.73 (2.19 to 6.38)**	**11.16 (5.61 to 22.09)**	**4.36 (2.27 to 8.36)**	**2.09 (1.19 to 3.65)**	**PfCT**

B

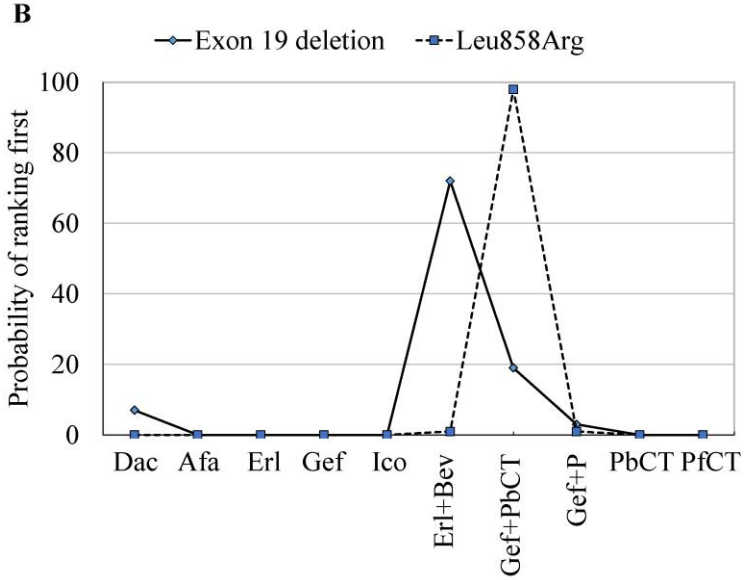
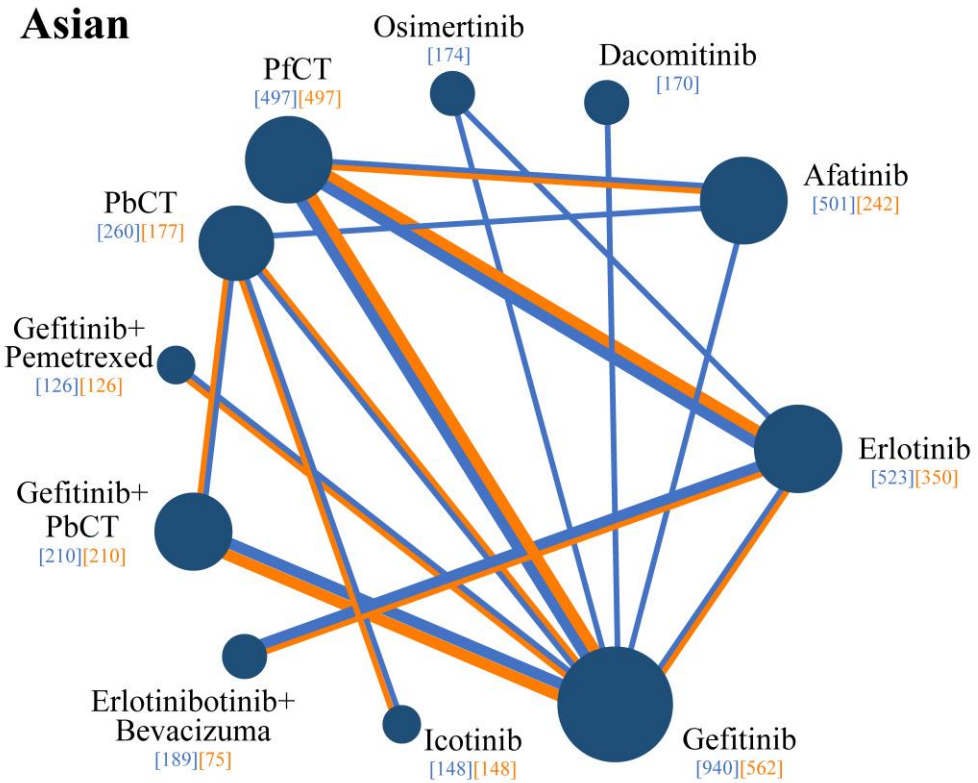


Figure S13: Pooled estimates (progression-free survival) of the second sensitivity analysis (exon 19 deletion and Leu858Arg subpopulation) excluding the FLAURA study.

