IRCCS Sacro Cuore Don Calabria
Cancer Care Center Negrar - Verona

ESMO Designated Centers of Integrated Oncology and Palliative Care

Con il Patrocinio di

AIOM · RAO · SICO · Società Italiana di Psico-Oncologia

STUDI CLINICI: METODOLOGIA

Coordinatore
Dr.ssa Stefania Gori

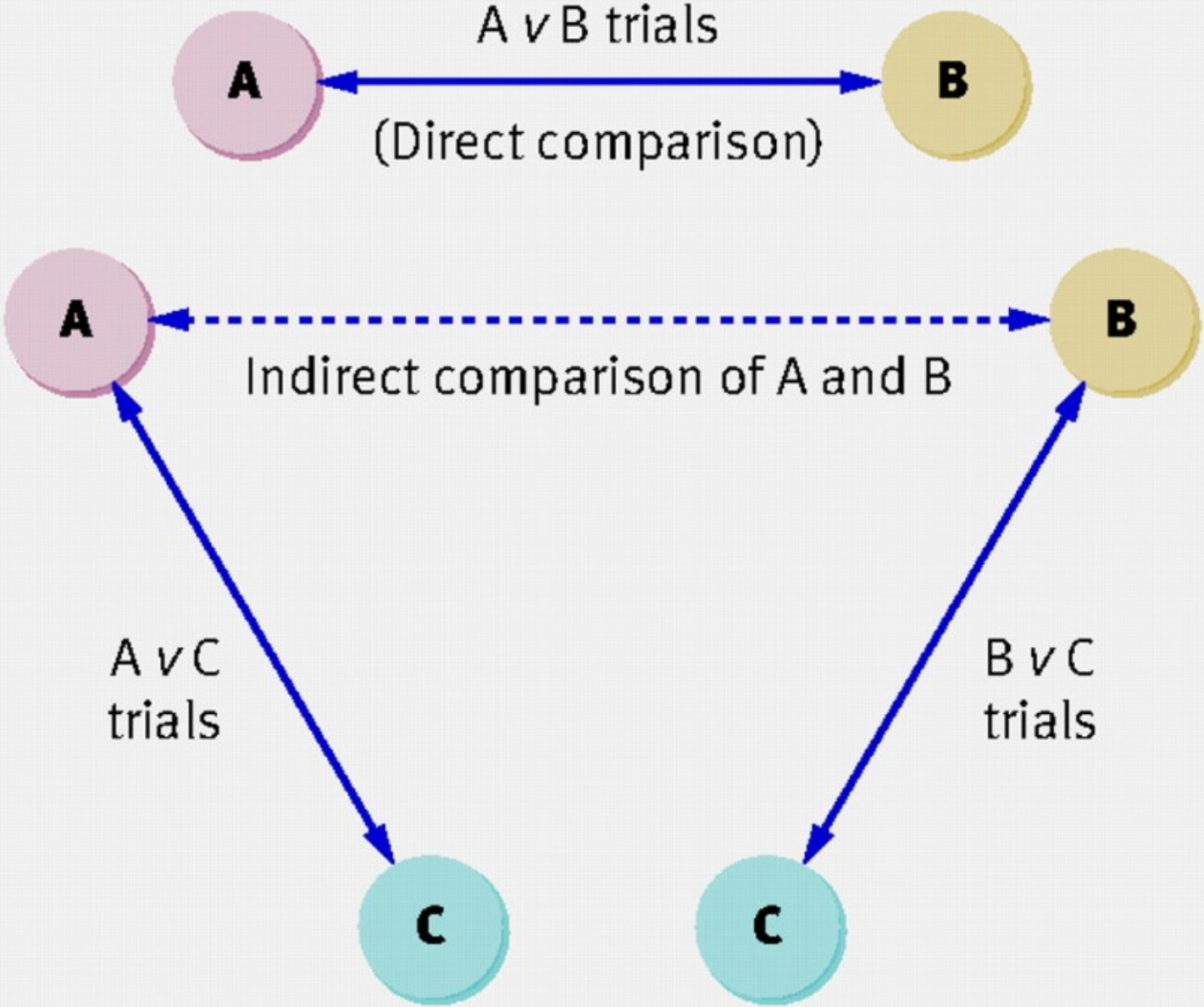
Evento ECM MODULO 2

FORMAZIONE AVANZATA

NEGRAR
8/9 Marzo
2019

Centro Formazione
IRCCS Ospedale Sacro Cuore
Don Calabria

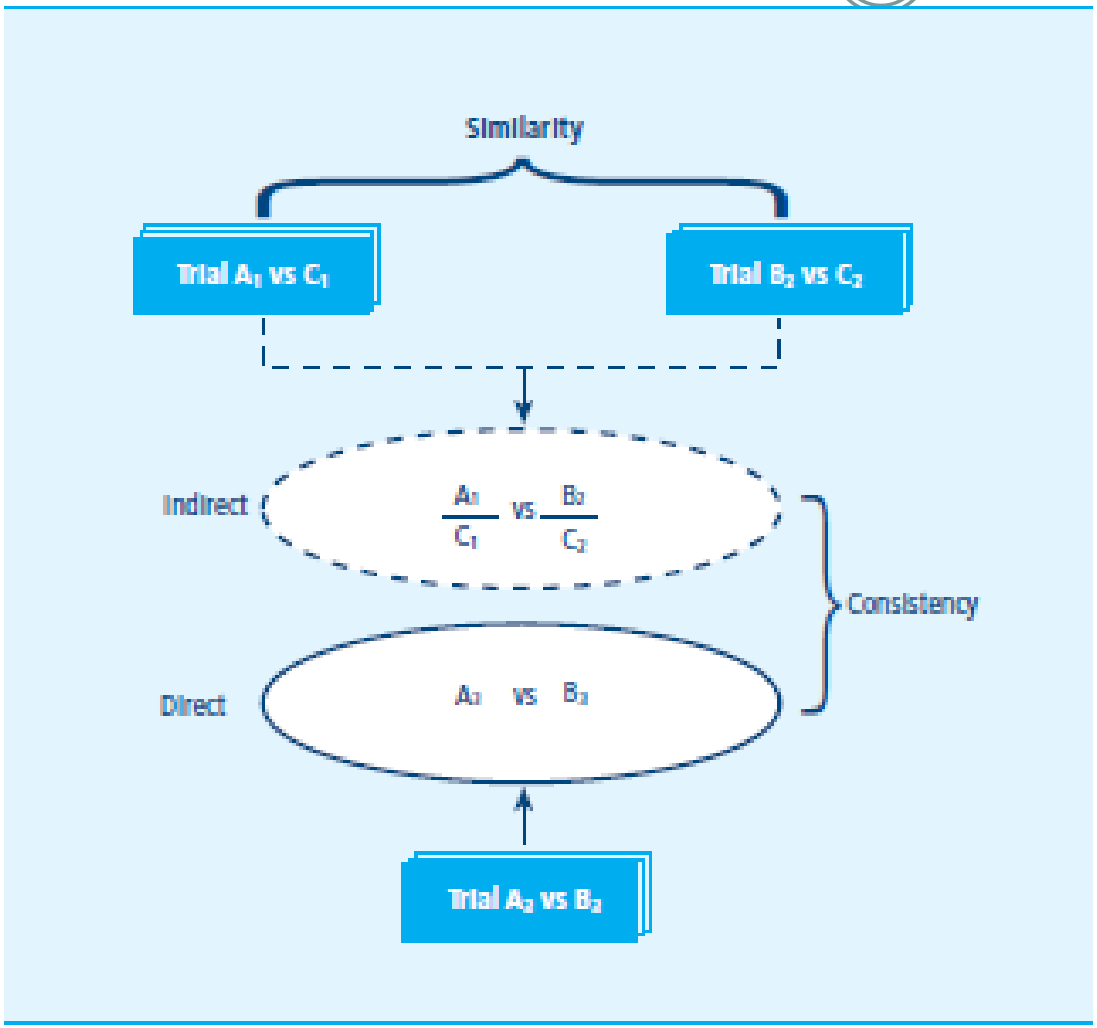
Confronti indiretti


A v B trials
A
B
(Direct comparison)
A
B
Indirect comparison of A and B
A v C
trials
B v C
trials
C
C

The best?

No head-to-head comparison

Head to Head vs. Indirect Comparisons



Head to Head comparison comes from a trial where A was directly compared to B.

