# 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,*]

*[1]Molecular Modeling and Biopharmaceutical Center, College of Pharmacy, University of Kentucky, 789 South Limestone Street, Lexington, KY 40536. [2]Department 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 experimental group | Negative counts in experimental group | Positive counts in control group | Negative counts 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 experimental group | Negative counts in experimental group | Positive counts in control group | Negative counts 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 pain** | | | | |
| **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** | O | X | X | O | O | O |
| **NCT00387127** | O | O | O | O | O | O |
| **NCT00558103** | O | O | O | O | O | X[a] |
| **NCT00374322** | O | O | O | O | O | O |
| **NCT00430781** | O | X | X | O | O | O |
| **NCT00680901** | O | O | O | O | O | O |
| **NCT00553358** | O | X | X | O | O | O |
| **NCT00371566** | O | O | X | O | O | X[a] |
| **NCT00424255** | O | O | O | O | O | O |
| **NCT00490139** | O | X | X | O | O | O |
| **NCT00073528** | O | O | O | O | O | O |
| **NCT00429299** | O | X | X | O | O | O |
| **NCT00390455** | O | O | O | O | O | O |
| **NCT00422903** | O | O | O | O | O | O |

| | | | | | | |
|---|---|---|---|---|---|---|
| **NCT00524303** | O | X | X | O | O | O |
| **NCT00075270** | O | O | O | O | O | O |
| **NCT00770809** | O | X | X | O | O | O |
| **NCT00281658** | O | O | O | O | O | O |
| **NCT00968968** | O | X | X | O | O | O |
| **NCT01160211** | O | X | X | O | O | O |
| | a: Patient number in experimental group and control group are not about equal | | | | | |
| **O** | Low Risk of Bias | | | | | |
| **X** | High Risk of Bias | | | | | |
| **?** | Not Enough Information | | | | | |

**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, Followed by Lapatinib | Chemoradiotherapy + Placebo, 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 + Lapatinib | Chemotherapy + Trastuzumab |
| **NCT00390455** | Lapatinib | Placebo |
| **NCT00422903** | Letrozole + Lapatinib | Letrozole + Placebo |
| **NCT00524303** | Trastuzumab + Lapatinib | Trastuzumab |
| **NCT00075270** | Lapatinib + Paclitaxel | Placebo + Paclitaxel |
| **NCT00770809** | Trastuzumab + Paclitaxel + Lapatinib | Trastuzumab + Paclitaxel |
| **NCT00281658** | Lapatinib + Paclitaxel | Placebo + Paclitaxel |
| **NCT00968968** | Lapatinib + Trastuzumab | Trastuzumab |
| **NCT01160211** | Lapatinib + Trastuzumab + Aromatase Inhibitors | Trastuzumab + Aromatase Inhibitors |

