

**Table S1. EGFR mutation subgroup analysis of first-line therapy for NSCLC**

Trial	Number of Patients with EGFR Mutation Testing	Therapy Regimen	EGFR Mutation-positive				EGFR Mutation-negative			
			n	CR + PR	ORR, (%)	OR (95% CI)	n	CR + PR	ORR, (%)	OR (95% CI)
Gefitinib vs Chemotherapy										
Mitsudomi <i>et al</i> , 2010	117	G	58	36	62.1	3.44 (1.61-7.38)	-	-	-	-
		CS + D	59	19	32.2		-	-	-	-
Han <i>et al</i> , 2012	96	G	26	22	84.6	9.17 (2.11-39.85)	27	7	25.9	0.33 (0.10-1.02)
		GP	16	6	37.5		27	14	51.9	-
Subtotal	213		159	83	52.2	4.23 (2.17-8.28)	54	21	38.9	0.33 (0.10-1.02)
Gefitinib vs Other targeted therapies										
Xie <i>et al</i> , 2015	50	G	27	15	55.6	0.80 (0.26-2.49)	-	-	-	-
		E	23	14	60.9		-	-	-	-
Park <i>et al</i> , 2016	319	G	159	89	56.0	0.55 (0.34-0.86)	-	-	-	-
		A	160	112	70.0		-	-	-	-
Subtotal	369		369	230	62.3	0.58 (0.38-0.88)	-	-	-	-

Abbreviation: EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; n: number of participants; G: gefitinib; CS + D: cisplatin + docetaxel; GP: gemcitabine + cisplatin; E: erlotinib; A: afatinib; CR: complete response; PR: partial response; ORR: objective response rate; OR: odds ratio; CI: confidence interval; -: not available.

**Table S2. EGFR Mutation Subgroup Analysis of Non-first-line Therapy for NSCLC**

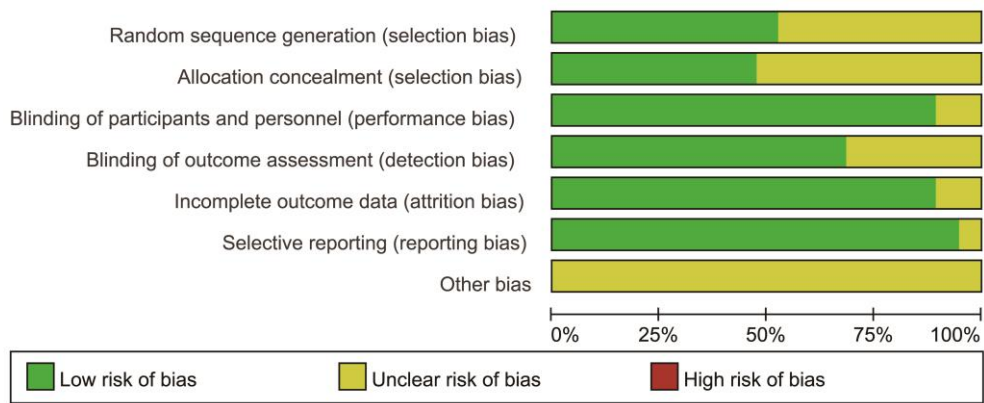
Trial	Number of Patients with EGFR Mutation Testing	Therapy Regimen	HR (95% CI) of OS		HR (95% CI) of PFS	
			EGFR Mutation- positive	EGFR Mutation-negative	EGFR Mutation- positive	EGFR Mutation-negative
<b>Gefitinib vs Chemotherapy</b>						
Kim <i>et al</i> , 2008	174	G vs D	1.09 (0.78-1.51)	-	-	-
Zhang <i>et al</i> , 2012	79	G vs P	-	-	0.17 (0.07-0.42)	0.86 (0.48-1.51)
Sun <i>et al</i> , 2012	71	G vs PE	-	-	0.30 (0.13-0.72)	0.56 (0.28-1.13)
Zhou <i>et al</i> , 2014	108	G vs PE	1.00 (0.42-2.46)	1.45 (0.90-2.34)	1.06 (0.48-2.33)	2.27 (1.41-3.70)
Subtotal	432		1.08 (0.79-1.47)	1.45 (0.90-2.34)	0.38 (0.13-1.14)	1.06 (0.46-2.45)
<b>Gefitinib vs Other targeted therapies</b>						
Shi <i>et al</i> , 2013	134	G vs I	0.91 (0.51-1.64)	1.08 (0.64-1.82)	1.28 (0.78-2.38)	1.43 (0.87-2.36)
Yang <i>et al</i> , 2017	256	G vs E	1.19 (0.89-1.59)	-	1.24 (0.95-1.61)	-
Subtotal	390		1.13 (0.87-1.46)	1.08 (0.64-1.82)	1.24 (0.98-1.58)	1.43 (0.87-2.36)

