Supporting Information

Clinical data mining reveals analgesic effects of lapatinib in cancer patients

Shuo Zhou, 1,2 Fang Zheng, 1,2,* and Chang-Guo Zhan 1,2,*

¹Molecular Modeling and Biopharmaceutical Center, College of Pharmacy, University of Kentucky, 789 South Limestone Street, Lexington, KY 40536. ²Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, 789 South Limestone Street, Lexington, KY 40536

Table S1. Data for various forms of pain reported as serious side effects in the clinical trials listed in Table 1. Only data from the six forms of pain discussed in the "Major Pain Events" section are listed here.

Headache

Clinical trial No.	Positive counts in	Negative counts in	Positive counts	Negative counts
	experimental group	experimental group	in control group	in control group
NCT00558103	1	37	0	13
NCT00374322	0	1573	1	1573
NCT00553358	0	152	1	148
NCT00490139	2	2059	1	2075
NCT00073528	0	654	2	622
NCT00390455	2	139	0	137
NCT00075270	1	292	0	286
NCT00770809	0	115	1	114

Arthralgia

Clinical trial No.	Positive counts in experimental group	Negative counts in experimental group	Positive counts in control group	Negative counts in control group
NCT00486954	1	130	0	129
NCT00490139	1	2060	0	2076
NCT00073528	2	652	5	619
NCT00390455	0	141	1	136
NCT00075270	2	291	0	286
NCT00680901	0	270	1	266

Bone pain

Clinical trial No.	Positive counts in	Negative counts in	Positive counts	Negative counts
	experimental group	experimental group	in control group	in control group
NCT00073528	1	651	1	623

NCT00390455	0	141	1	136
NCT00374322	0	1573	1	1573
NCT00680901	0	270	1	266
NCT00770809	0	115	1	114
Myalgia				
Clinical trial No.	Positive counts in experimental group	Negative counts in experimental group	Positive counts in control group	Negative counts in control group
NCT00490139	2	2059	0	2076
NCT00075270	0	293	1	285
NCT00770809	3	112	2	113
NCT00374322	0	1573	1	1573
NCT00424255	1	348	1	335
Pain in extremity				
Clinical trial No.	Positive counts in experimental group	Negative counts in experimental group	Positive counts in control group	Negative counts in control group
NCT00073528	1	653	0	624
NCT00075270	3	290	0	286
Musculoskeletal pai	n			
Clinical trial No.	Positive counts in experimental group	Negative counts in experimental group	Positive counts in control group	Negative counts in control group
NCT00073528	1	653	0	624

Table S2. Analysis of risks of bias about clinical trials used in this meta-analysis.

Clinical Trial #	Random Sequence Generation	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
NCT00486954	О	X	X	О	О	О
NCT00387127	О	О	O	О	O	О
NCT00558103	О	О	0	О	0	X ^a
NCT00374322	О	O	O	О	O	О
NCT00430781	О	X	X	О	0	О
NCT00680901	О	O	O	О	O	О
NCT00553358	О	X	X	О	0	О
NCT00371566	О	О	X	O	О	X ^a
NCT00424255	О	О	O	О	O	О
NCT00490139	О	X	X	O	O	О
NCT00073528	О	О	О	О	0	О
NCT00429299	0	X	X	О	О	0
NCT00390455	О	О	О	О	0	О
NCT00422903	О	О	О	О	О	О

NCT00524303	0	X	X	О	О	0
NCT00075270	О	О	О	О	O	0
NCT00770809	0	X	X	О	О	О
NCT00281658	О	О	О	О	O	О
NCT00968968	0	X	X	О	О	O
NCT01160211	О	X	X	О	O	О
	a: Patient numbe	r in experimenta	l group and cont	rol group are no	ot about equal	
0	Low Risk of Bias					
X	High Risk of Bias					
?	Not Enough Info	rmation				

Table S3. Patient counts of different kinds of pain tolled this meta-analysis.

Pain Type	Patient
	Count
Headache	12661
Arthralgia	11268
Myalgia	8420
Musculoskeletal pain	7664
Pain in extremity	6887
Bone pain	6563
Pharyngolaryngeal pain	3438
Chest pain	2679
Neck pain	2191
Oral pain	1567
Skin pain	1284
Toothache	979
Breast pain	849
Ear pain	750
Pain in jaw	579
Tumor Pain	579
Groin Pain	579
Lymph node pain	579
Pleuritic pain	579
Neuralgia	579
Procedural Pain	197
Pelvic Pain	150
Cancer Pain	51

Table S4. Drug used in experimental group and control group in the 20 trials analyzed