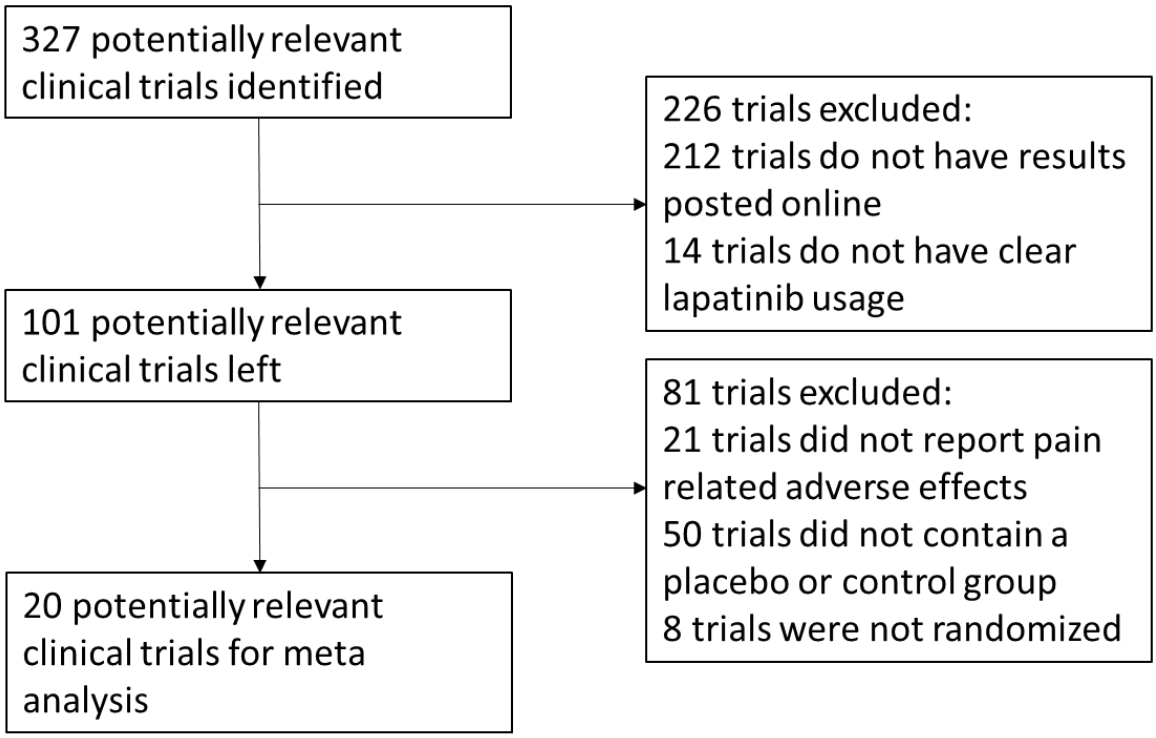


**Figure S1**. Flow chart for the study selection process of this meta-analysis

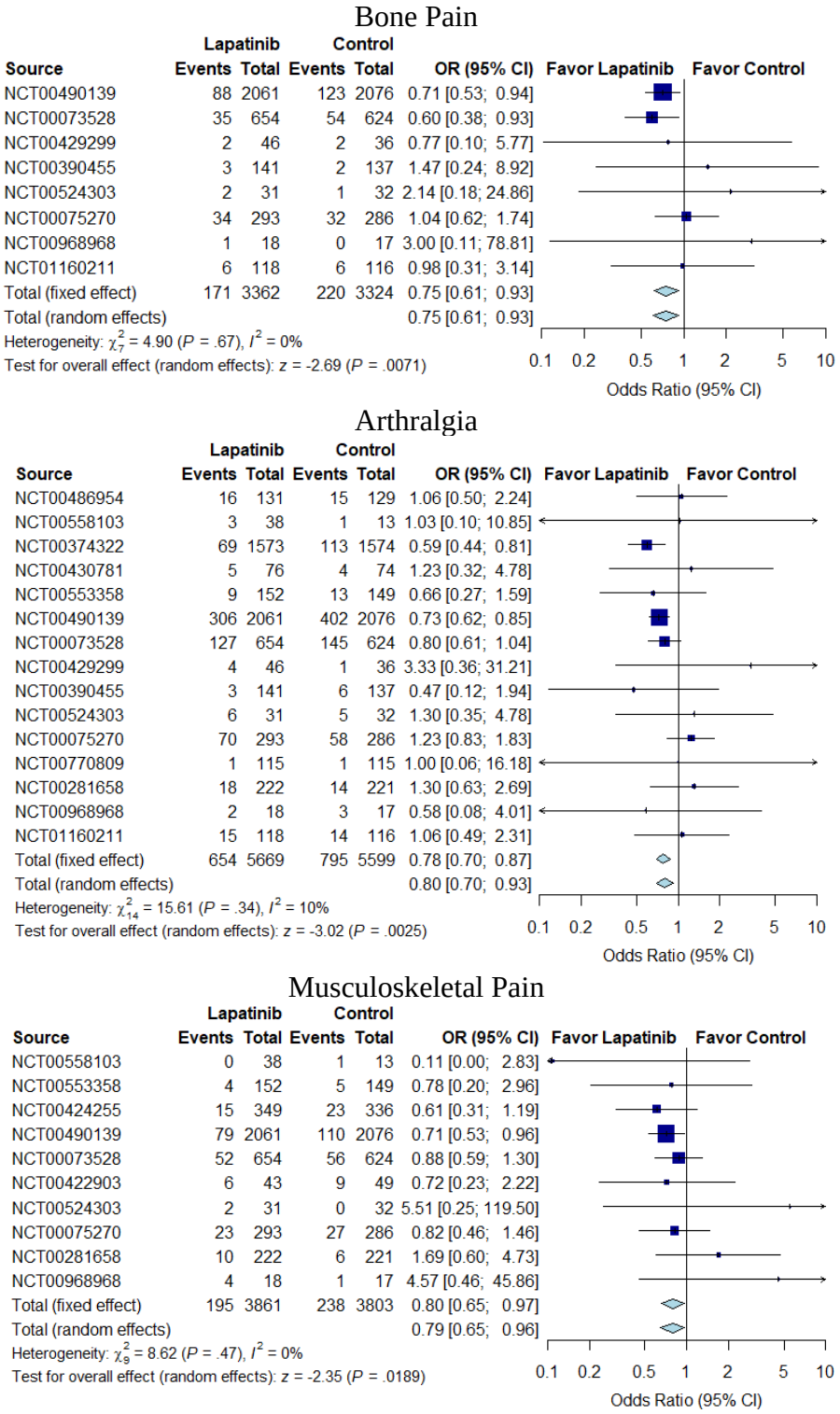


**Figure S2-1**. Overall effect of lapatinib treatment on bone pain, arthralgia, and musculoskeletal pain. Sizes of data markers are proportional to the amount of data contributed by each trial. OR, odds ratio; CI, confidence interval.

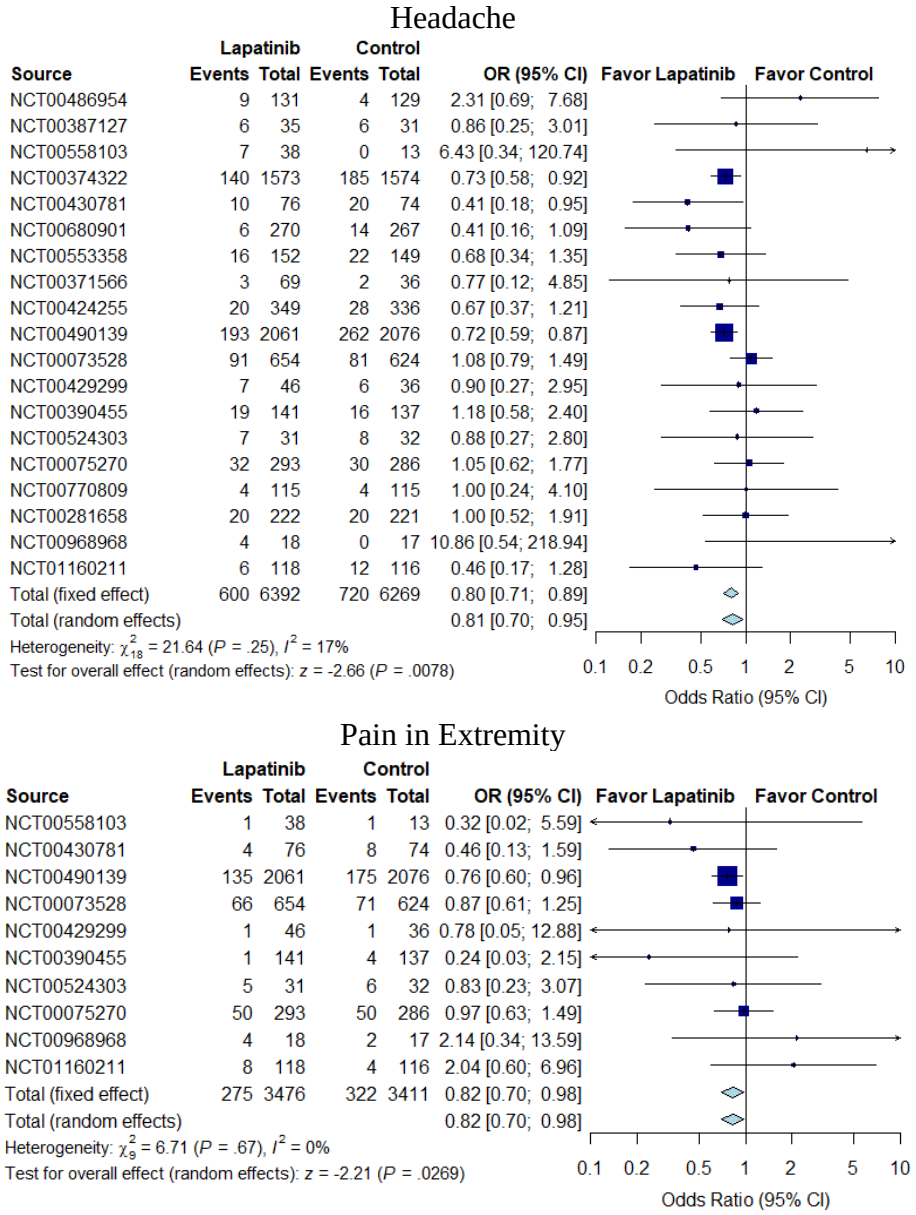


**Figure S2-2**. Overall effect of lapatinib treatment on headache and pain in extremity. Sizes of data markers are proportional to the amount of data contributed by each trial. OR, odds ratio; CI, confidence interval.

Myalgia

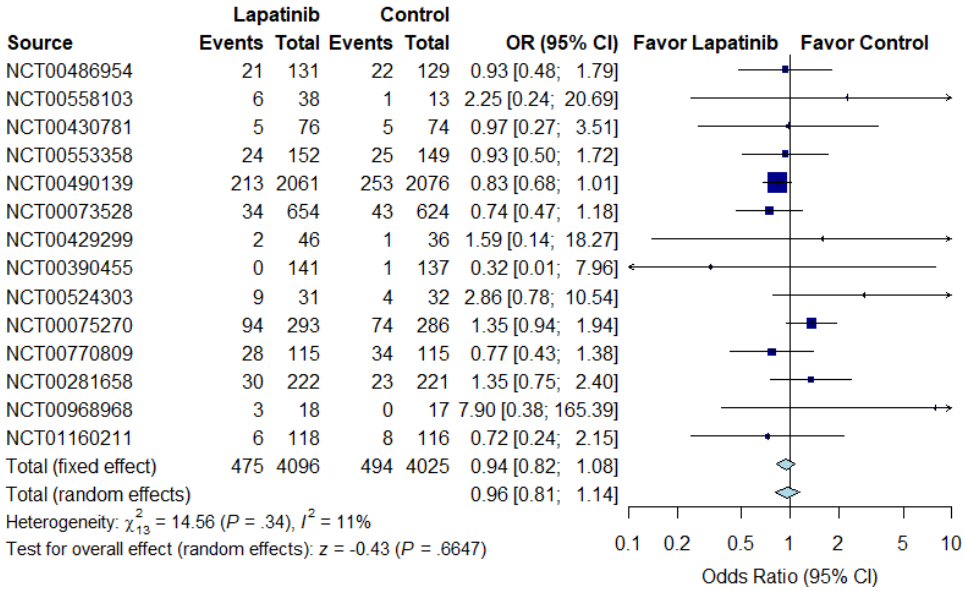


**Figure S2-3**. Overall effect of lapatinib treatment on myalgia. Sizes of data markers are proportional to the amount of data contributed by each trial. OR, odds ratio; CI, confidence interval.