Abbreviation: EGFR: epidermal growth factor receptor; NSCLC: non-small cell lung cancer; G: gefitinib; D: docetaxel; P: placebo; PE: pemetrexed; I: icotinib; E: erlotinib; HR: hazard ratio; PFS: progression-free survival; OS: overall survival; CI: confidence interval; -: not available.

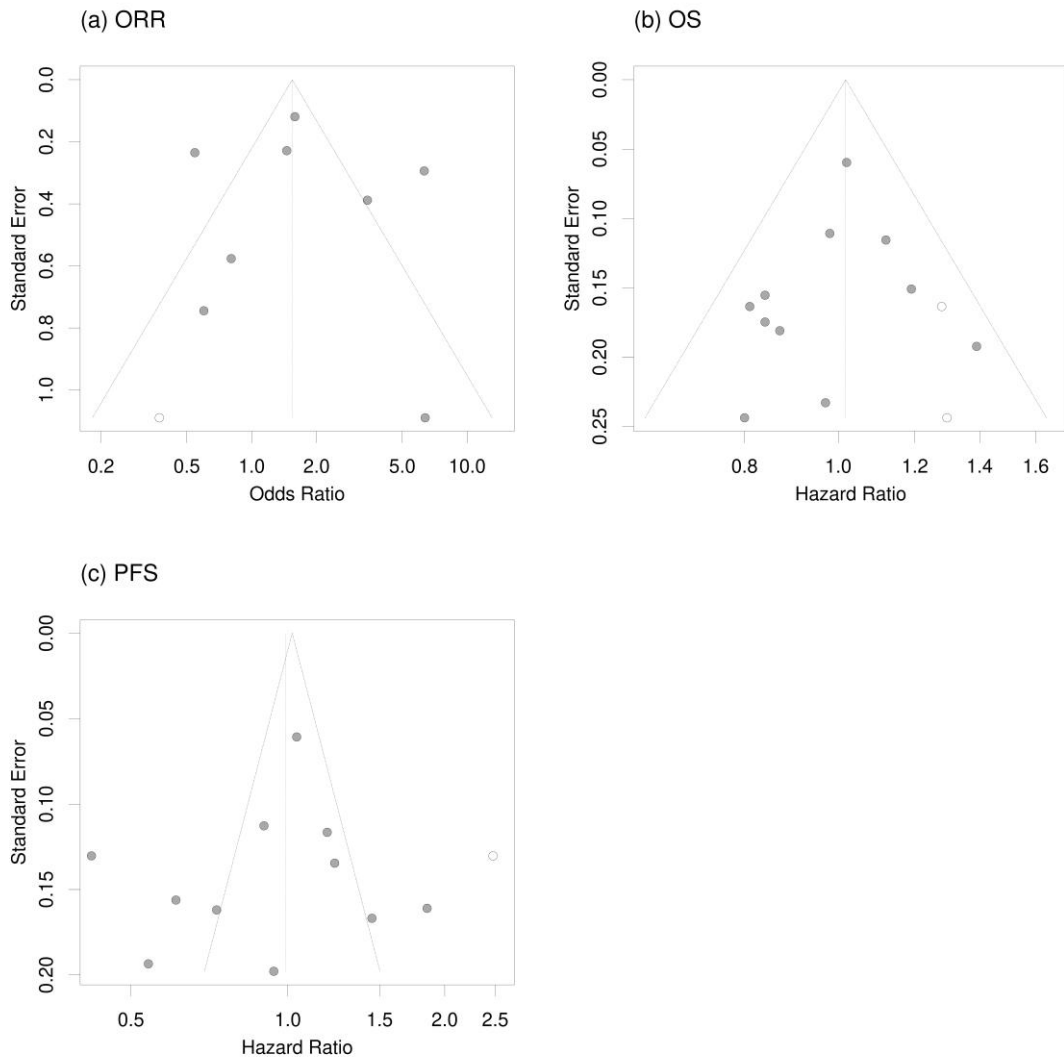
**Table S3. Comparison of toxicity between gefitinib and controlled agents for NSCLC**