Indirect Comparison comes from multiple studies where A and B may have been compared to the same comparator (i.e., C) but have never been compared to each other in the same study,

Indirect Comparisons

- **Indirect comparison refers to a comparison of different** healthcare interventions using data from separate studies, in contrast to a direct comparison within randomized controlled trials. Indirect comparison is often used because of a lack of, or insufficient, evidence from head-to-head comparative trials.

- **Naive indirect comparison is a comparison of the results of** individual arms from different trials as if they were from the same randomized trials. This method provides evidence equivalent to that of observational studies and should be avoided in the analysis of data from randomized trials.

- **Adjusted indirect comparison (including mixed treatment** comparison) is an indirect comparison of different treatments adjusted according to the results of their direct comparison with a common control, so that the strength of the randomized trials is preserved. Empirical evidence indicates that results of adjusted indirect comparison are usually, but not always, consistent with the results of direct comparison.

What is indirect comparison? Fujian Song BMed MMed PhD Reader in Research Synthesis, Faculty of Health, University of East Anglia
www.whatisseries.co.uk http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/What_is_ind_comp.pdf

Indirect Comparisons

Basic assumptions underlying indirect comparisons include:

- ✓ **homogeneity** assumption for standard meta-analysis,
- ✓ **similarity** assumption for adjusted indirect comparison and
- ✓ **consistency** assumption for the combination of direct and indirect evidence. It is essential to fully understand and appreciate these basic assumptions in order to use adjusted indirect and mixed treatment comparisons appropriately.

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Oncology
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Incorporating Geriatric Oncology

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Is there evidence for different effects among EGFR-TKIs? Systematic review and meta-analysis of EGFR tyrosine kinase inhibitors (TKIs) *versus* chemotherapy as first-line treatment for patients harboring EGFR mutations

Eva Regina Haspinger[a], Francesco Agustoni[a], Valter Torri[b], Francesco Gelsomino[a], Marco Platania[a], Nicoletta Zilembo[a], Rosaria Gallucci[a], Marina Chiara Garassino[a,*], Michela Cinquini[b]

[a] *Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
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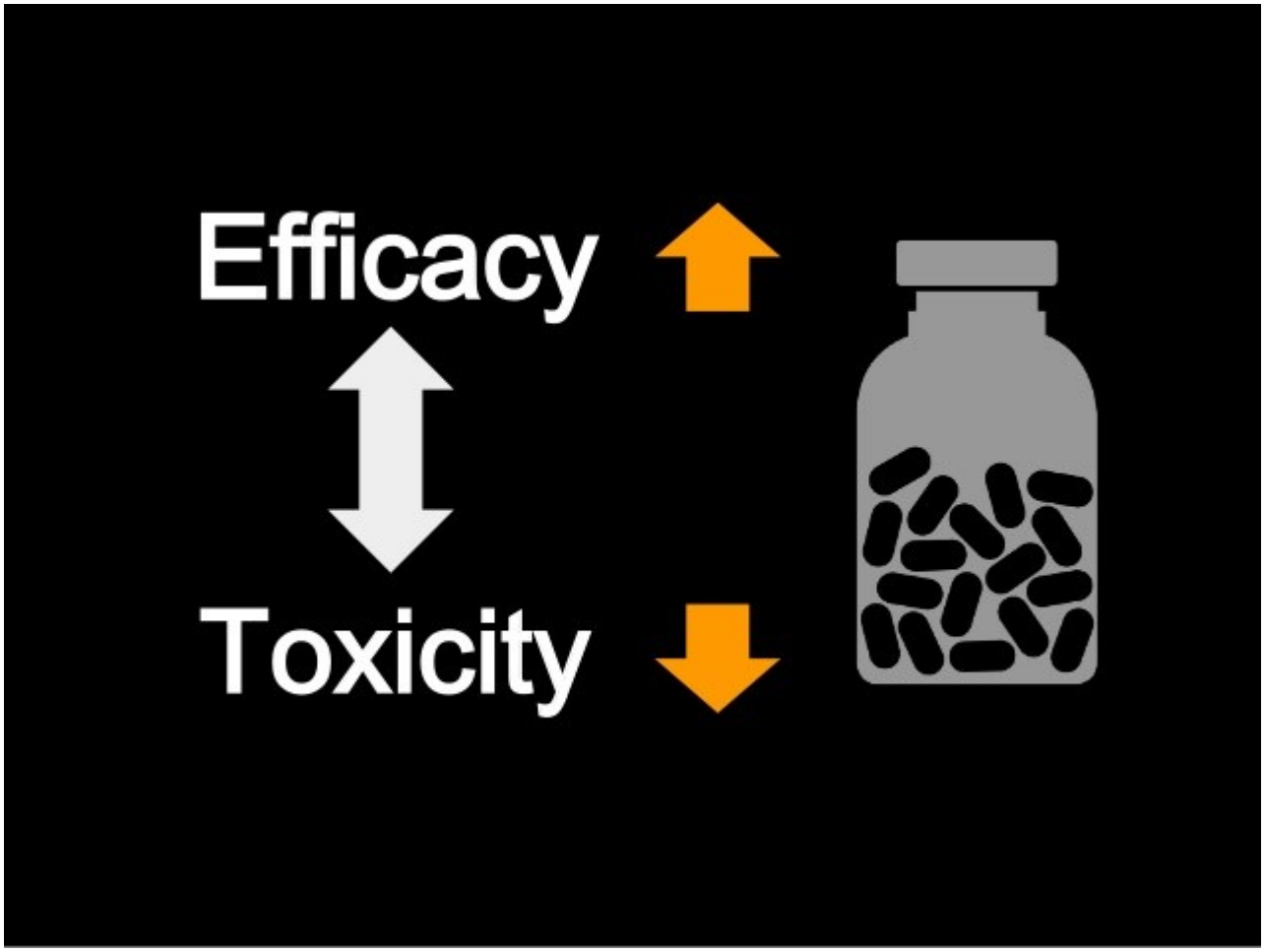
Accepted 11 November 2014


Efficacy
Toxicity

Population:

- ✓ previously untreated
- ✓ any age and race
- ✓ histologically proven NSCLC harbouring activating EGFR-mutation

Intervention:

- ✓ EGFR-TKIs (Erlotinib, Gefitinib, Afatinib)

Comparison:

- ✓ Platinum-based chemotherapy

Outcomes:

- ✓ PFS (whenever possible independently reviewed data)
- ✓ PFS in exon 19 deletion
- ✓ PFS in L858R mutation
- ✓ OS
- ✓ ORR (complete and/or partial and/or stable)
- ✓ Treatment related toxic events

Search strategy

PubMed, Cancer-Lit, Embase-databases and Cochrane-Library were searched for RCTs up to June 2014 with no language or publication status restrictions. Search terms were “TKI” [Substance Name] and “Carcinoma, NSCLC”[Substance Name]. The proceedings of the 2008–2014 conferences of the American Society of Clinical Oncology(ASCO), European Society of Medical Oncology (ESMO)and International Association for the Study of Lung Cancer (IASLC), World Conference of Lung Cancer were also searched for relevant abstracts. Any unpublished RCTs were considered for inclusion.