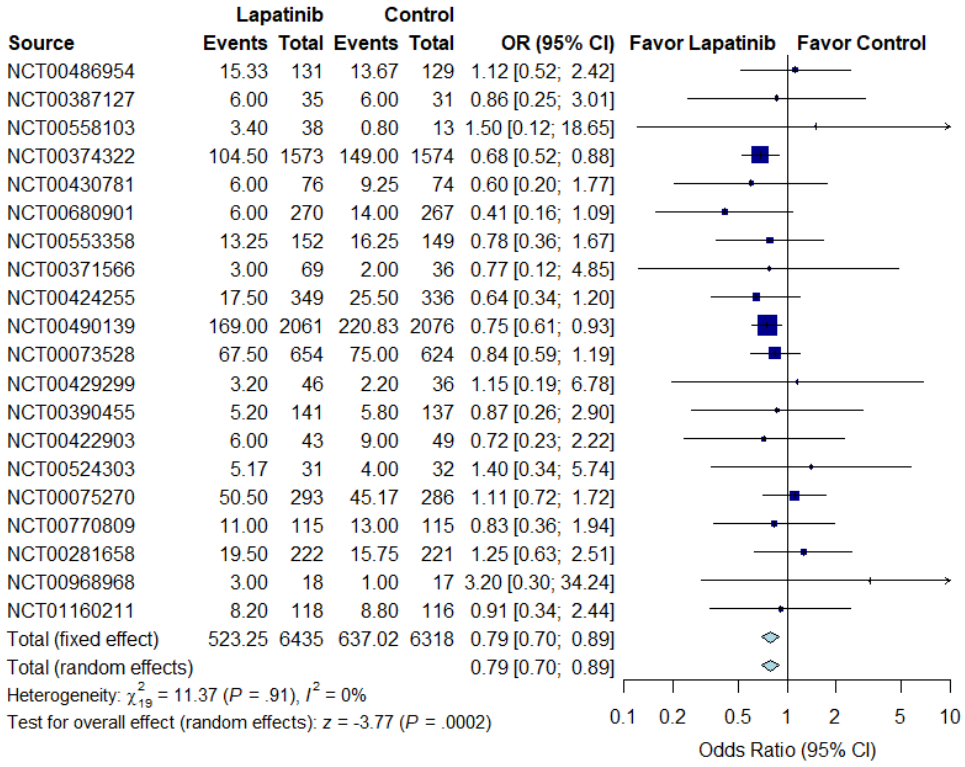


**Figure S2-4**. Overall effect of the lapatinib treatment on various forms of pain. Sizes of data markers are proportional to the amount of data contributed by each trial. OR, odds ratio; CI, confidence interval.