Clinical trial #	Experimental group	Control group
NCT00486954	Lapatinib + Paclitaxel	Paclitaxel Alone
NCT00387127	Chemoradiotherapy + Lapatinib,	Chemoradiotherapy + Placebo,
	Followed by Lapatinib	Followed by Placebo
NCT00558103	Lapatinib + Pazopanib	Pazopanib
NCT00374322	Lapatinib	Placebo
NCT00430781	Lapatinib + Pazopanib	Pazopanib
NCT00680901	CapeOx + Lapatinib	CapeOx + Placebo
NCT00553358	Lapatinib + Trastuzumab	Trastuzumab
NCT00371566	Lapatinib	Placebo
NCT00424255	Lapatinib	Placebo
NCT00490139	Lapatinib + Trastuzumab	Trastuzumab
NCT00073528	Letrozole + Lapatinib	Letrozole + Placebo
NCT00429299	Chemoradiotherapy + Trastuzumab	Chemotherapy + Trastuzumab
	+ Lapatinib	
NCT00390455	Lapatinib	Placebo
NCT00422903	Letrozole + Lapatinib	Letrozole + Placebo
NCT00524303	Trastuzumab + Lapatinib	Trastuzumab
NCT00075270	Lapatinib + Paclitaxel	Placebo + Paclitaxel
NCT00770809	Trastuzumab + Paclitaxel +	Trastuzumab + Paclitaxel
	Lapatinib	
NCT00281658	Lapatinib + Paclitaxel	Placebo + Paclitaxel
NCT00968968	Lapatinib + Trastuzumab	Trastuzumab
NCT01160211	Lapatinib + Trastuzumab +	Trastuzumab + Aromatase
	Aromatase Inhibitors	Inhibitors

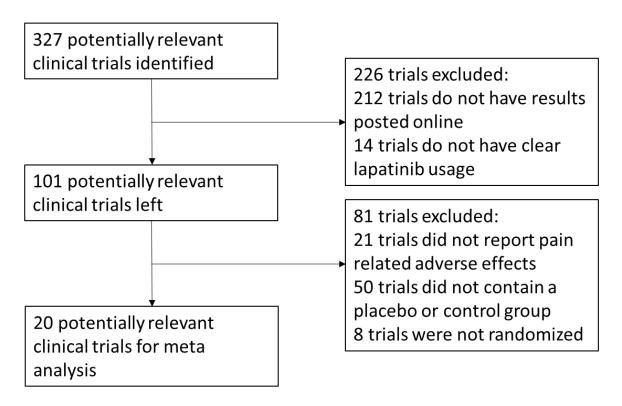
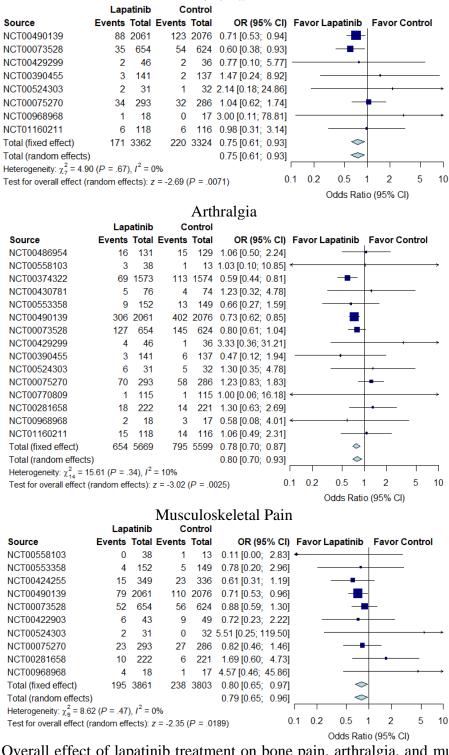
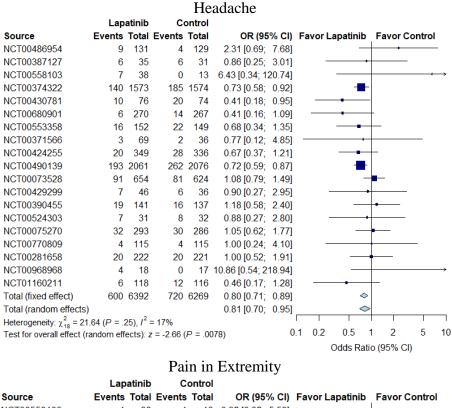


Figure S1. Flow chart for the study selection process of this meta-analysis



Bone Pain

Figure S2-1. Overall effect of lapatinib treatment on bone pain, arthralgia, and musculoskeletal pain. Sizes of data markers are proportional to the amount of data contributed by each trial. OR, odds ratio; CI, confidence interval.