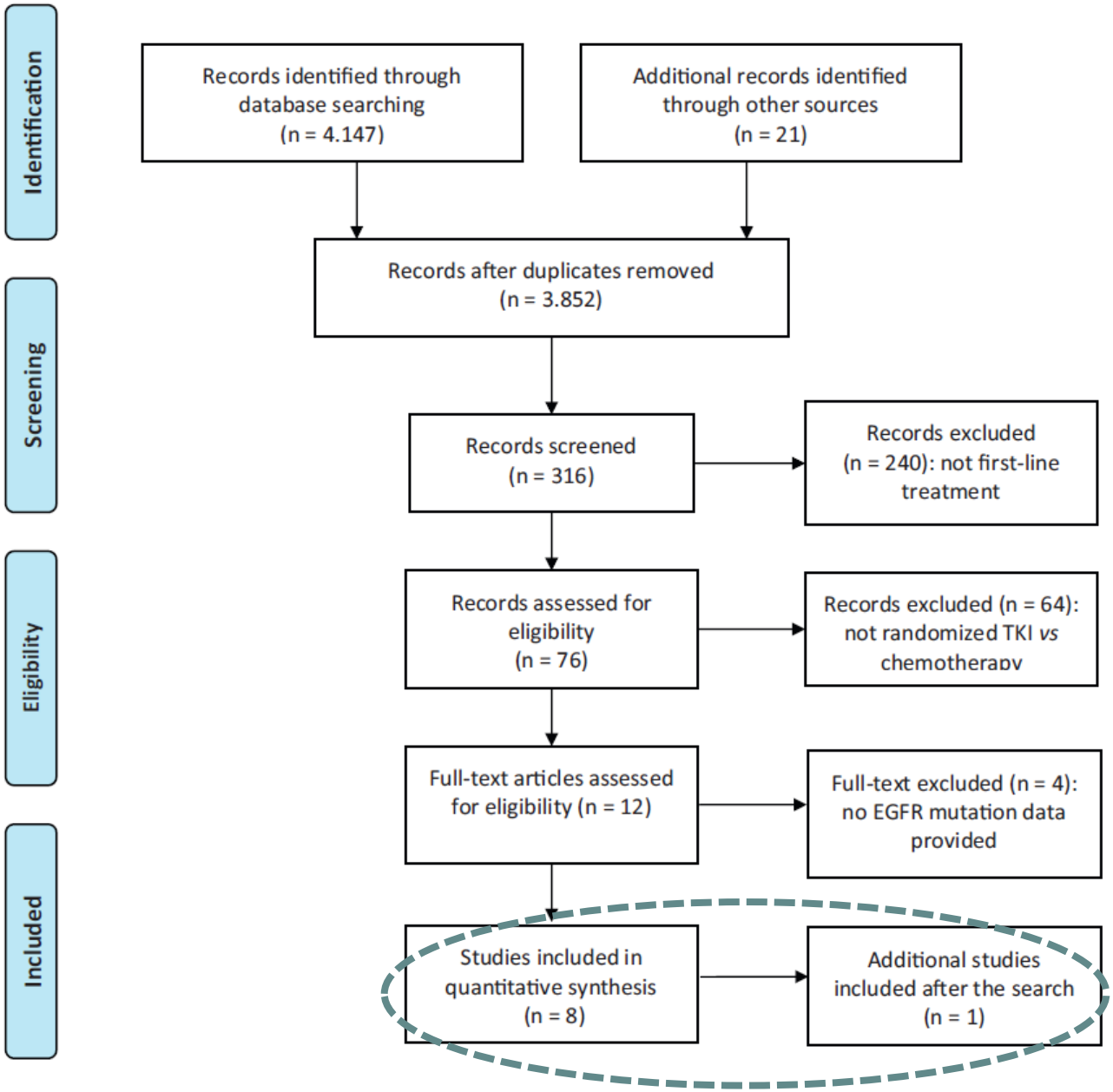


Fig. 1. Flow diagram for the selection of studies included in this meta-analysis.

From: Moher D, Liberati A, Telzlaff J, Altman DG, The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the Prisma statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097.

Table 1
Characteristics of the 9 clinical trials included in the meta-analysis.

Trial	Primary end-point	TKI	Chemotherapy	Patients (TKI/CT)	EGFR + patients (%)	Asiatic patients (%)	Crossover (%)[a]
IPASS Mok, 2009	Progression-free survival	Gefitinib	Carboplatin + paclitaxel	1.217 (609/608)	21.4	99.8	39.5
WJTOG3405 Mitsudomi, 2010	Progression-free survival	Gefitinib	Cisplatin + paclitaxel	177 (88/89)	100	100	59.3
NEJ002 Maemondo, 2010	Progression-free survival	Gefitinib	Carboplatin + paclitaxel	228 (114/114)	100	100	94.6
First-SIGNAL Han, 2012	Overall survival	Gefitinib	Cisplatin + gemcitabine	309 (159/150)	13.6	100	75.0
TORCH Gridelli, 2012	Overall survival	Erlotinib	Cisplatin + gemcitabine	760 (380/380)	5.1	0	60.9
OPTIMAL Zhou, 2011	Progression-free survival	Erlotinib	Carboplatin + gemcitabine	154 (82/72)	100	100	NA
EURTAC Rosell, 2011	Progression-free survival	Erlotinib	Cisplatin/carboplatin + docetaxel/gemcitabine	173 (86/87)	100	0	76.0
LUX-Lung 3 Sequist, 2012	Progression-free survival	Afatinib	Cisplatin + pemetrexed	345 (230/115)	100	100	75.0
LUX-Lung 6 Wu, 2013	Progression-free survival	Afatinib	Cisplatin + gemcitabine	364 (242/122)	100	100	56.0

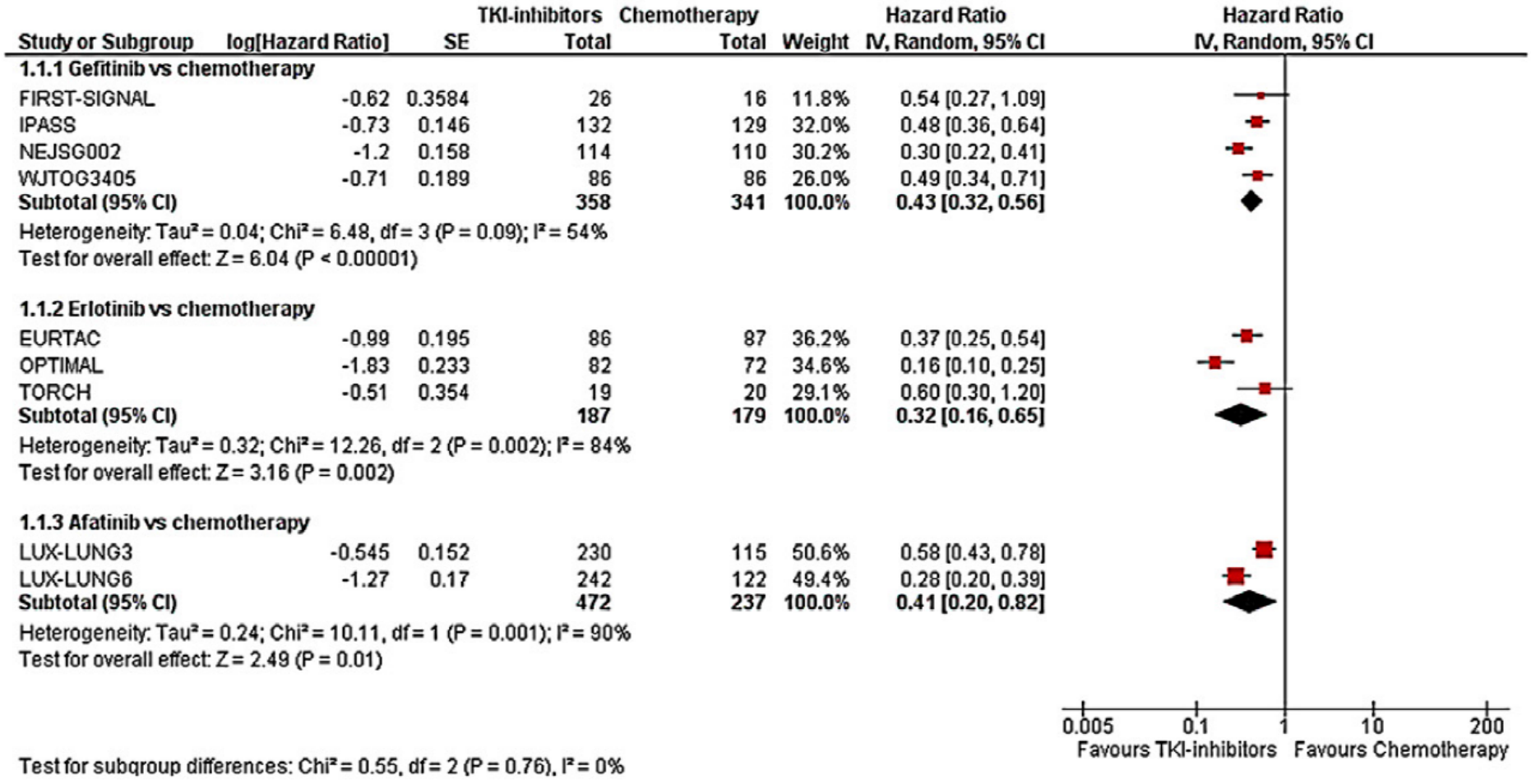
[a] Patients who have been treated with crossover from chemotherapy to TKI in second-line.