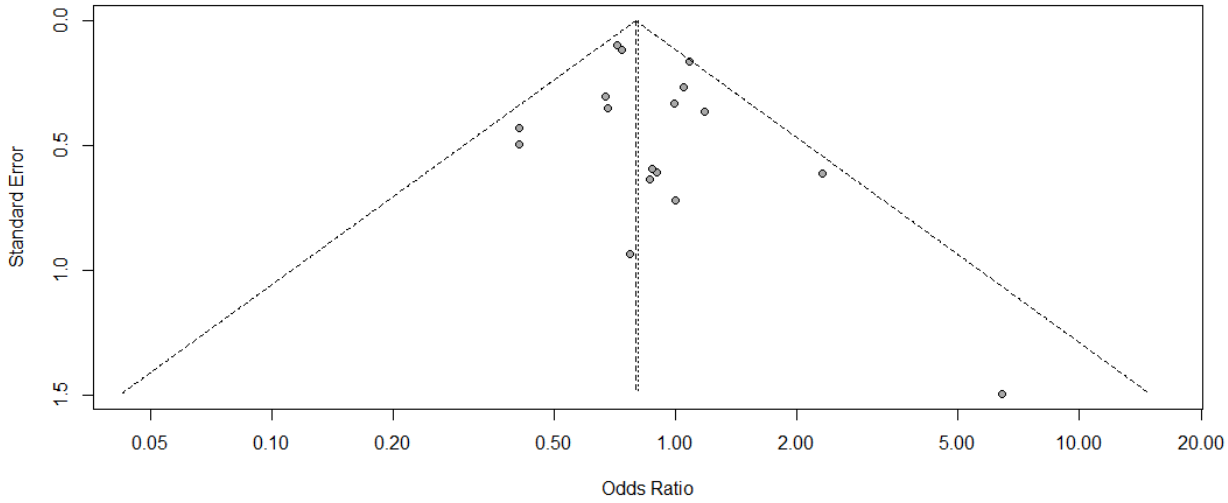


**Figure S3-1**. Funnel plot for headache

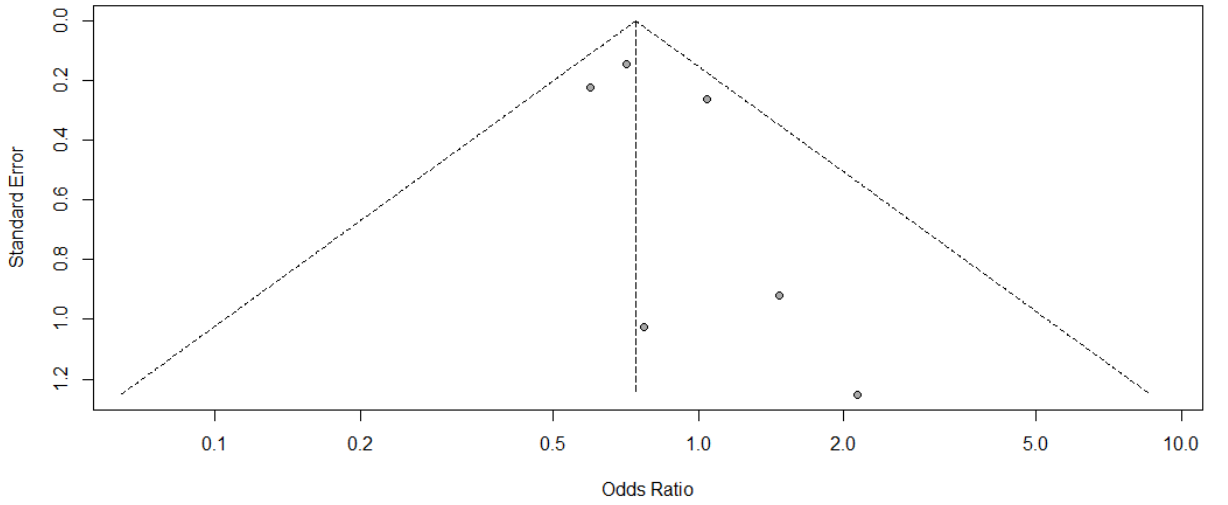


**Figure S3-2**. Funnel plot for bone pain

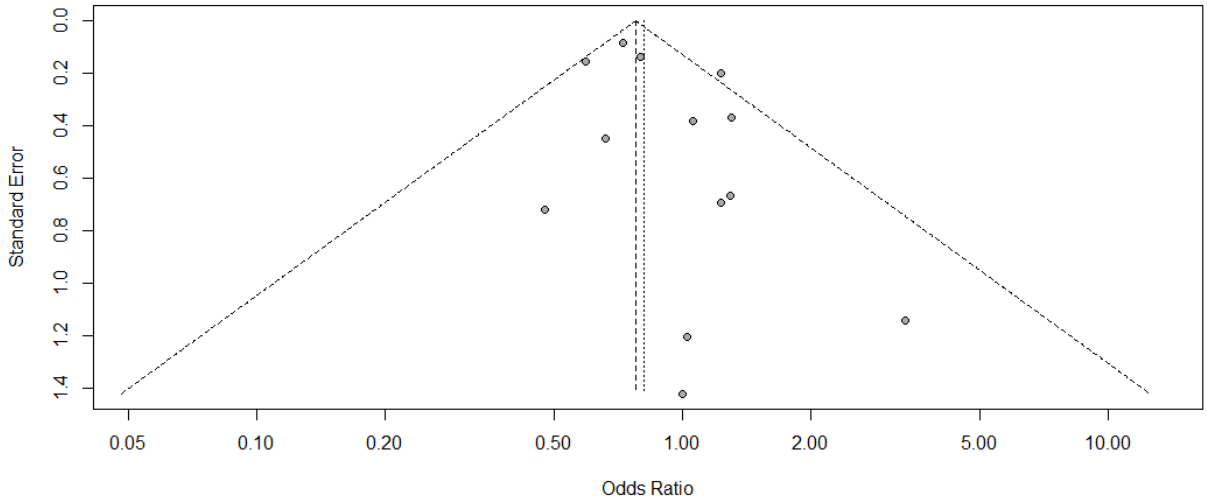


**Figure S3-3**. Funnel plot for arthralgia

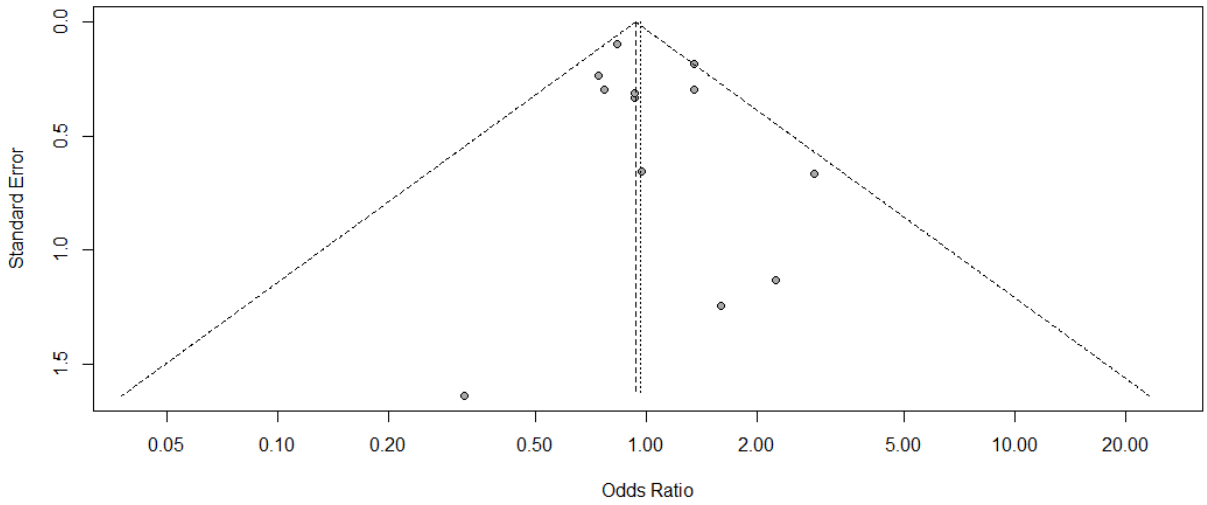


**Figure S3-4**. Funnel plot for myalgia

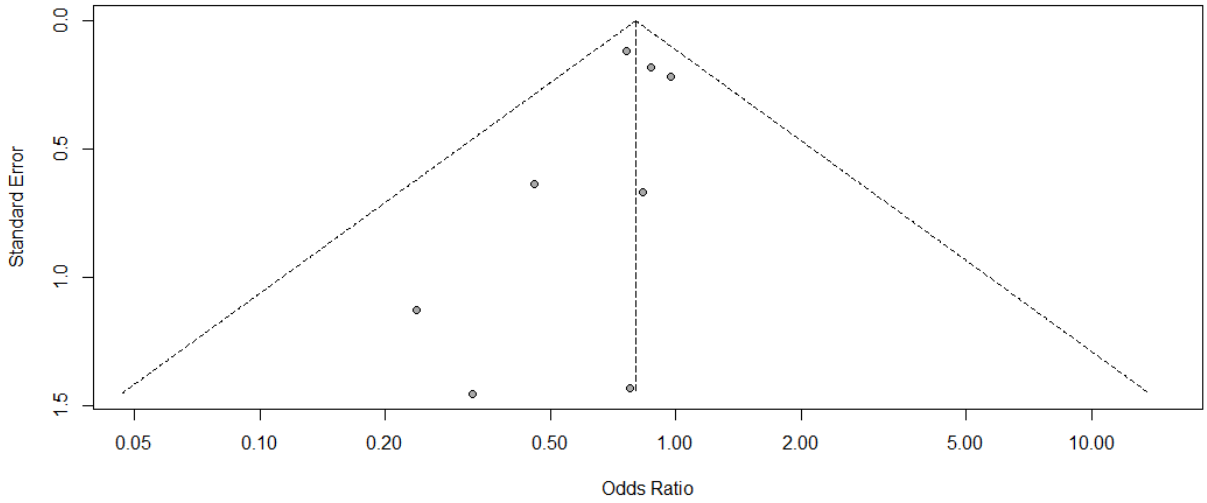