Toxicity	All Grade						Grade $\geq 3$					
	n	Incidence, (%)		OR (95% CI)	Heterogeneity		n	Incidence, (%)		OR (95% CI)	Heterogeneity	
		Gefitinib	Control		I <sup>2</sup>	P value		Gefitinib	Control		I <sup>2</sup>	P value
<b>Hematologic Toxicity</b>												
Leukopenia	7	2.0	9.3	0.19 (0.05-0.71)	91%	< 0.001	5	0.8	11.3	0.08 (0.05-0.13)	30%	0.220
Neutropenia	8	2.7	31.4	0.03 (0.02-0.04)	51%	0.050	8	8.0	38.0	0.02 (0.01-0.04)	56%	0.020
Anemia	8	4.5	11.4	0.25 (0.13-0.46)	81%	< 0.001	7	1.0	3.7	0.38 (0.11-1.37)	66%	0.010
<b>Nonhematologic Toxicity</b>												
Rash	15	51.2	17.4	7.17 (4.32-11.90)	92%	< 0.001	12	3.7	1.5	4.27 (2.75-6.64)	33%	0.120
Diarrhea	16	36.7	23.8	2.22 (1.71-2.89)	75%	< 0.001	12	3.2	3.5	1.49 (1.02-2.16)	0%	0.520
Dry skin	10	16.3	1.9	10.82 (4.91-23.87)	82%	< 0.001	1	0.7	0.5	1.96 (0.69-5.51)	-	-
Anorexia	9	16.1	23.9	0.52 (0.32-0.85)	90%	< 0.001	9	2.4	4.7	0.59 (0.24-1.44)	75%	< 0.001
Abnormal hepatic function	8	15.5	7.7	2.63 (1.38-5.01)	89%	< 0.001	8	2.4	4.7	8.98 (3.55-22.73)	60%	0.010
Nausea	4	14.1	26.8	0.40 (0.23-0.69)	92%	< 0.001	9	1.1	2.1	0.30 (0.16-0.55)	0%	0.920
Pruritus	7	9.9	4.0	4.00 (2.10-7.62)	82%	< 0.001	3	0.3	0.1	3.37 (0.82-13.87)	0%	0.850
Asthenic conditions	10	9.7	19.9	0.38 (0.27-0.54)	68%	0.030	4	1.2	2.5	0.45 (0.31-0.67)	21%	0.280
Fatigue	12	5.2	12.6	0.25 (0.14-0.46)	84%	< 0.001	6	1.9	3.9	0.38 (0.13-1.14)	67%	0.010
Alopecia	3	4.7	30.3	0.09 (0.04-0.17)	89%	< 0.001	0	-	-	-	-	-
Neurotoxicity	3	4.1	18.8	0.20 (0.05-0.75)	97%	< 0.001	2	0.1	1.4	0.06 (0.02-0.20)	0%	0.920
Mucositis	2	2.2	2.4	0.79 (0.52-1.20)	0%	0.410	2	0.3	0.3	0.83 (0.34-2.05)	62%	0.110
Neuropathy	8	1.0	5.3	0.18 (0.04-0.74)	89%	< 0.001	4	0.1	0.7	0.21 (0.07-0.65)	33%	0.210

Abbreviations: NSCLC: non-small cell lung cancer; N: number of studies; OR: odds ratio; CI: confidence interval.



**Figure S1. Quality of RCTs included in the meta-analysis of gefitinib compared to controls for NSCLC.** The Cochrane risk-of-bias graph reviewed author’s judgments about each risk of bias item presented as percentages across all included studies, and it were prepared with the RevMan 5.3 risk-of-bias tool. Each horizontal bar denotes one of seven aspects of bias assessment, in which, green, yellow, and red color is used to stand for the proportion of RCTs with low, unclear, and high risk of bias, respectively. Abbreviations: RCT: randomized clinical trial; NSCLC: non-small cell lung cancer.



**Figure S2. Funnel plots of ORR, OS and PFS with trim and fill analysis.** (a) A funnel plot for meta-analysis of ORR; (b) A funnel plot for meta-analysis of OS; (c) A funnel plot for meta-analysis of PFS. Original studies were showed as closed circles and imputed studies were showed as hollow circles when the trim-and-fill method was applied. Abbreviations: ORR: objective response rate; OS: overall survival; PFS: progression-free survival.