Data synthesis:

- ✓ HR for PFS and OS
- ✓ RR for the Others

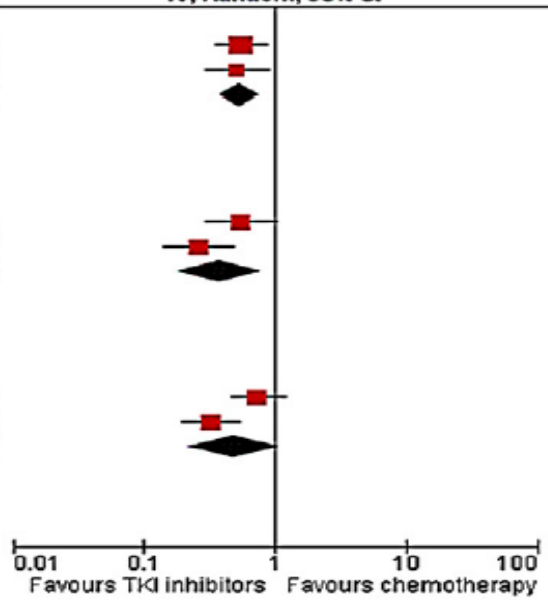
PFS

Panel A


Study or Subgroup | log[Hazard Ratio] | SE | TKI-inhibitors Total | Chemotherapy Total | Weight | Hazard Ratio IV, Random, 95% CI
1.1.1 Gefitinib vs chemotherapy
FIRST-SIGNAL -0.62 0.3584 26 16 11.8% 0.54 [0.27, 1.09]
IPASS -0.73 0.146 132 129 32.0% 0.48 [0.36, 0.64]
NEJSG002 -1.2 0.158 114 110 30.2% 0.30 [0.22, 0.41]
WJTOG3405 -0.71 0.189 86 86 26.0% 0.49 [0.34, 0.71]
Subtotal (95% CI) 358 341 100.0% 0.43 [0.32, 0.56]
Heterogeneity: Tau² = 0.04; Chi² = 6.48, df = 3 (P = 0.09); I² = 54%
Test for overall effect: Z = 6.04 (P < 0.00001)
1.1.2 Erlotinib vs chemotherapy
EURTAC -0.99 0.195 86 87 36.2% 0.37 [0.25, 0.54]
OPTIMAL -1.83 0.233 82 72 34.6% 0.16 [0.10, 0.25]
TORCH -0.51 0.354 19 20 29.1% 0.60 [0.30, 1.20]
Subtotal (95% CI) 187 179 100.0% 0.32 [0.16, 0.65]
Heterogeneity: Tau² = 0.32; Chi² = 12.26, df = 2 (P = 0.002); I² = 84%
Test for overall effect: Z = 3.16 (P = 0.002)
1.1.3 Afatinib vs chemotherapy
LUX-LUNG3 -0.545 0.152 230 115 50.6% 0.58 [0.43, 0.78]
LUX-LUNG6 -1.27 0.17 242 122 49.4% 0.28 [0.20, 0.39]
Subtotal (95% CI) 472 237 100.0% 0.41 [0.20, 0.82]
Heterogeneity: Tau² = 0.24; Chi² = 10.11, df = 1 (P = 0.001); I² = 90%
Test for overall effect: Z = 2.49 (P = 0.01)
Test for subgroup differences: Chi² = 0.55, df = 2 (P = 0.76), I² = 0%
Hazard Ratio IV, Random, 95% CI
0.005
0.1
1
10
200
Favours TKI-inhibitors
Favours Chemotherapy

Exon 21

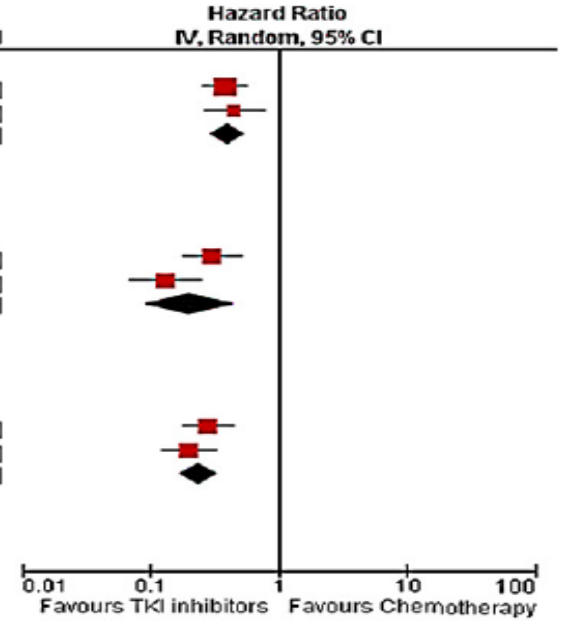
Study or Subgroup	log[Hazard Ratio]	SE	TKI-inhibitors Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
1.15.1 Gefitinib						
IPASS	-0.6	0.23	64	47	61.4%	0.55 [0.35, 0.86]
WJTOG3405	-0.67	0.29	36	49	38.6%	0.51 [0.29, 0.90]
Subtotal (95% CI)			**100**	**96**	**100.0%**	**0.53 [0.38, 0.76]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 3.48 (P = 0.0005)						
1.15.2 Erlotinib						
EURTAC	-0.6	0.32	29	29	50.0%	0.55 [0.29, 1.03]
OPTIMAL	-1.35	0.32	39	33	50.0%	0.26 [0.14, 0.49]
Subtotal (95% CI)			**68**	**62**	**100.0%**	**0.38 [0.18, 0.79]**
Heterogeneity: Tau² = 0.18; Chi² = 2.75, df = 1 (P = 0.10); I² = 64%						
Test for overall effect: Z = 2.60 (P = 0.009)						
1.15.3 Afatinib						
LUX-LUNG3	-0.31	0.24	91	47	50.7%	0.73 [0.46, 1.17]
LUX-LUNG6	-1.14	0.26	74	64	49.3%	0.32 [0.19, 0.53]
Subtotal (95% CI)			**165**	**111**	**100.0%**	**0.49 [0.22, 1.10]**
Heterogeneity: Tau² = 0.28; Chi² = 5.50, df = 1 (P = 0.02); I² = 82%						
Test for overall effect: Z = 1.73 (P = 0.08)						



Test for subgroup differences: Chi² = 0.70, df = 2 (P = 0.70), I² = 0%

Exon 19

Study or Subgroup	log[Hazard Ratio]	SE	TKI - inhibitors Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
1.14.1 Gefitinib						
IPASS	-0.97	0.2	66	74	64.6%	0.38 [0.26, 0.56]
WJTOG3405	-0.8	0.27	50	37	35.4%	0.45 [0.26, 0.76]
Subtotal (95% CI)			**116**	**111**	**100.0%**	**0.40 [0.29, 0.55]**
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 5.66 (P < 0.00001)						
1.14.2 Erlotinib						
EURTAC	-1.2	0.26	57	58	52.5%	0.30 [0.18, 0.50]
OPTIMAL	-2.04	0.32	43	39	47.5%	0.13 [0.07, 0.24]
Subtotal (95% CI)			**100**	**97**	**100.0%**	**0.20 [0.09, 0.46]**
Heterogeneity: Tau² = 0.27; Chi² = 4.15, df = 1 (P = 0.04); I² = 76%						
Test for overall effect: Z = 3.81 (P = 0.0001)						
1.14.3 Afatinib						
LUX-LUNG3	-1.27	0.23	113	57	52.0%	0.28 [0.18, 0.44]
LUX-LUNG6	-1.61	0.24	98	88	48.0%	0.20 [0.12, 0.32]
Subtotal (95% CI)			**211**	**145**	**100.0%**	**0.24 [0.17, 0.33]**
Heterogeneity: Tau² = 0.00; Chi² = 1.05, df = 1 (P = 0.31); I² = 4%						
Test for overall effect: Z = 8.44 (P < 0.00001)						