A. Pooled hazard ratios (95% credible intervals) for exon 19 deletion (upper triangle) and Leu858Arg (lower triangle) subpopulations. Result in each cell is presented as hazard ratio (95% credible interval) for the comparison of row-defining treatment versus column-defining treatment. Hazard ratio <1 favor row-defining treatment. Significant results are in bold and underlined. **C.** Ranking curves indicating the probability of each comparable treatment being ranked first in exon 19 deletion (solid line) and Leu858Arg (dotted line) subpopulations. Dac=dacomitinib; Afa=afatinib; Erl=erlotinib; Gef=gefitinib; Ico=icotinib; Bev=bevacizumab; Gef+P=Gefitinib plus pemetrexed; PbCT=pemetrexed-based chemotherapy; PfCT=pemetrexed-free chemotherapy.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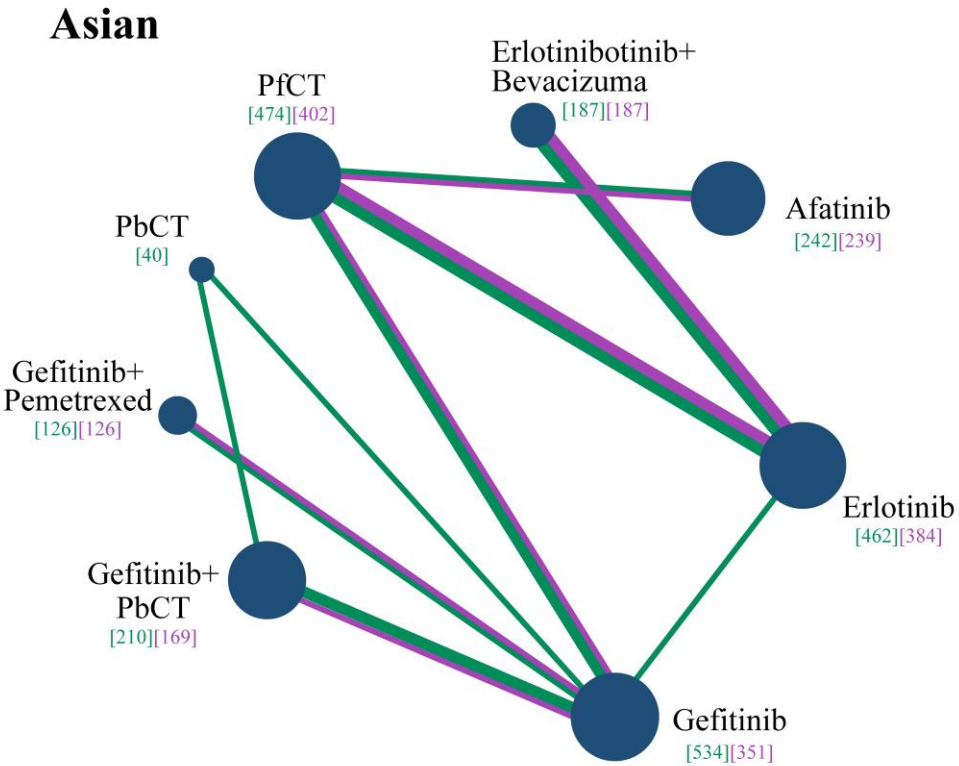
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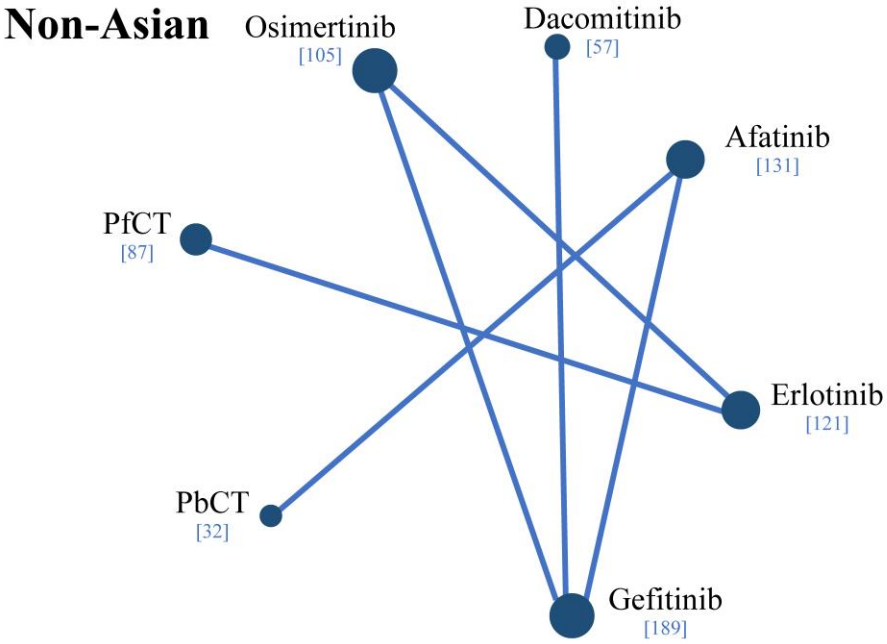
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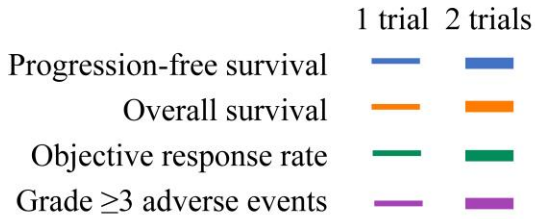