	Lap	atinib	C	ontrol							
Source	Events	Total	Events	Total	OR (95	% CI)	Favo	Lapatinib	Favo	or Contro	d
NCT00558103	1	38	1	13	0.32 [0.02;	5.59]	-	-	_		
NCT00430781	4	76	8	74	0.46 [0.13;	1.59]	_		\vdash		
NCT00490139	135	2061	175	2076	0.76 [0.60;	0.96]		-	-		
NCT00073528	66	654	71	624	0.87 [0.61;	1.25]		-	┿		
NCT00429299	1	46	1	36	0.78 [0.05;	12.88]	-		_		→
NCT00390455	1	141	4	137	0.24 [0.03;	2.15]	-	•——	_	-	
NCT00524303	5	31	6	32	0.83 [0.23;	3.07]			_		
NCT00075270	50	293	50	286	0.97 [0.63;	1.49]		_	-		
NCT00968968	4	18	2	17	2.14 [0.34;	13.59]			_	•	→
NCT01160211	8	118	4	116	2.04 [0.60;	6.96]		_	┼		-
Total (fixed effect)	275	3476	322	3411	0.82 [0.70;	0.98]		•	>		
Total (random effects)					0.82 [0.70;	0.98]		<	>		
Heterogeneity: $\chi_9^2 = 6.71$	1 (P = .67)), I ² = (0%								
Test for overall effect (ra	andom eff	ects): z	z = -2.21	(P = .0)	269)	0	0.1	2 0.5	1 2	5	10
								Odds Rat	io (95%	6 CI)	

Figure S2-2. Overall effect of lapatinib treatment on headache and pain in extremity. Sizes of data markers are proportional to the amount of data contributed by each trial. OR, odds ratio; CI, confidence interval.

Myalgia

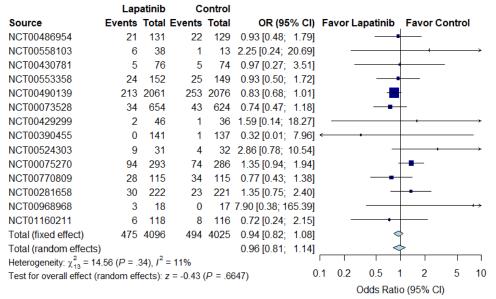


Figure S2-3. Overall effect of lapatinib treatment on myalgia. Sizes of data markers are proportional to the amount of data contributed by each trial. OR, odds ratio; CI, confidence interval.

	Lap	atinib	C	ontrol						
Source	Events	Total	Events	Total	OR (95% CI	Favo	r Lapatinib	Favor	Control	I
NCT00486954	15.33	131	13.67	129	1.12 [0.52; 2.42]			•		
NCT00387127	6.00	35	6.00	31	0.86 [0.25; 3.01]				_	
NCT00558103	3.40	38	0.80	13	1.50 [0.12; 18.65]					\rightarrow
NCT00374322	104.50	1573	149.00	1574	0.68 [0.52; 0.88]		-			
NCT00430781	6.00	76	9.25	74	0.60 [0.20; 1.77]	·	+	_		
NCT00680901	6.00	270	14.00	267	0.41 [0.16; 1.09]	-	-	+		
NCT00553358	13.25	152	16.25	149	0.78 [0.36; 1.67]					
NCT00371566	3.00	69	2.00	36	0.77 [0.12; 4.85]		•			
NCT00424255	17.50	349	25.50	336	0.64 [0.34; 1.20]			+		
NCT00490139	169.00	2061	220.83	2076	0.75 [0.61; 0.93]		-			
NCT00073528	67.50	654	75.00	624	0.84 [0.59; 1.19]	l	-	+		
NCT00429299	3.20	46	2.20	36	1.15 [0.19; 6.78]	-				
NCT00390455	5.20	141	5.80	137	0.87 [0.26; 2.90]				_	
NCT00422903	6.00	43	9.00	49	0.72 [0.23; 2.22]	l	-	_		
NCT00524303	5.17	31	4.00	32	1.40 [0.34; 5.74]					
NCT00075270	50.50	293	45.17	286	1.11 [0.72; 1.72]	l	_	-		
NCT00770809	11.00	115	13.00	115	0.83 [0.36; 1.94]	l		_		
NCT00281658	19.50	222	15.75	221	1.25 [0.63; 2.51]				-	
NCT00968968	3.00	18	1.00	17	3.20 [0.30; 34.24]	l			+	\rightarrow
NCT01160211	8.20	118	8.80	116	0.91 [0.34; 2.44]	l				
Total (fixed effect)	523.25	6435	637.02	6318	0.79 [0.70; 0.89]	l	♦			
Total (random effects)					0.79 [0.70; 0.89]	l	♦			
Heterogeneity: $\chi_{19}^2 = 11$.	37 (P = .9)	91), <i>I</i> 2 :	= 0%					1		
Test for overall effect (ra	andom eff	ects): z	z = -3.77 (P = .00	002)	0.1 0.	2 0.5	1 2	5	10
							Odds Rati	o (95%	CI)	

Figure S2-4. Overall effect of the lapatinib treatment on various forms of pain. Sizes of data markers are proportional to the amount of data contributed by each trial. OR, odds ratio; CI, confidence interval.