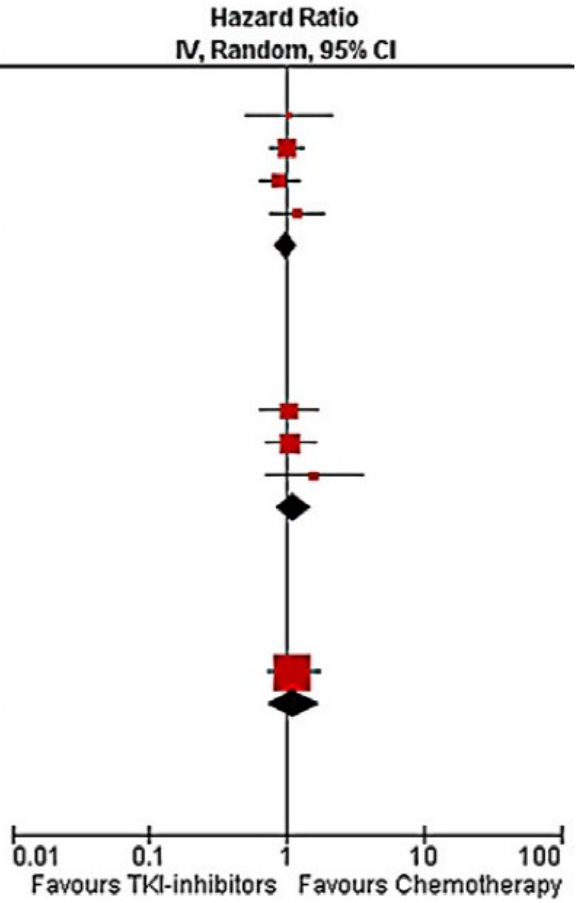
Test for subgroup differences: Chi² = 6.04, df = 2 (P = 0.05), I² = 66.9%

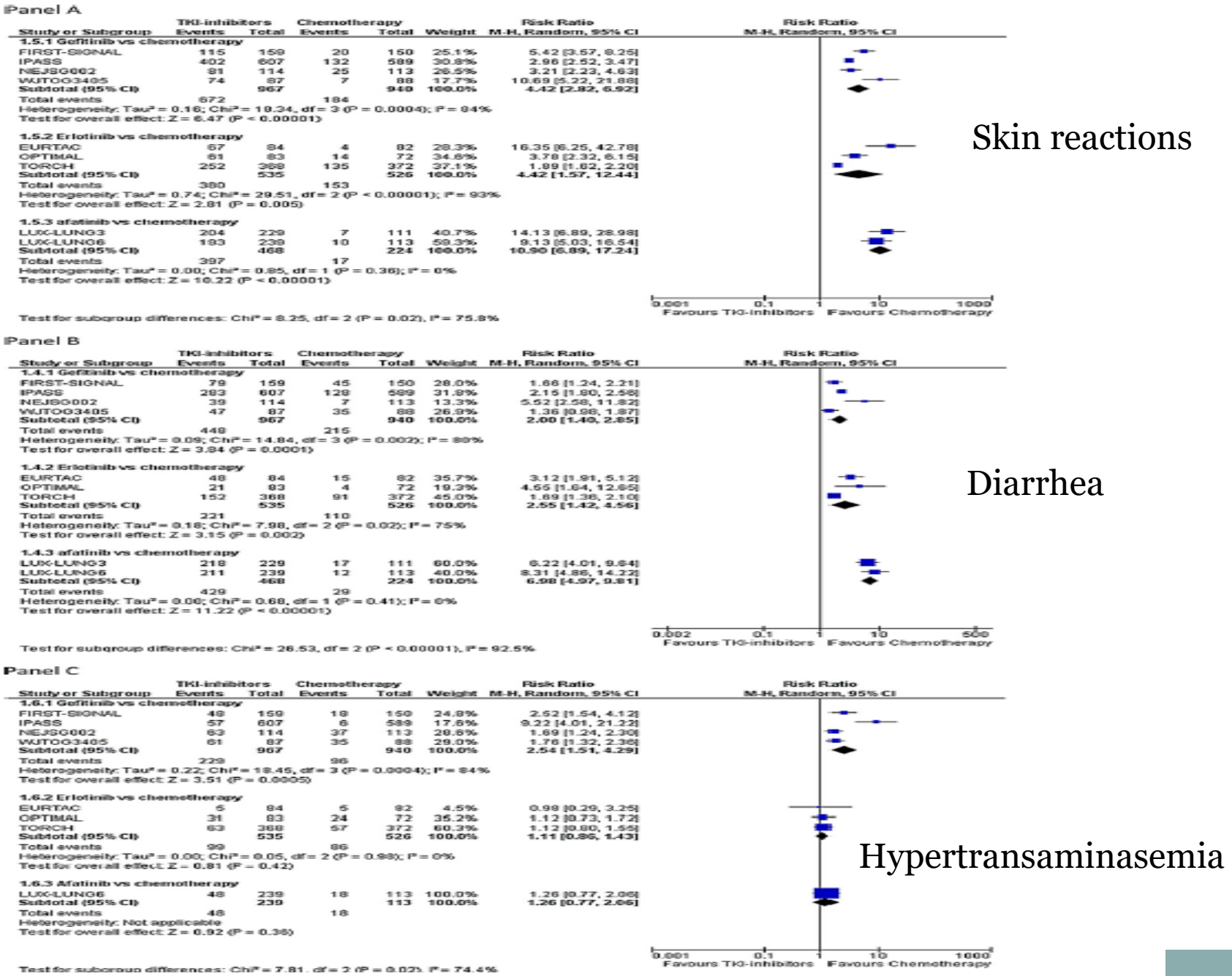
OS

Panel B

Study or Subgroup	log[Hazard Ratio]	SE	TKI-inhibitors Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
1.2.1 Gefitinib vs chemotherapy						
FIRST-SIGNAL	0.0392	0.3755	26	16	6.4%	1.04 [0.50, 2.17]
IPASS	0	0.143	132	129	44.3%	1.00 [0.76, 1.32]
NEJSG002	-0.12	0.171	114	110	31.0%	0.89 [0.63, 1.24]
WJTOG3405	0.17	0.223	86	86	18.2%	1.19 [0.77, 1.84]
Subtotal (95% CI)			**358**	**341**	**100.0%**	**1.00 [0.83, 1.20]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.08$, df = 3 (P = 0.78); $I^2 = 0\%$						
Test for overall effect: Z = 0.04 (P = 0.97)						
1.2.2 Erlotinib vs chemotherapy						
EURTAC	0.039	0.24	86	87	39.5%	1.04 [0.65, 1.66]
OPTIMAL	0.0677	0.219	82	72	47.4%	1.07 [0.70, 1.64]
TORCH	0.457	0.416	19	20	13.1%	1.58 [0.70, 3.57]
Subtotal (95% CI)			**187**	**179**	**100.0%**	**1.11 [0.83, 1.50]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.82$, df = 2 (P = 0.66); $I^2 = 0\%$						
Test for overall effect: Z = 0.71 (P = 0.48)						
1.2.3 Afatinib						
LUX-LUNG3	0.11	0.22	230	115	100.0%	1.12 [0.73, 1.72]
Subtotal (95% CI)			**230**	**115**	**100.0%**	**1.12 [0.73, 1.72]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.62)						