1 trial
2 trials
Progression-free survival
Overall survival
Objective response rate
Grade ≥3 adverse events

Figure S14. Network diagrams for the third sensitivity analysis stratifying patients by Asian and non-Asian.

A. Comparisons on progression-free survival (blue line) and overall survival (orange line) in Asian patients. **B.** Comparisons on objective response rate (green line) and grade ≥3 adverse events (purple line) in Asian patients. **C.** Comparisons on progression-free survival in non-Asian patients. Each circular node represents a type of treatment. The node size is proportional to the total number of patients receiving a treatment (in square brackets). Each line represents a type of head-to-head comparison. The width of lines is proportional to the number of trials comparing the connected treatments. PbCT=pemetrexed-based chemotherapy; PfCT=pemetrexed-free chemotherapy.

A Progression-free Survival (Asian)

Overall Survival (Asian)

Osi	1.01 (0.72 to 1.42)	**0.58 (0.42 to 0.78)**	**0.59 (0.47 to 0.73)**	**0.52 (0.41 to 0.64)**	**0.44 (0.27 to 0.73)**	1.03 (0.72 to 1.45)	1.11 (0.83 to 1.50)	0.77 (0.53 to 1.12)	**0.27 (0.19 to 0.38)**	**0.18 (0.14 to 0.24)**
-	Dac	**0.57 (0.41 to 0.81)**	**0.58 (0.42 to 0.81)**	**0.51 (0.40 to 0.66)**	**0.44 (0.26 to 0.74)**	1.02 (0.66 to 1.57)	1.10 (0.80 to 1.53)	0.77 (0.52 to 1.13)	**0.27 (0.18 to 0.39)**	**0.18 (0.13 to 0.25)**
-	-	Afa	1.02 (0.76 to 1.36)	0.90 (0.72 to 1.12)	0.77 (0.50 to 1.18)	**1.79 (1.19 to 2.65)**	**1.93 (1.44 to 2.58)**	1.34 (0.92 to 1.94)	**0.47 (0.36 to 0.60)**	**0.32 (0.25 to 0.41)**
-	-	1.26 (0.88 to 1.80)	Erl	0.88 (0.71 to 1.09)	0.75 (0.46 to 1.24)	**1.75 (1.33 to 2.30)**	**1.9 (1.42 to 2.54)**	1.32 (0.92 to 1.90)	**0.46 (0.33 to 0.65)**	**0.32 (0.25 to 0.40)**
-	-	1.27 (0.89 to 1.80)	1.01 (0.78 to 1.30)	Gef	0.86 (0.55 to 1.35)	**1.99 (1.41 to 2.81)**	**2.16 (1.76 to 2.64)**	**1.50 (1.11 to 2.01)**	**0.52 (0.39 to 0.69)**	**0.36 (0.30 to 0.43)**
-	-	1.36 (0.72 to 2.57)	1.08 (0.60 to 1.95)	1.07 (0.63 to 1.82)	Ico	**2.35 (1.33 to 4.11)**	**2.54 (1.58 to 4.08)**	**1.76 (1.03 to 3.02)**	**0.61 (0.43 to 0.87)**	**0.42 (0.26 to 0.67)**
-	-	1.02 (0.59 to 1.76)	0.81 (0.54 to 1.22)	0.81 (0.50 to 1.31)	0.75 (0.37 to 1.55)	Erl+Bev	1.09 (0.73 to 1.62)	0.76 (0.48 to 1.19)	**0.26 (0.17 to 0.41)**	**0.18 (0.13 to 0.26)**
-	-	0.76 (0.49 to 1.17)	**0.60 (0.42 to 0.86)**	**0.60 (0.47 to 0.77)**	**0.56 (0.33 to 0.96)**	0.75 (0.43 to 1.29)	Gef+PbCT	**0.70 (0.49 to 1.00)**	**0.24 (0.18 to 0.33)**	**0.17 (0.13 to 0.22)**
-	-	0.98 (0.56 to 1.71)	0.78 (0.47 to 1.28)	0.77 (0.50 to 1.19)	0.72 (0.36 to 1.43)	0.96 (0.50 to 1.84)	1.29 (0.78 to 2.13)	Gef+P	**0.35 (0.23 to 0.53)**	**0.24 (0.17 to 0.34)**
-	-	1.40 (0.80 to 2.46)	1.11 (0.67 to 1.85)	1.10 (0.71 to 1.71)	1.03 (0.77 to 1.39)	1.38 (0.71 to 2.66)	**1.84 (1.18 to 2.89)**	1.44 (0.78 to 2.67)	PbCT	**0.69 (0.51 to 0.93)**
-	-	1.21 (0.92 to 1.60)	0.96 (0.77 to 1.20)	0.95 (0.77 to 1.18)	0.89 (0.50 to 1.59)	1.19 (0.74 to 1.90)	**1.60 (1.14 to 2.23)**	1.24 (0.77 to 2.01)	0.87 (0.53 to 1.42)	PfCT