**Figure S3-5**. Funnel plot for pain in extremity

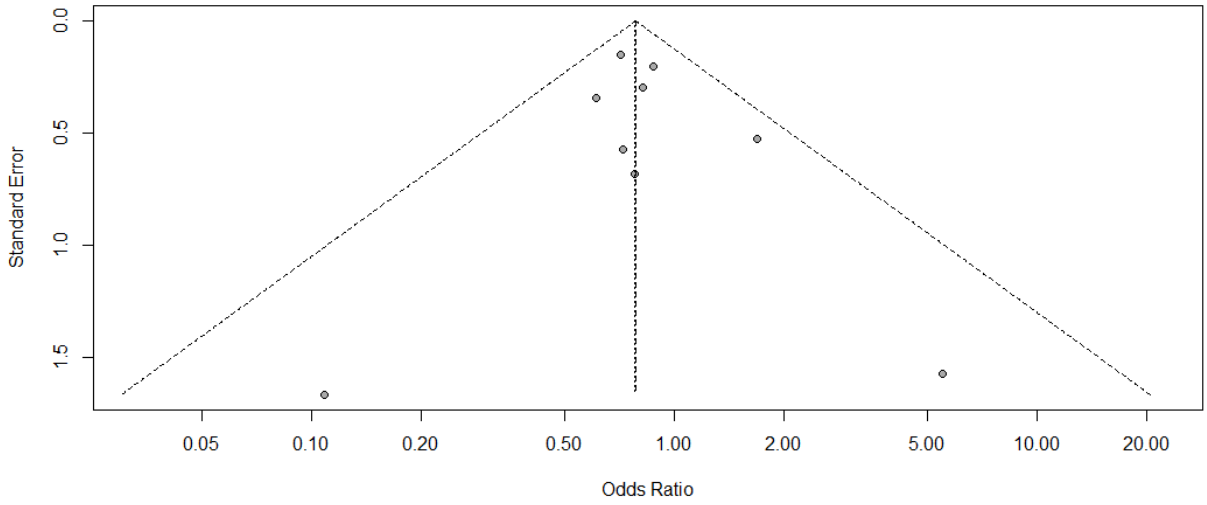


**Figure S3-6**. Funnel plot for musculoskeletal pain

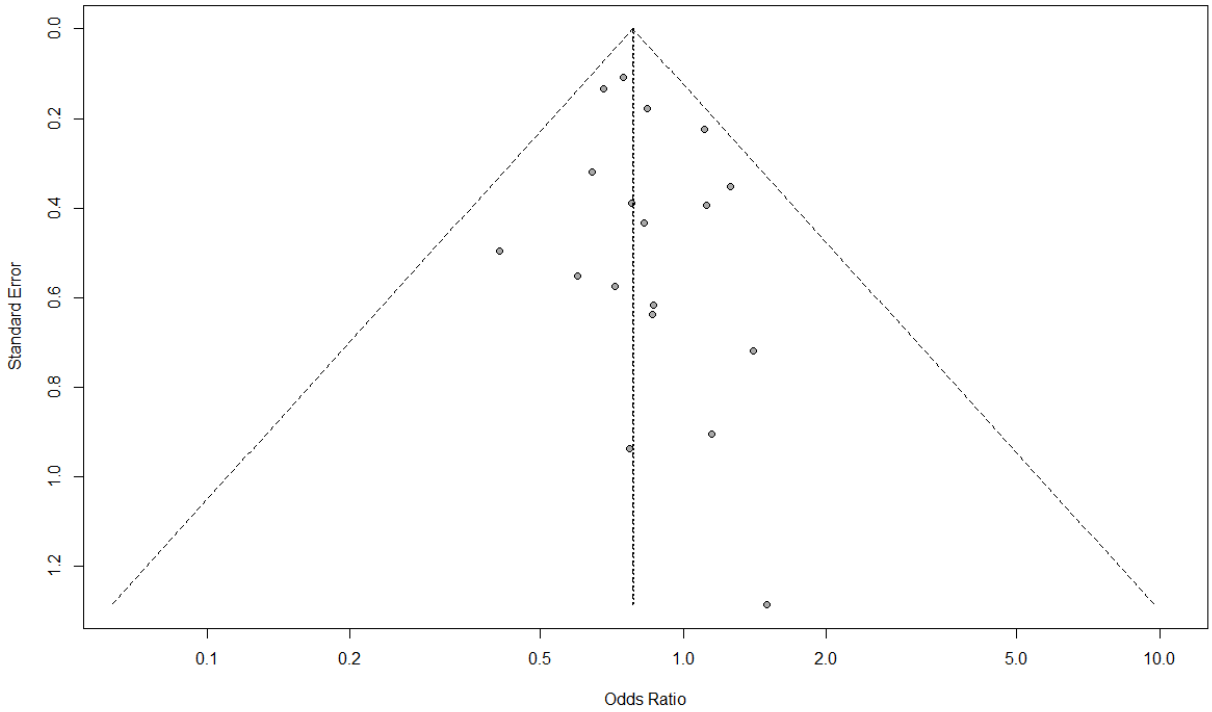


**Figure S3-7**. Funnel plot for the overall effect analysis

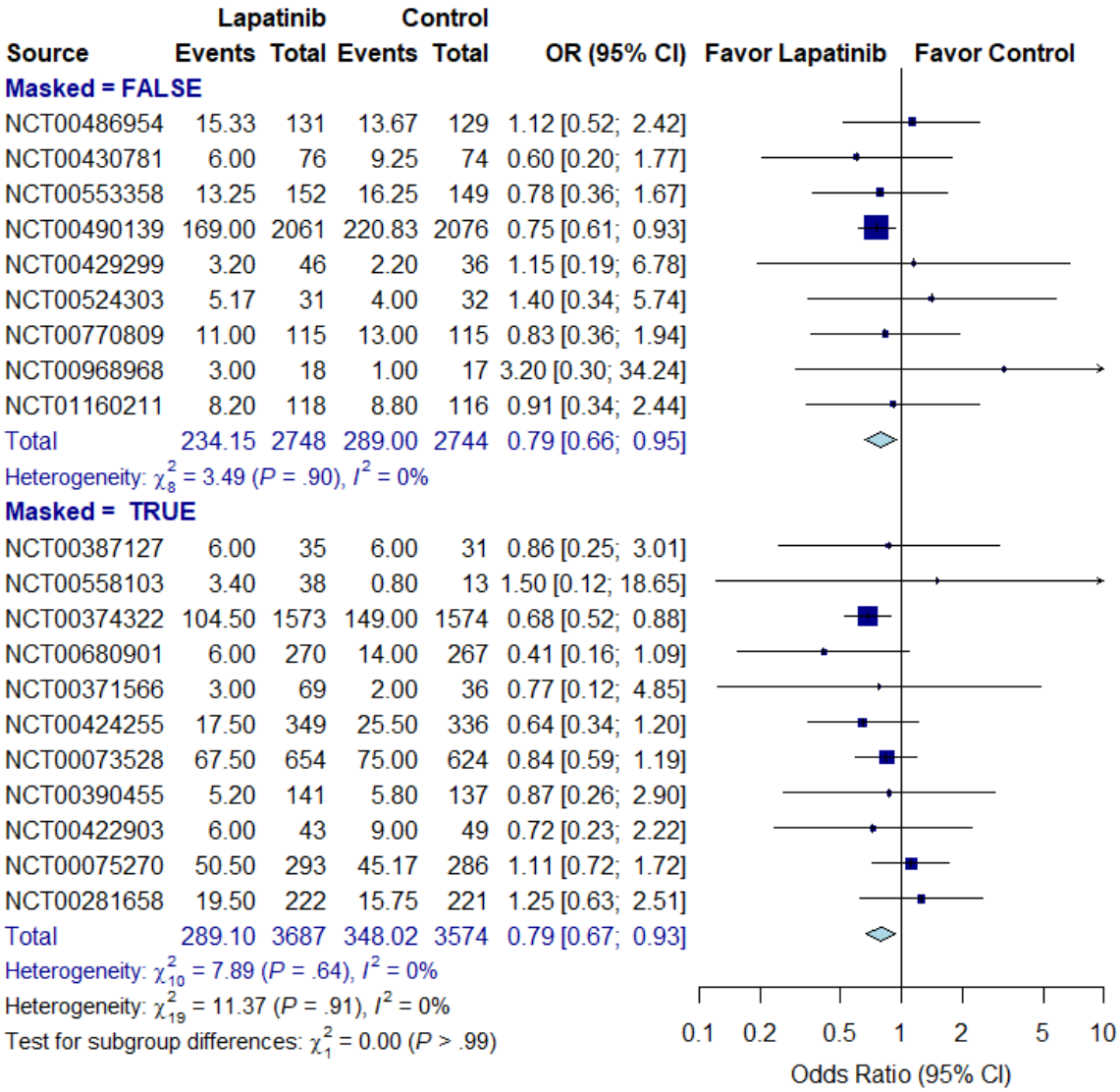


**Figure S4-1**. Overall pain-relieving effect of lapatinib, grouped by the factor concerning whether the trials were masked or not.