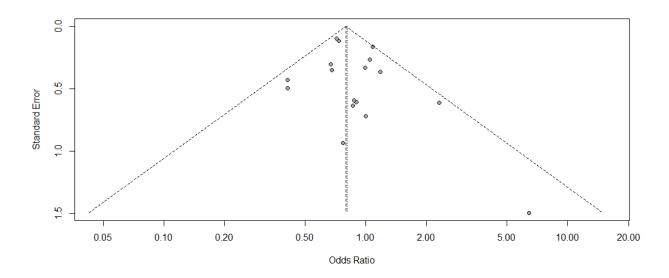


Figure S3-1. Funnel plot for headache

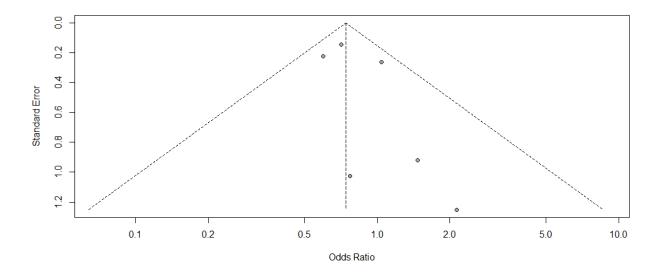


Figure S3-2. Funnel plot for bone pain

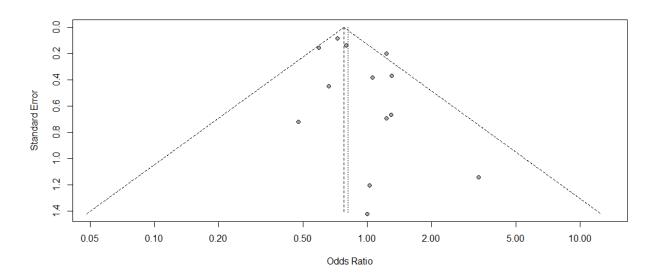


Figure S3-3. Funnel plot for arthralgia

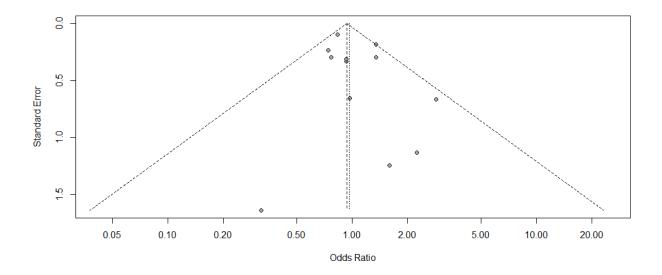


Figure S3-4. Funnel plot for myalgia

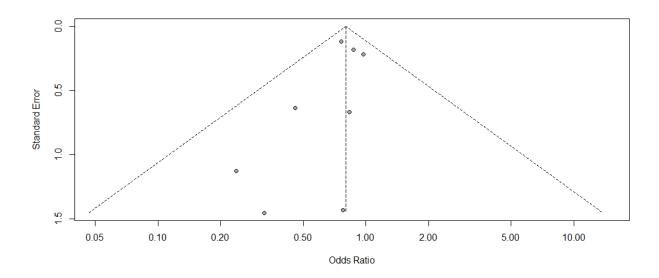


Figure S3-5. Funnel plot for pain in extremity

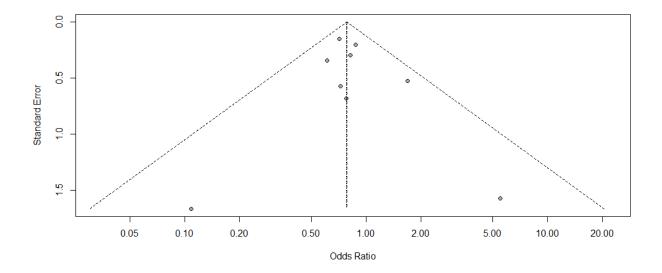


Figure S3-6. Funnel plot for musculoskeletal pain

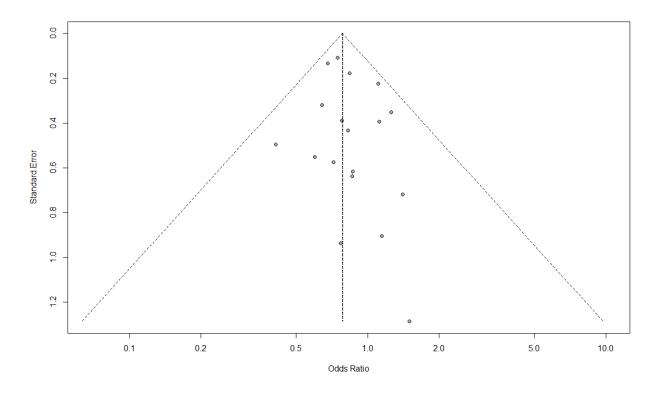