B Grade ≥3 Adverse Events (Asian)

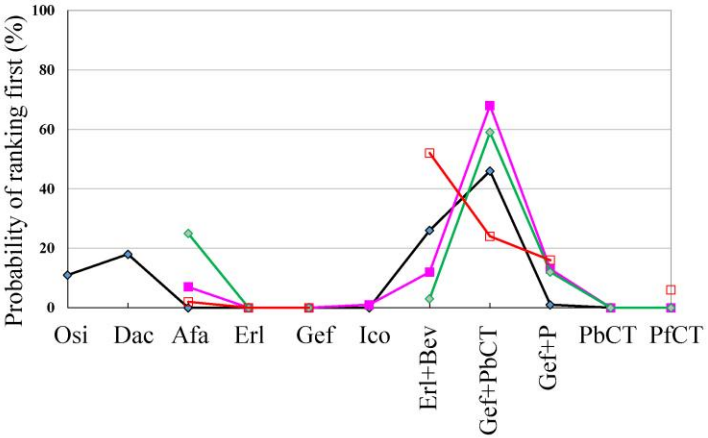
Objective Response Rate (Asian)

Dac	1.52 (0.24 to 9.55)	1.34 (0.16 to 11.05)	0.19 (0.02 to 1.63)	0.33 (0.03 to 4.31)	0.42 (0.03 to 5.82)	-	0.37 (0.09 to 1.63)
0.42 (0.09 to 1.66)	Afa	0.88 (0.14 to 5.69)	**0.12 (0.04 to 0.39)**	0.22 (0.02 to 2.33)	0.28 (0.02 to 3.16)	-	**0.24 (0.08 to 0.73)**
0.55 (0.12 to 2.30)	1.32 (0.55 to 3.40)	Erl	0.14 (0.02 to 1.24)	0.25 (0.06 to 1.07)	0.31 (0.06 to 1.51)	-	0.28 (0.06 to 1.25)
0.55 (0.09 to 2.82)	1.32 (0.53 to 3.27)	1.00 (0.27 to 3.44)	Gef	1.75 (0.13 to 24.34)	2.22 (0.15 to 32.80)	-	1.98 (0.41 to 9.57)
1.44 (0.25 to 7.66)	**3.48 (1.01 to 12.66)**	**2.63 (1.09 to 6.28)**	2.64 (0.58 to 12.80)	Ico	1.27 (0.15 to 10.98)	-	1.13 (0.14 to 9.28)
0.78 (0.10 to 5.30)	1.89 (0.39 to 9.68)	1.42 (0.38 to 5.32)	1.42 (0.24 to 9.26)	0.54 (0.11 to 2.60)	Erl+Bev	-	0.89 (0.10 to 7.86)
0.13 (0.02 to 0.81)	0.33 (0.08 to 1.42)	**0.25 (0.08 to 0.75)**	0.25 (0.05 to 1.41)	**0.09 (0.03 to 0.29)**	**0.17 (0.03 to 0.97)**	PbCT	-
0.15 (0.04 to 0.49)	**0.35 (0.17 to 0.83)**	**0.26 (0.12 to 0.60)**	**0.26 (0.09 to 0.94)**	**0.10 (0.03 to 0.34)**	**0.19 (0.04 to 0.88)**	1.08 (0.28 to 4.40)	PfCT