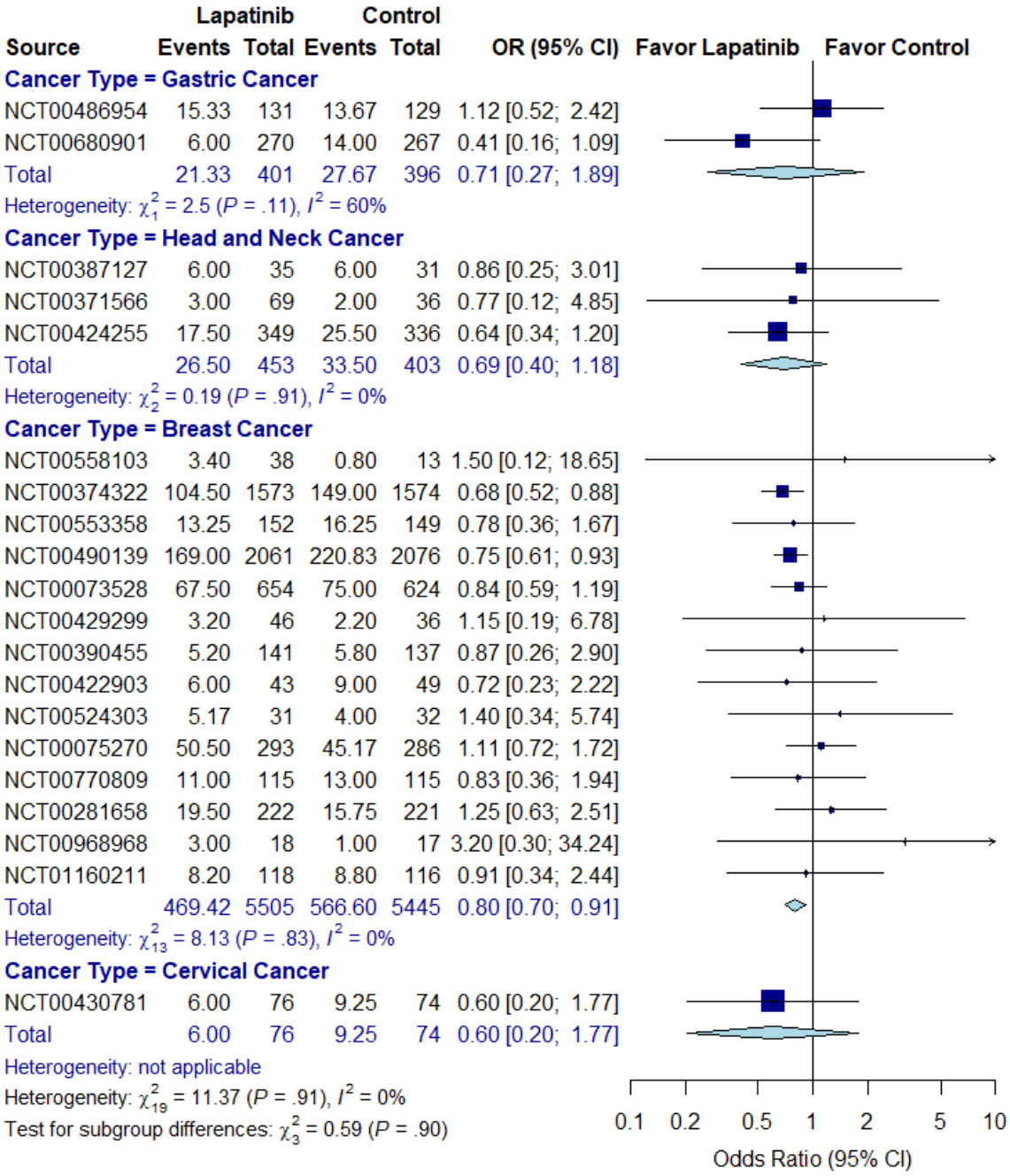


**Figure S4-2**. Overall pain-relieving effect of lapatinib, grouped by the cancer type of the recruited patients.

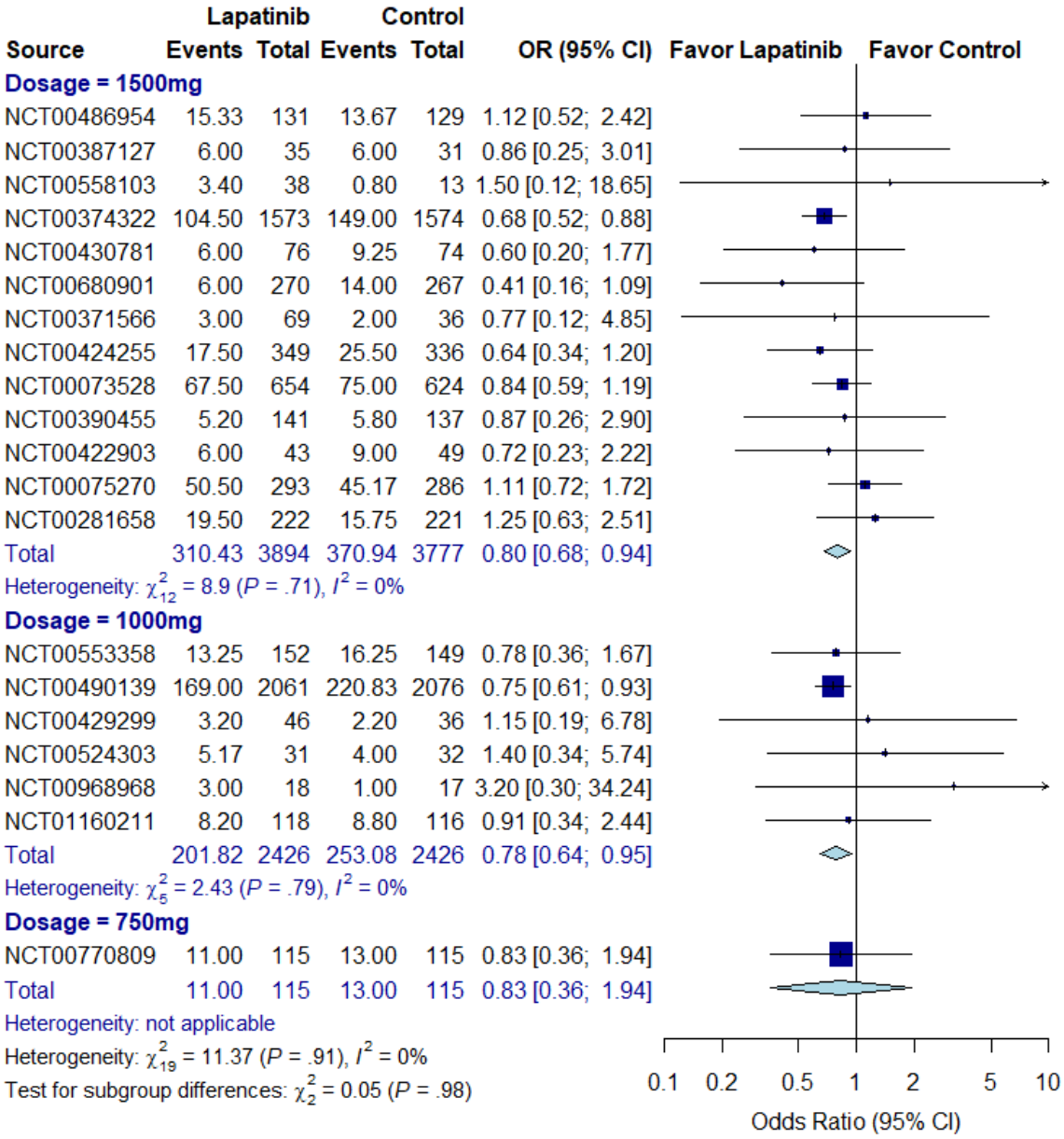


**Figure S4-3**. Overall pain-relieving effect of lapatinib, grouped by the dosage of lapatinib used in these trials.

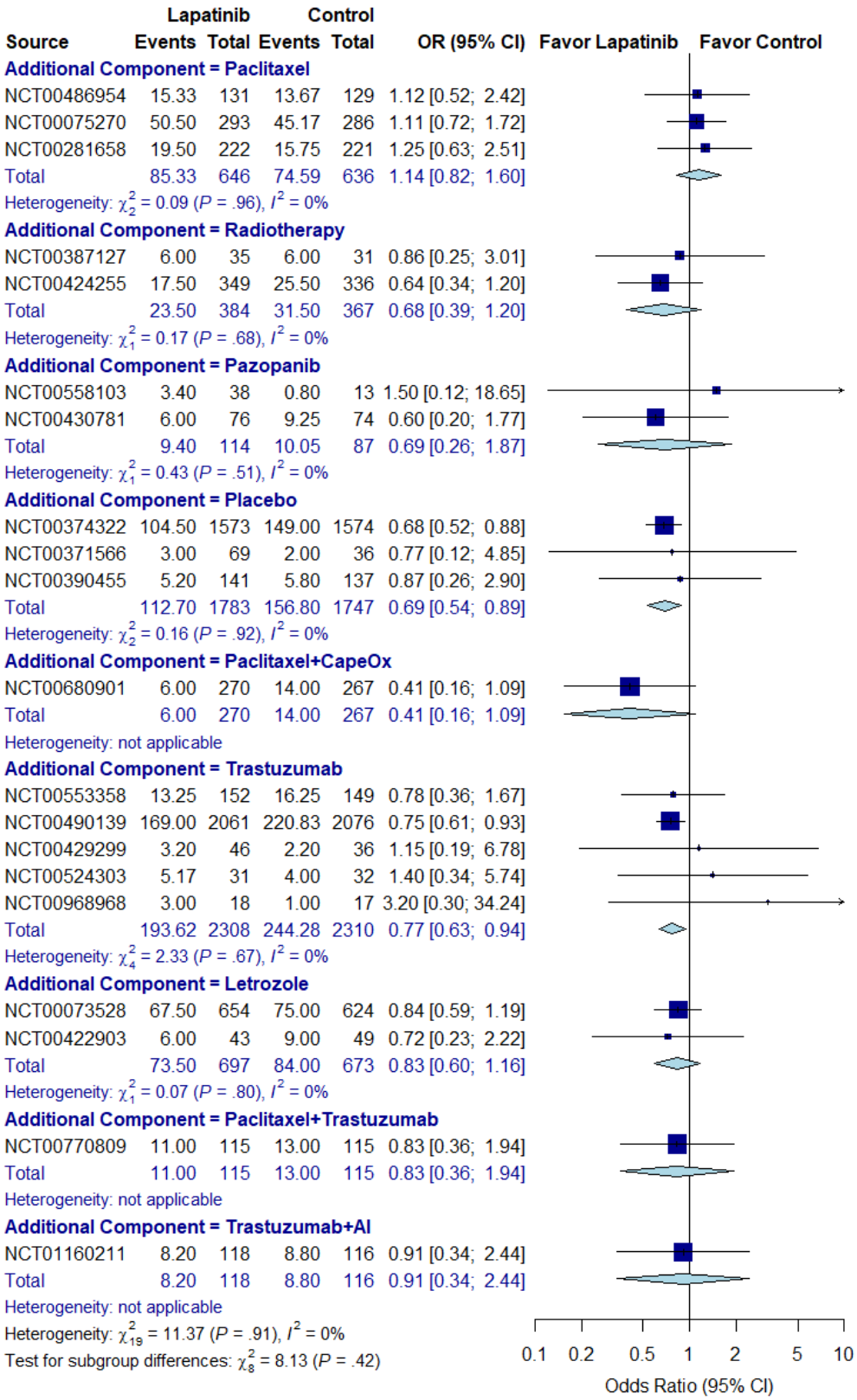