Figure S3-7. Funnel plot for the overall effect analysis

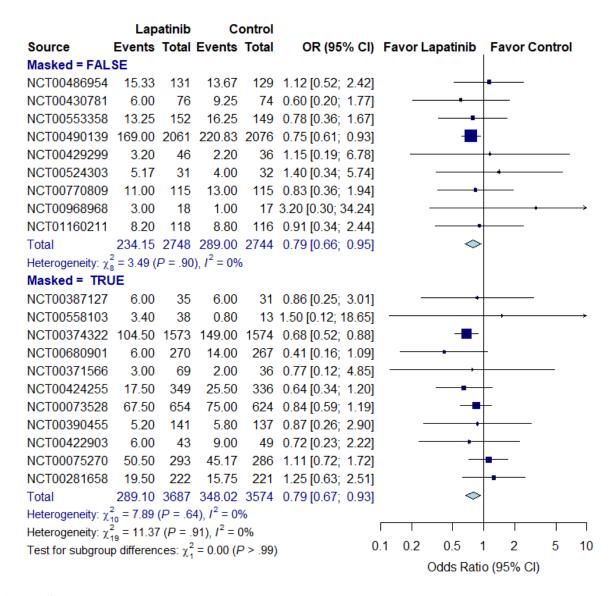


Figure S4-1. Overall pain-relieving effect of lapatinib, grouped by the factor concerning whether the trials were masked or not.

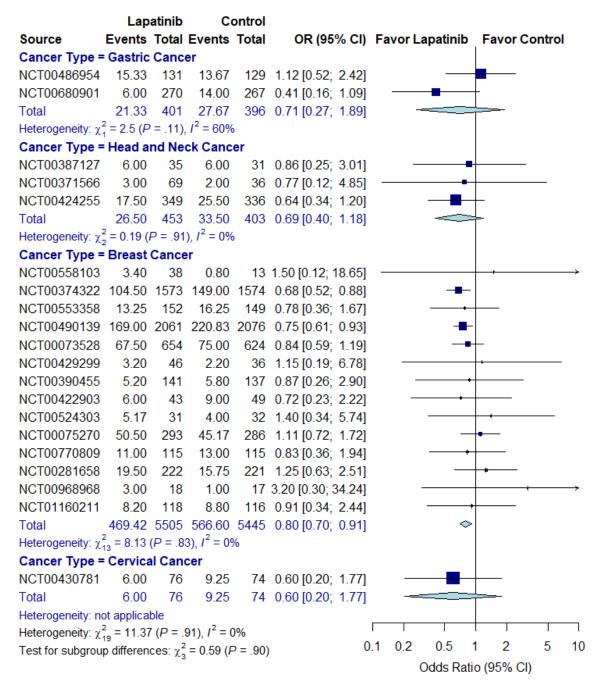


Figure S4-2. Overall pain-relieving effect of lapatinib, grouped by the cancer type of the recruited patients.

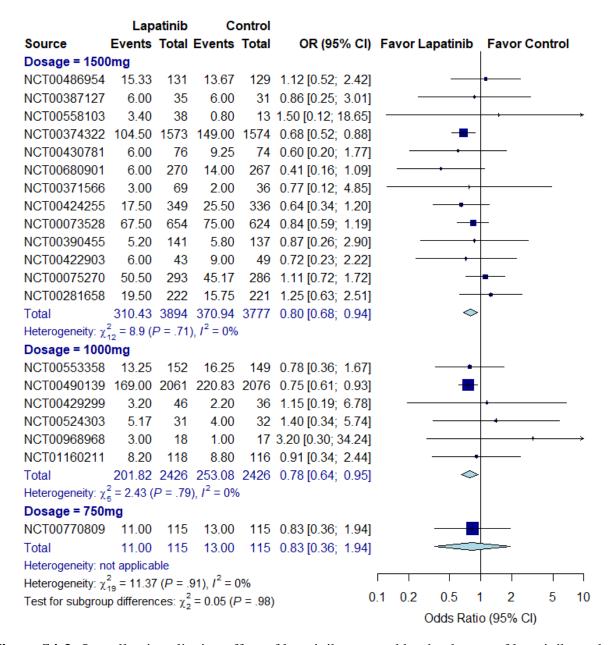


Figure S4-3. Overall pain-relieving effect of lapatinib, grouped by the dosage of lapatinib used in these trials.