Test for subgroup differences: $Chi^2 = 0.51$, df = 2 (P = 0.77), $I^2 = 0\%$




Panel A
TKI-inhibitors
Chemotherapy
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.5.1 Gefitinib vs chemotherapy
FIRST-SIGNAL 115 159 20 150 25.1% 5.42 [3.57, 8.25]
IPASS 402 607 132 589 30.8% 2.96 [2.52, 3.47]
NEJSG002 81 114 25 113 26.5% 3.21 [2.23, 4.63]
WJTOG3405 74 87 7 88 17.7% 10.69 [5.22, 21.88]
Subtotal (95% CI) 967 940 100.0% 4.42 [2.82, 6.92]
Total events 672 184
Heterogeneity: Tau² = 0.16; Chi² = 19.34, df = 3 (P = 0.0004); I² = 84%
Test for overall effect: Z = 6.47 (P < 0.00001)
1.5.2 Erlotinib vs chemotherapy
EURTAC 67 84 4 82 28.3% 16.35 [6.25, 42.78]
OPTIMAL 61 83 14 72 34.6% 3.78 [2.32, 6.15]
TORCH 252 368 135 372 37.1% 1.89 [1.62, 2.20]
Subtotal (95% CI) 535 526 100.0% 4.42 [1.57, 12.44]
Total events 380 153
Heterogeneity: Tau² = 0.74; Chi² = 29.51, df = 2 (P < 0.00001); I² = 93%
Test for overall effect: Z = 2.81 (P = 0.005)
1.5.3 afatinib vs chemotherapy
LUX-LUNG3 204 229 7 111 40.7% 14.13 [6.89, 28.98]
LUX-LUNG6 193 239 10 113 59.3% 9.13 [5.03, 16.54]
Subtotal (95% CI) 468 224 100.0% 10.90 [6.89, 17.24]
Total events 397 17
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 10.22 (P < 0.00001)
Test for subgroup differences: Chi² = 8.25, df = 2 (P = 0.02), I² = 75.8%
0.001 0.1 1 10 1000
Favours TKI-inhibitors Favours Chemotherapy
Skin reactions
Panel B
TKI-inhibitors
Chemotherapy
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.4.1 Gefitinib vs chemotherapy
FIRST-SIGNAL 79 159 45 150 28.0% 1.66 [1.24, 2.21]
IPASS 283 607 128 589 31.8% 2.15 [1.80, 2.56]
NEJSG002 39 114 7 113 13.3% 5.52 [2.58, 11.82]
WJTOG3405 47 87 35 88 26.9% 1.36 [0.98, 1.87]
Subtotal (95% CI) 967 940 100.0% 2.00 [1.40, 2.85]
Total events 448 215
Heterogeneity: Tau² = 0.09; Chi² = 14.84, df = 3 (P = 0.002); I² = 80%
Test for overall effect: Z = 3.94 (P = 0.0001)
1.4.2 Erlotinib vs chemotherapy
EURTAC 48 84 15 82 35.7% 3.12 [1.91, 5.12]
OPTIMAL 21 83 4 72 19.3% 4.55 [1.64, 12.65]
TORCH 152 368 91 372 45.0% 1.69 [1.36, 2.10]
Subtotal (95% CI) 535 526 100.0% 2.55 [1.42, 4.56]
Total events 221 110
Heterogeneity: Tau² = 0.16; Chi² = 7.98, df = 2 (P = 0.02); I² = 75%
Test for overall effect: Z = 3.15 (P = 0.002)
1.4.3 afatinib vs chemotherapy
LUX-LUNG3 218 229 17 111 60.0% 6.22 [4.01, 9.64]
LUX-LUNG6 211 239 12 113 40.0% 8.31 [4.88, 14.22]
Subtotal (95% CI) 468 224 100.0% 6.98 [4.97, 9.81]
Total events 429 29
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 11.22 (P < 0.00001)
Test for subgroup differences: Chi² = 26.53, df = 2 (P < 0.00001), I² = 92.5%
0.002 0.1 1 10 500
Favours TKI-inhibitors Favours Chemotherapy
Diarrhea
Panel C
TKI-inhibitors
Chemotherapy
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.6.1 Gefitinib vs chemotherapy
FIRST-SIGNAL 48 159 19 150 24.8% 2.52 [1.54, 4.12]
IPASS 57 607 6 589 17.6% 9.22 [4.01, 21.22]
NEJSG002 63 114 37 113 28.6% 1.69 [1.24, 2.30]
WJTOG3405 61 87 35 88 29.0% 1.76 [1.32, 2.36]
Subtotal (95% CI) 967 940 100.0% 2.54 [1.51, 4.29]
Total events 229 96
Heterogeneity: Tau² = 0.22; Chi² = 18.45, df = 3 (P = 0.0004); I² = 84%
Test for overall effect: Z = 3.51 (P = 0.0005)
1.6.2 Erlotinib vs chemotherapy
EURTAC 5 84 5 82 4.5% 0.98 [0.29, 3.25]
OPTIMAL 31 83 24 72 35.2% 1.12 [0.73, 1.72]
TORCH 63 368 57 372 60.3% 1.12 [0.80, 1.56]
Subtotal (95% CI) 535 526 100.0% 1.11 [0.86, 1.43]
Total events 99 86
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)
1.6.3 Afatinib vs chemotherapy
LUX-LUNG6 48 239 18 113 100.0% 1.26 [0.77, 2.06]
Subtotal (95% CI) 239 113 100.0% 1.26 [0.77, 2.06]
Total events 48 18
Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Chi² = 7.81, df = 2 (P = 0.02), I² = 74.4%
0.001 0.1 1 10 1000
Favours TKI-inhibitors Favours Chemotherapy
Hypertransaminasemia

So, who's the best?

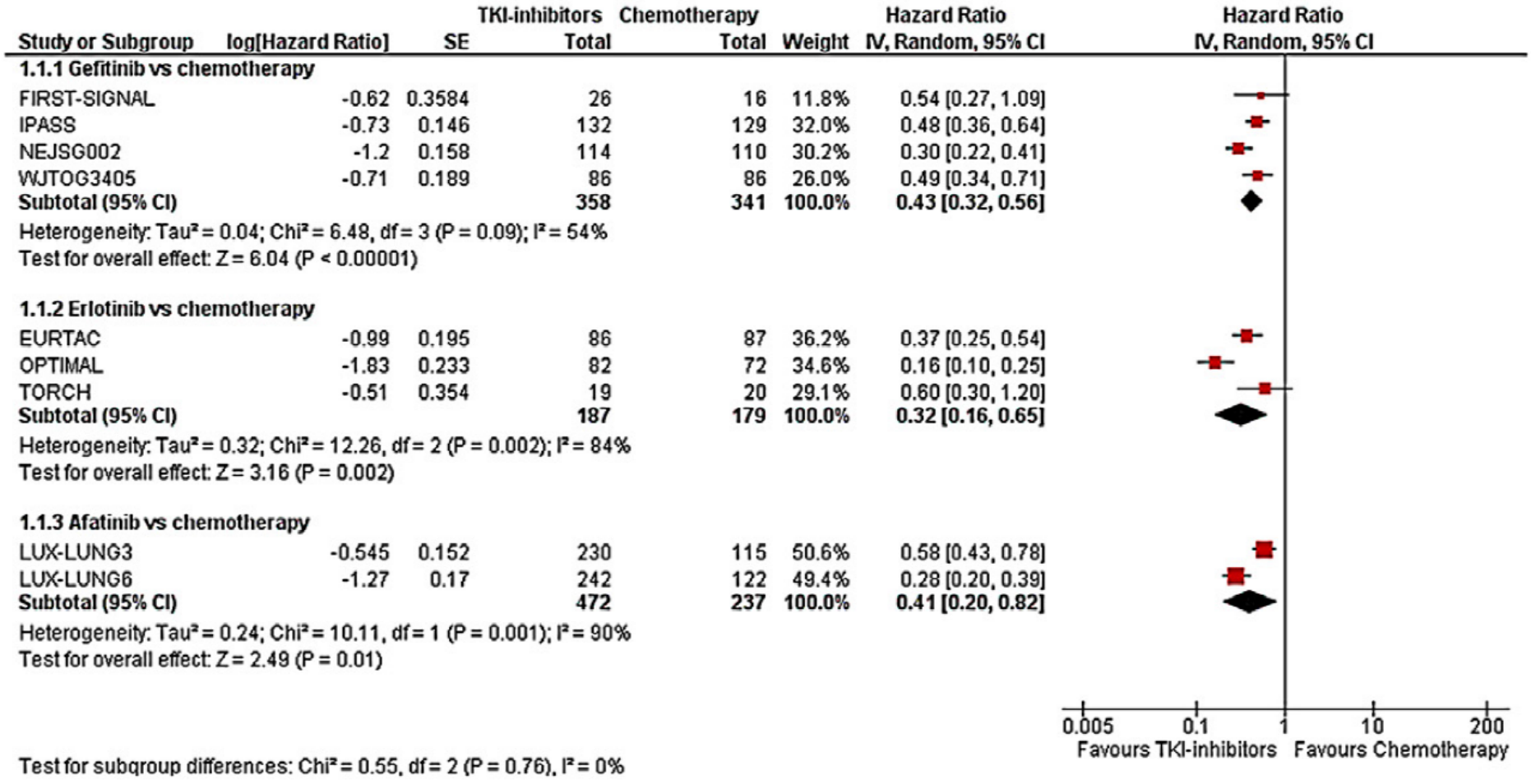
HOMOGENEITY ASSUMPTION

- When multiple trials are available for a given comparison, the results from multiple trials can be pooled in meta-analyses before an adjusted indirect comparison is conducted.
- For a meta-analysis to be valid, it is commonly established that results from different trials should be sufficiently homogeneous from a clinical and statistical perspective.
- This is usually demonstrated by a 2-tailed p value for homogeneity at Pearson chi-squared test or Cochran Q test > 0.10 and a I^2 (inconsistency) < 50%.
- When homogeneity is unlikely (e.g. I^2>50%) than heterogeneity and inconsistency are likely.