**Figure S4-4**. Overall pain-relieving effect of lapatinib, grouped by the additional components involved in these trials.

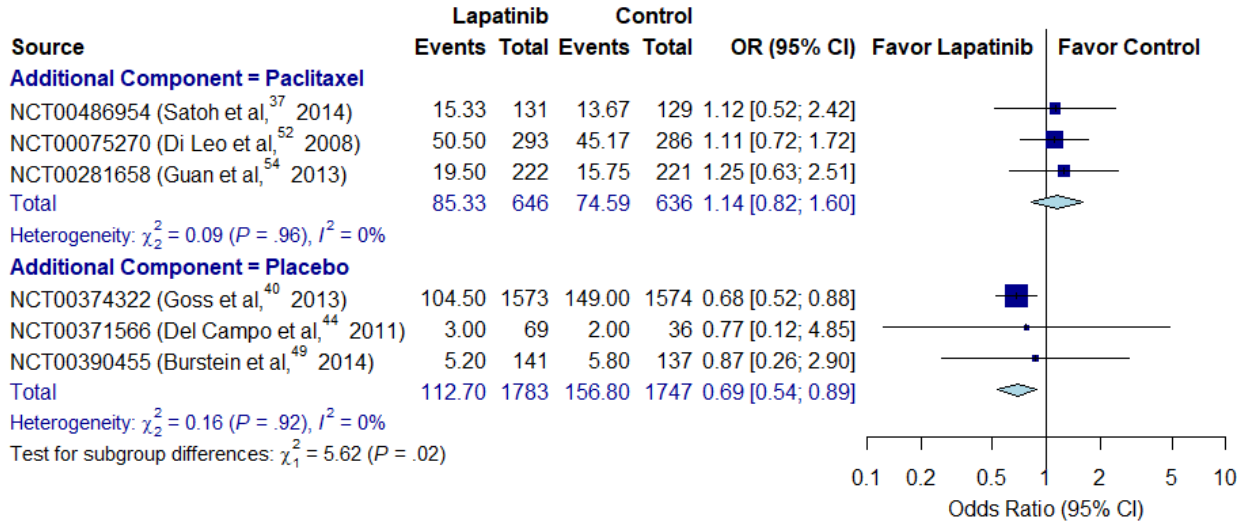


**Figure S4-5**. Overall pain-relieving effect of lapatinib, comparing only the group with paclitaxel used and the pure placebo control group.