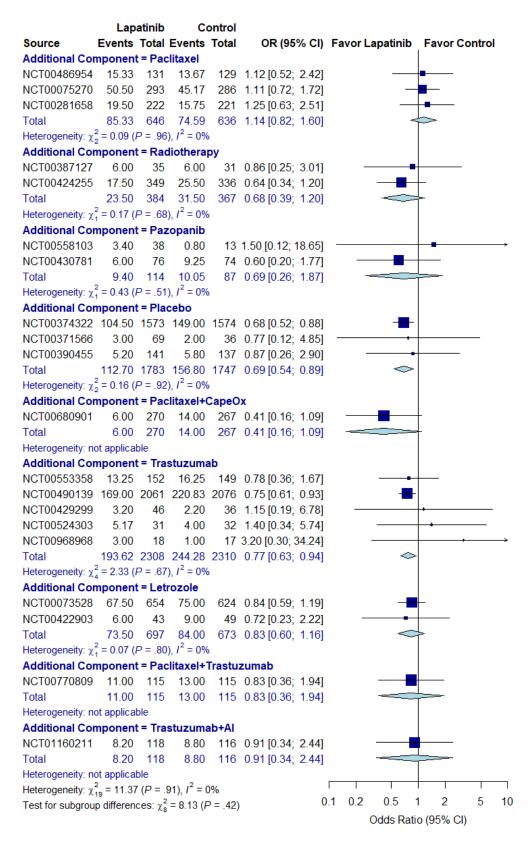


Figure S4-4. Overall pain-relieving effect of lapatinib, grouped by the additional components involved in these trials.

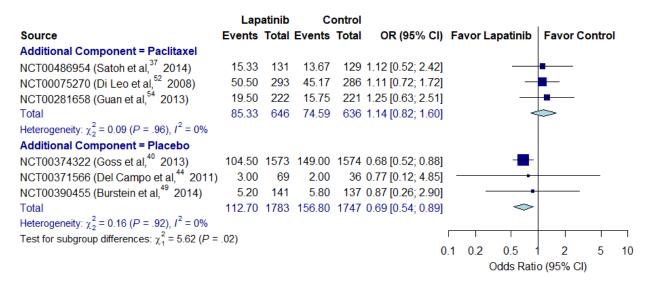


Figure S4-5. Overall pain-relieving effect of lapatinib, comparing only the group with paclitaxel used and the pure placebo control group.

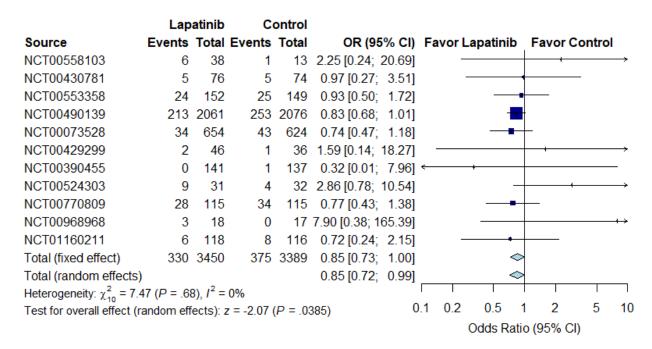


Figure S5-1. Effect of lapatinib on myalgia, when NCT00075270, NCT00486954, and NCT00281658 were excluded.

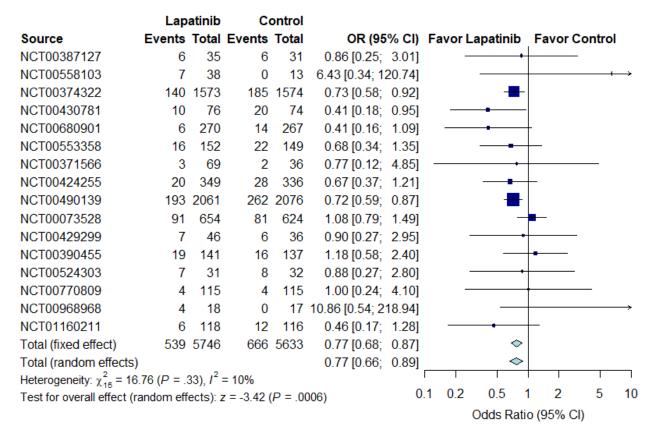


Figure S5-2. Effect of lapatinib on headache, when NCT00075270, NCT00486954, and NCT00281658 were excluded.

	Lap	atinib	C	ontrol							
Source	Events	Total	Events	Total	OR (95% CI)	Fa	vor L	apatinib	Fav	or Conti	ol
NCT00490139	88	2061	123	2076	0.71 [0.53; 0.94]			-			
NCT00073528	35	654	54	624	0.60 [0.38; 0.93]			-			
NCT00429299	2	46	2	36	0.77 [0.10; 5.77]	—		+			-
NCT00390455	3	141	2	137	1.47 [0.24; 8.92]		_		+		
NCT00524303	2	31	1	32	2.14 [0.18; 24.86]					+	\longrightarrow
NCT00968968	1	18	0	17	3.00 [0.11; 78.81]	—				-	\longrightarrow
NCT01160211	6	118	6	116	0.98 [0.31; 3.14]				\leftarrow		
Total (fixed effect)	137	3069	188	3038	0.71 [0.56; 0.89]			\Diamond			
Total (random effects))				0.71 [0.56; 0.89]						
Heterogeneity: $\chi_6^2 = 3.0$	5 (P = .80)), $I^2 = 0$	0%						I	1	l
Test for overall effect (r	andom eff	ects): z	z = -3.01 (P = .0	026)	0.1	0.2	0.5	1 2	2 5	10
							(Odds Rati	o (95°	% CI)	

Figure S5-3. Effect of lapatinib on bone pain, when NCT00075270, NCT00486954, and NCT00281658 were excluded.