Song, What is …? 2009; Higgins et al, BMJ 2003

PFS

Panel A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Test for overall effect: Z = 6.04 (P < 0.00001)
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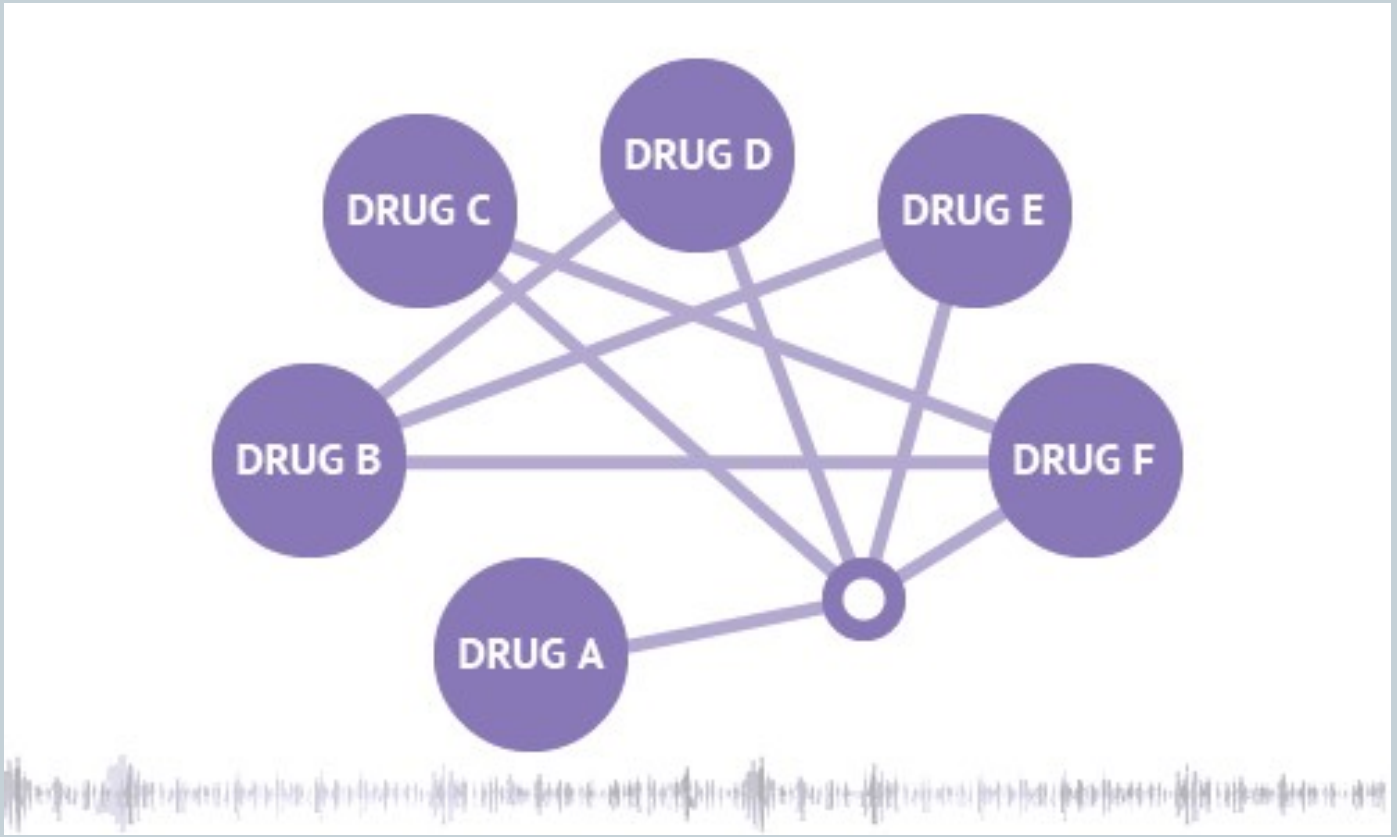
OPTIMAL -1.83 0.233 82 72 34.6% 0.16 [0.10, 0.25]
TORCH -0.51 0.354 19 20 29.1% 0.60 [0.30, 1.20]
Subtotal (95% CI) 187 179 100.0% 0.32 [0.16, 0.65]
Heterogeneity: Tau² = 0.32; Chi² = 12.26, df = 2 (P = 0.002); I² = 84%
Test for overall effect: Z = 3.16 (P = 0.002)
1.1.3 Afatinib vs chemotherapy
LUX-LUNG3 -0.545 0.152 230 115 50.6% 0.58 [0.43, 0.78]
LUX-LUNG6 -1.27 0.17 242 122 49.4% 0.28 [0.20, 0.39]
Subtotal (95% CI) 472 237 100.0% 0.41 [0.20, 0.82]
Heterogeneity: Tau² = 0.24; Chi² = 10.11, df = 1 (P = 0.001); I² = 90%
Test for overall effect: Z = 2.49 (P = 0.01)
Test for subgroup differences: Chi² = 0.55, df = 2 (P = 0.76), I² = 0%
Hazard Ratio IV, Random, 95% CI
0.005
0.1
1
10
200
Favours TKI-inhibitors
Favours Chemotherapy

CONSISTENCY ASSUMPTION

- When both direct and indirect evidence is available, an assumption of evidence consistency is required to quantitatively combine the direct and indirect estimates.
- It is important to investigate possible causes of discrepancy between the direct and indirect evidence, such as the play of chance, invalid indirect comparison, bias in head-to-head comparative trials, and clinically meaningful heterogeneity
- When the direct comparison differs from the adjusted indirect comparison, we should usually give more credibility to evidence from head-to-head comparative trials. However, evidence from direct comparative trials may not always be valid.

Song, What is …? 2009; Song et al, J Clin Epidemiol 2008

No head-to head comparisons



SIMILARITY ASSUMPTION

- For an adjusted indirect comparison (A vs B) to be valid, a similarity assumption is required in terms of moderators of relative treatment effect.
- That is, patients included should be sufficiently similar in the two sets of control arms (C_1 from the trial comparing A vs C_1, and C_2, from the trial comparing B vs C_2).
- This is crucial as only a large theoretical overlap between patients enrolled in C_1 and C_2 enables the relative effect estimated by trials of A versus C_1 to be generalizable to patients in trials of B versus C_1, and the relative effect estimated by trials of B versus C_2 to be generalizable to patients in trials of A versus C_2.

Song, What is …? 2009

Study		
FIRST-SIGNAL	Cisplatin 75 mg/m Gemcitabine 1 1	very 3 weeks ycles
IPASS	Carbo mg	eeks up to 6 weeks
NEJG002		
WJTOG3405		s up to 6 weeks
EURTAC		
OPT	day	i.v. 4 cycles
TORCH	day 1 50 mg/m2	i.v. every 3 weeks up to 6 weeks
LUX-LUNG	mg/m2 ed 500mg/m2	i.v. 6 cycles
LUX-LUNG VI	latin 75 mg/m2 emcitabine 1000 mg/m2 day 1&8	i.v. Up to 6 cycles

STANDARD CHEMOTHERAPY

COMPUTATIONS

- The log relative risk of the adjusted indirect comparison of A and B ($\ln RR_{A \text{ vs } B}$) can be estimated by:

$$\ln RR_{A \text{ vs } B} = \ln RR_{A \text{ vs } C1} - \ln RR_{B \text{ vs } C2}$$

- and its standard error is:

$$SE(\ln RR_{A \text{ vs } B}) =$$
$$\sqrt{[SE(\ln RR_{A \text{ vs } C1})^2 + SE(\ln RR_{B \text{ vs } C2})^2]}$$

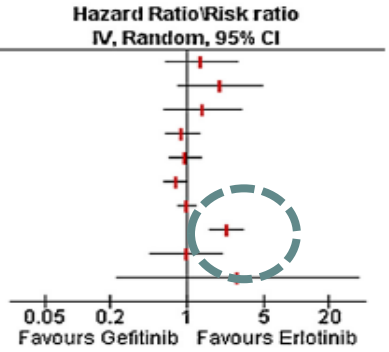
- Similar computations can be envisioned for odds ratio, absolute risk reductions, weighted mean differences, and standardized mean differences.