C Progression-free Survival (non-Asian)

Osi	**0.38 (0.21 to 0.69)**	**0.47 (0.27 to 0.81)**	**0.34 (0.23 to 0.49)**	**0.34 (0.23 to 0.49)**	**0.32 (0.15 to 0.69)**	**0.13 (0.07 to 0.22)**
	Dac	1.23 (0.68 to 2.24)	0.88 (0.44 to 1.77)	0.89 (0.56 to 1.39)	0.83 (0.37 to 1.88)	**0.33 (0.15 to 0.73)**
		Afa	0.72 (0.37 to 1.38)	0.72 (0.49 to 1.06)	0.67 (0.39 to 1.17)	**0.27 (0.12 to 0.57)**
			Erl	1.00 (0.59 to 1.69)	0.93 (0.40 to 2.22)	**0.37 (0.25 to 0.55)**
				Gef	0.94 (0.48 to 1.84)	**0.37 (0.19 to 0.72)**
					PbCT	0.39 (0.15 to 1.01)
						PfCT

D (Asian)



(non-Asian)

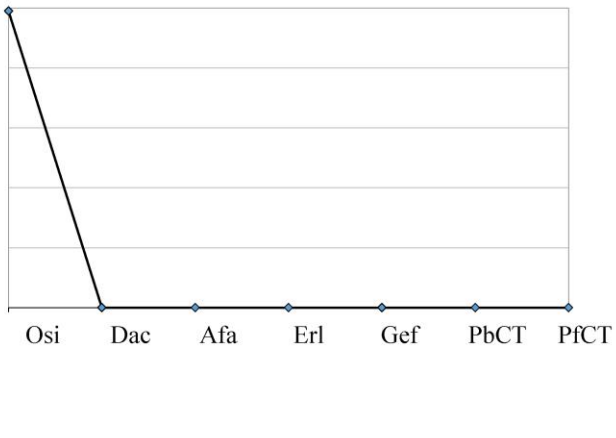


Figure S15: Pooled estimates of the third sensitivity analysis stratifying patients by Asian and non-Asian.

A. Pooled hazard ratios (95% credible intervals) for progression-free survival (upper triangle) and overall survival (lower triangle) for Asian patients. **B.** Pooled odds ratios (95% credible

intervals) for grade ≥3 adverse events (upper triangle) and objective response rate (lower triangle) for Asian patients. **C.** Pooled hazard ratios (95% credible intervals) for progression-free survival for non-Asian patients. Result in each cell is presented as hazard ratio or odds ratio (95% credible interval) for the comparison of row-defining treatment versus column-defining treatment. Hazard ratio <1 and odds ratio >1 favor row-defining treatment. Significant results are in bold and underlined. **D.** Ranking curves indicating the probability of each comparable treatment being ranked first on progression-free survival (black line), overall survival (pink line), objective response rate (green line) and grade ≥3 adverse events (red line) for Asian (left) and non-Asian (right) patients. Osi=osimertinib; Dac=dacomitinib; Afa=afatinib; Erl=erlotinib; Gef=gefitinib; Ico=icotinib; Bev=bevacizumab; Gef+P=Gefitinib plus pemetrexed; PbCT=pemetrexed-based chemotherapy; PfCT=pemetrexed-free chemotherapy.