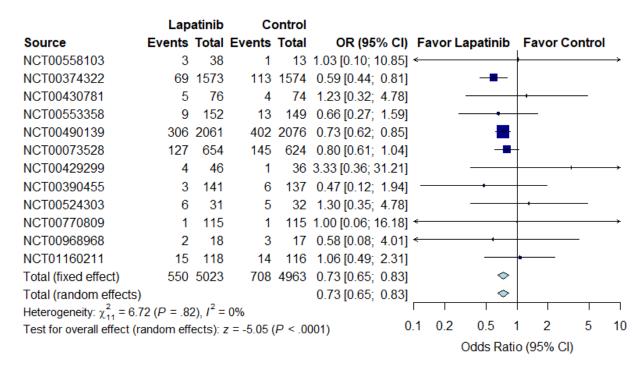


Figure S5-4. Effect of lapatinib on arthralgia, when NCT00075270, NCT00486954, and NCT00281658 were excluded.

	Lap	atinib	C	ontrol							
Source	Events	Total	Events	Total	OR (95%	CI) F	Favor La	apatinib	Favo	r Contro	ol
NCT00558103	1	38	1	13	0.32 [0.02; 5.5	59] +		+			
NCT00430781	4	76	8	74	0.46 [0.13; 1.5	59]		•			
NCT00490139	135	2061	175	2076	0.76 [0.60; 0.9	96]		-			
NCT00073528	66	654	71	624	0.87 [0.61; 1.2	25]		-	_		
NCT00429299	1	46	1	36	0.78 [0.05; 12.8	88] <					\longrightarrow
NCT00390455	1	141	4	137	0.24 [0.03; 2.1	15] 숙	•			-	
NCT00524303	5	31	6	32	0.83 [0.23; 3.0	07]		-			
NCT00968968	4	18	2	17	2.14 [0.34; 13.5	59]				•	→
NCT01160211	8	118	4	116	2.04 [0.60; 6.9	96]			-		_
Total (fixed effect)	225	3183	272	3125	0.80 [0.66; 0.9	96]		\Diamond			
Total (random effects)					0.80 [0.66; 0.9	96]		\Diamond			
Heterogeneity: $\chi_{g}^{2} = 6.09$	5 (P = .64	$I^2 = 0$	0%			Г	I				
Test for overall effect (r	andom eff	ects): z	z = -2.35 (P = .0	187)	0.1	0.2	0.5	1 2	5	10
			(Odds Rati	o (95%	GCI)					

Figure S5-5. Effect of lapatinib on pain in extremity, when NCT00075270, NCT00486954, and NCT00281658 were excluded.

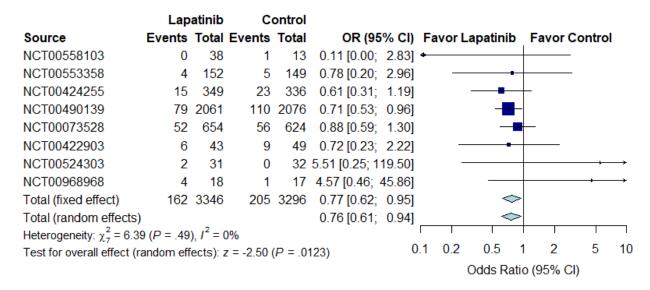


Figure S5-6. Effect of lapatinib on musculoskeletal pain, when NCT00075270, NCT00486954, and NCT00281658 were excluded.

	Afa	atinib	C	ontrol								
Pain	Events	Total	Events	Total	OR (95% CI)	Fa	vor A	Afatinib		avor C	Contro	I
Pain in extremity	27	390	4	195	3.55 [1.22; 10.30]				-		-	\rightarrow
Headache	21	390	9	195	1.18 [0.53; 2.62]			_	-	_		
Chest pain	27	390	11	195	1.24 [0.60; 2.56]							
Test for overall eff	ect: z = 1	.44 (P	= .1491)				ı	ı	ı	ı	ı	
					0).1	0.2	0.5	1	2	5	10
								Odds Ra	atio	(95% C	I)	

Figure S6. Effects of afatinib on various forms of pain. Data from NCT00656136.¹

Formula for Calculation of Odds Ratio (OR):

	Diseased	Healthy
Exposed	$D_{ m E}$	$H_{ m E}$
Not exposed	$D_{ m N}$	$H_{ m N}$

$OR = (D_E/H_E)/(D_N/H_N) = (D_EH_N)/(D_NH_E)$

For synthesis of the data from multiple trials, the detailed procedure of the random-effects model² used to calculate the weight of each trial used in the meta-analysis can be found in reference.³

References

- Miller, V. A. *et al.* Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. **13**, 528-538 (2012).
- Veroniki, A. A. *et al.* Methods to estimate the between-study variance and its uncertainty in meta-analysis. *Res Synth Methods* **7**, 55-79, doi:10.1002/jrsm.1164 (2016).
- 3 Schwarzer, G., Carpenter, J. R. & Rücker, G. *Meta-analysis with R.* (Springer, 2015).