Higgins et al, BMJ 2003; Song, What is …? 2009; http://www.metcardio.org/macros/IMT.xls

Panel A

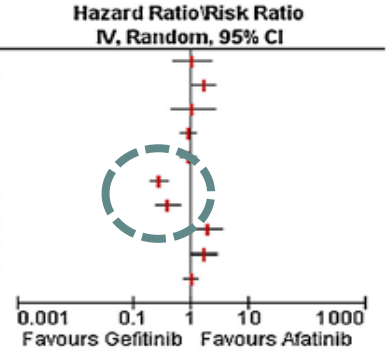
Study or Subgroup	log[Hazard Ratio\Risk ratio]	SE	Weight	Hazard Ratio\Risk ratio IV, Random, 95% CI
Progression-free survival	0.295	0.385		1.34 [0.63, 2.86]
PFS-exon 19	0.693	0.447		2.00 [0.83, 4.80]
PFS-L858R	0.332	0.417		1.39 [0.62, 3.16]
Overall survival	-0.104	0.177		0.90 [0.64, 1.27]
Objective response rate	-0.036	0.168		0.96 [0.69, 1.34]
Diarrhea	-0.223	0.121		0.80 [0.63, 1.01]
Rash	0	0.101		1.00 [0.82, 1.22]
Hypertransaminasemia	0.83	0.175		2.29 [1.63, 3.23]
Treatment discontinuation	-0.019	0.384		0.98 [0.46, 2.08]
Treatment-related death	1.05	1.295		2.86 [0.23, 36.17]

Image of Fig. 5



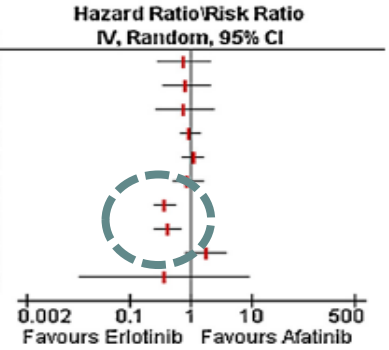
Panel B

Study or Subgroup	log[Hazard Ratio\Risk Ratio]	SE	Weight	Hazard Ratio\Risk Ratio IV, Random, 95% CI
Progression-free survival	0.048	0.387		1.05 [0.49, 2.24]
PFS-exon 19	0.511	0.235		1.67 [1.05, 2.64]
PFS-L858R	0.078	0.447		1.08 [0.45, 2.60]
Overall survival	-0.099	0.167		0.91 [0.65, 1.26]
Objective response rate	-0.097	0.157		0.91 [0.67, 1.23]
Diarrhea	-1.25	0.187		0.29 [0.20, 0.41]
Rash	-0.903	0.244		0.41 [0.25, 0.65]
Hypertransaminasemia	0.701	0.276		2.02 [1.17, 3.46]
Treatment discontinuation	0.531	0.273		1.70 [1.00, 2.90]
Treatment-related death	0.022	0.136		1.02 [0.78, 1.33]



Panel C

Study or Subgroup	log[Hazard Ratio\Risk Ratio]	SE	Weight	Hazard Ratio\Risk Ratio IV, Random, 95% CI
Progression-free survival	-0.248	0.507		0.78 [0.29, 2.11]
PFS-exon 19	-0.182	0.449		0.83 [0.35, 2.01]
PFS-L858R	-0.254	0.558		0.78 [0.26, 2.32]
Objective response rate	-0.061	0.186		0.94 [0.65, 1.35]
Overall survival	0.094	0.204		1.10 [0.74, 1.64]
Hypertransaminasemia	-0.127	0.285		0.88 [0.50, 1.54]
Diarrhea	-1.01	0.2		0.36 [0.25, 0.54]
Rash	-0.903	0.245		0.41 [0.25, 0.66]
Treatment discontinuation	0.55	0.395		1.73 [0.80, 3.76]
Treatment-related death	-1.03	1.637		0.36 [0.01, 8.83]



Interpretation - Quality

- Rubbish studies = unbelievable results
- If all the trials in a meta-analysis were of very low quality, then you should be less certain of your conclusions.
- Instead of “Treatment X cures Y disease”, try “There is some evidence that Treatment X cures Y disease, but the data should be interpreted with caution.”

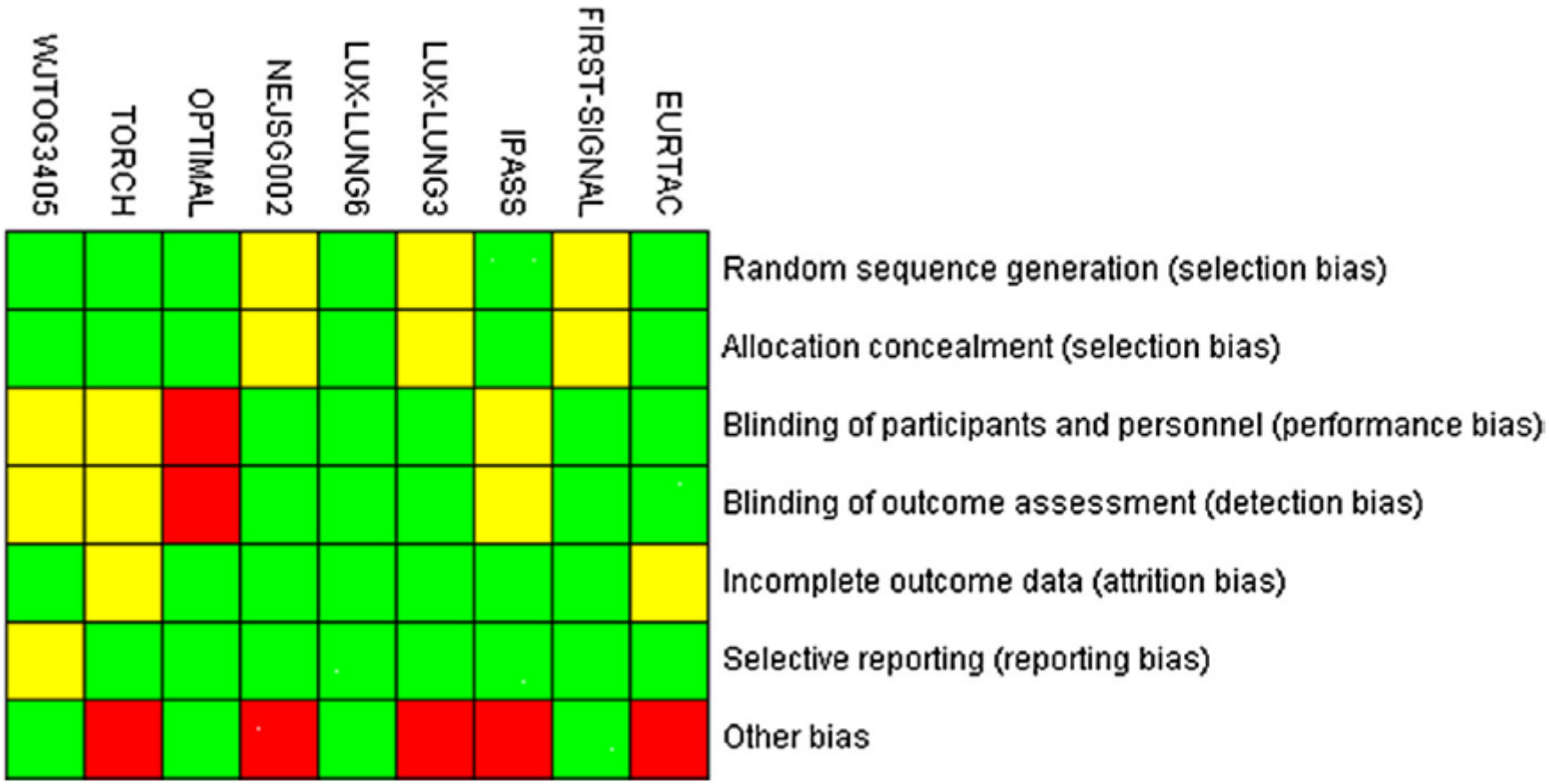


Fig. 6. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

TAKE HOME MESSAGES

- Adjusted indirect comparison meta-analysis represents a simple yet robust tool to make statistical and clinical inference despite the lack of conclusive evidence from head-to-head randomized clinical trials.

- Despite being not at the uppermost level of the hierarchy of evidence based medicine, it can often provide results equivalent to those of subsequent direct comparisons.