ROBIS analysis

Phase I

Category	Target question (e.g. overview or guideline)
Patients/Population(s):	Cancer patients
Intervention(s):	Therapy with lapatinib
Comparator(s):	Same therapy to the intervention group except lapatinib
Outcome(s):	Number of patients complaining about pains as adverse
	effects

Phase II

1. Study eligibility criteria

Signaling questions/Reviews	1.1 Did the review adhere to predefined objectives and eligibility criteria?	1.2 Were the eligibility criteria appropriate for the review question?	1.3 Were eligibility criteria unambiguous?	1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate	1.5 Were any restrictions in eligibility criteria based on sources of information appropriate
Bone pain	Υ	Υ	Υ	Υ	Υ
Arthralgia	Υ	Υ	Υ	Υ	Υ
Musculoskeletal pain	Υ	Υ	Υ	Υ	Υ
Headache	Υ	Υ	Υ	Υ	Υ
Pain in extremity	Υ	Υ	Υ	Υ	Υ
Myalgia	Υ	Υ	Υ	Υ	Υ
Overall	Υ	Υ	Υ	Υ	Υ

2. Identification and selection of studies

Signaling questions/Reviews	2.1 Did the search include an appropriate range of database/electronic sources for published and unpublished reports?	2.2 Were methods additional to database searching used to identify relevant reports?	2.3 Were the terms and structure of the search strategy likely to retrieve as many as eligible studies as possible	2.4 Were restrictions based on date, publication format, or language appropriate?	2.5 Were efforts made to minimize error in selection of studies
Bone pain	Υ	N	Υ	Υ	Υ

ROBIS analysis

Arthralgia	Υ	N	Υ	Υ	Υ
Musculoskeletal pain	Υ	N	Υ	Υ	Υ
Headache	Υ	N	Υ	Υ	Υ
Pain in extremity	Υ	N	Υ	Υ	Υ
Myalgia	Υ	N	Υ	Υ	Υ
Overall	Υ	N	Υ	Υ	Υ

3. Data collection and study appraisal

Signaling	3.1 Were	3.2 Were	3.3 Were	3.4 Was risk of	3.5 Were
questions/Reviews	efforts	sufficient	all relevant	bias (or	efforts made
	made to	study	study	methodologic	to minimize
	minimize	characteristics	results	quality)	error in risk
	error in	available for	collected	formally	of bias
	data	both authors	for use in	assessed using	assessment?
	collection?	and readers to	the	appropriate	
		be able to	synthesis?	criteria?	
		interpret the			
		results?			
Bone pain	Υ	Υ	Υ	Υ	Υ
Arthralgia	Υ	Υ	Υ	Υ	Υ
Musculoskeletal pain	Υ	Υ	Υ	Υ	Υ
Headache	Υ	Υ	Υ	Υ	Υ
Pain in extremity	Υ	Υ	Υ	Υ	Υ
Myalgia	Υ	Υ	Υ	Υ	Υ
Overall	Υ	Υ	Υ	Υ	Υ

4. Synthesis and findings

Signaling questions/Reviews	4.1 Did the synthesis include all studies that it should?	4.2 Were all predefined analyses reported or departures explained?	4.3 Was the synthesis appropriate given the nature and similarity in the research question, study designs, and outcomes across included studies?	4.4 Was between- study variation minimal or addressed in the synthesis	4.5 Were the findings robust, for example, as demonstrated through funnel plot or sensitivity analyses?	4.6 Were biases in primary studies minimal or addressed in the synthesis?
Bone pain	Υ	Υ	Υ	Υ	Υ	Υ

ROBIS analysis

Arthralgia	Υ	Υ	Υ	Υ	Υ	Υ
Musculoskeletal	Υ	Υ	Υ	Υ	Υ	Υ
pain						
Headache	Υ	Υ	Υ	Υ	Υ	Υ
Pain in extremity	Υ	Υ	Υ	Υ	Υ	Υ
Myalgia	Υ	Υ	Υ	Υ	Υ	Υ
Overall	Υ	Υ	Υ	Υ	Υ	Υ

Phase III

Risk of bias in the review

Signaling questions/Reviews	A. Did the interpretation of findings address all of the concerns identified in domain 1 to 4 of Phase 2?	B. Was the relevance of identified studies to the review's research question appropriately considered?	C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?
Bone pain	Y	Y	N
Arthralgia	Y	Y	N
Musculoskeletal pain	Y	Y	N
Headache	Y	Y	N
Pain in extremity	Y	Y	N
Myalgia	Y	Y	N
Overall	Y	Y	N