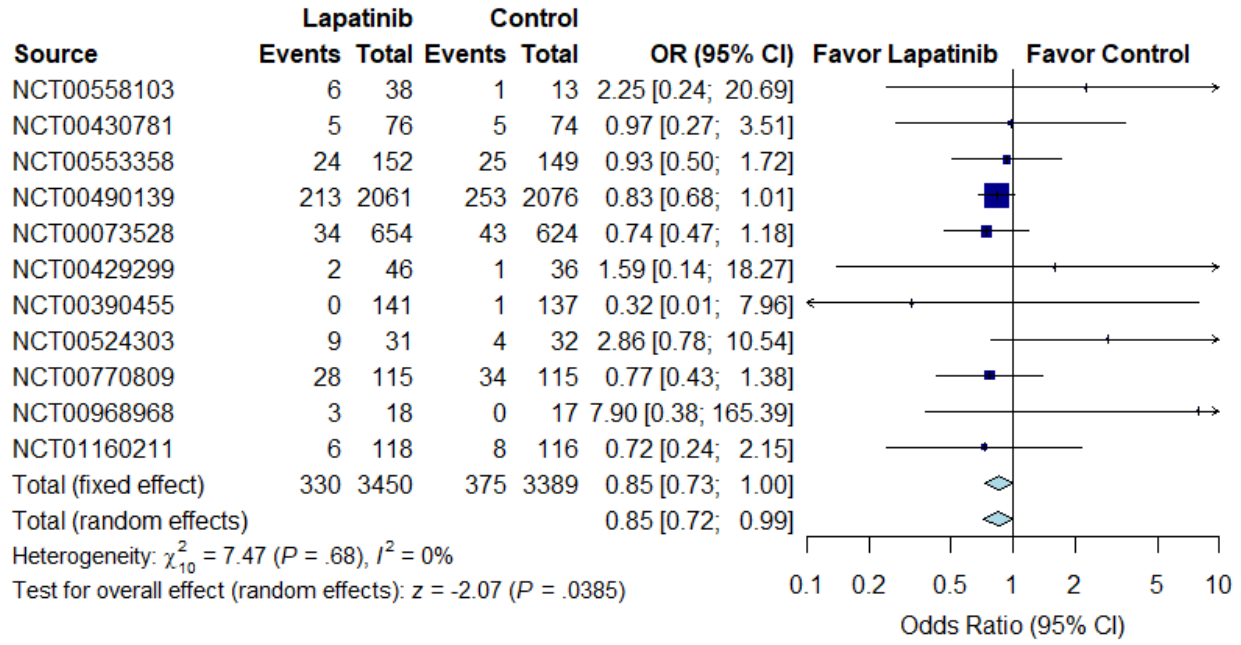


**Figure S5-1**. Effect of lapatinib on myalgia, when NCT00075270, NCT00486954, and NCT00281658 were excluded.

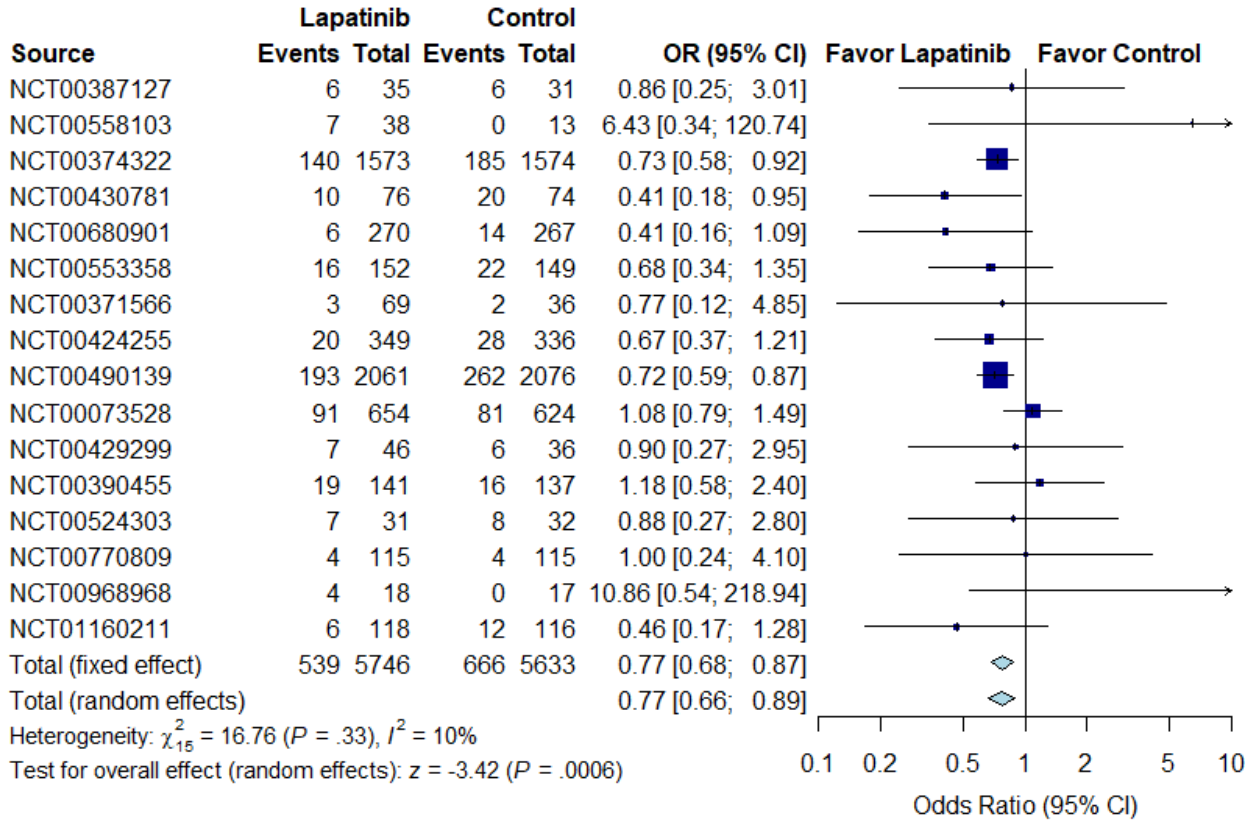


**Figure S5-2**. Effect of lapatinib on headache, when NCT00075270, NCT00486954, and NCT00281658 were excluded.

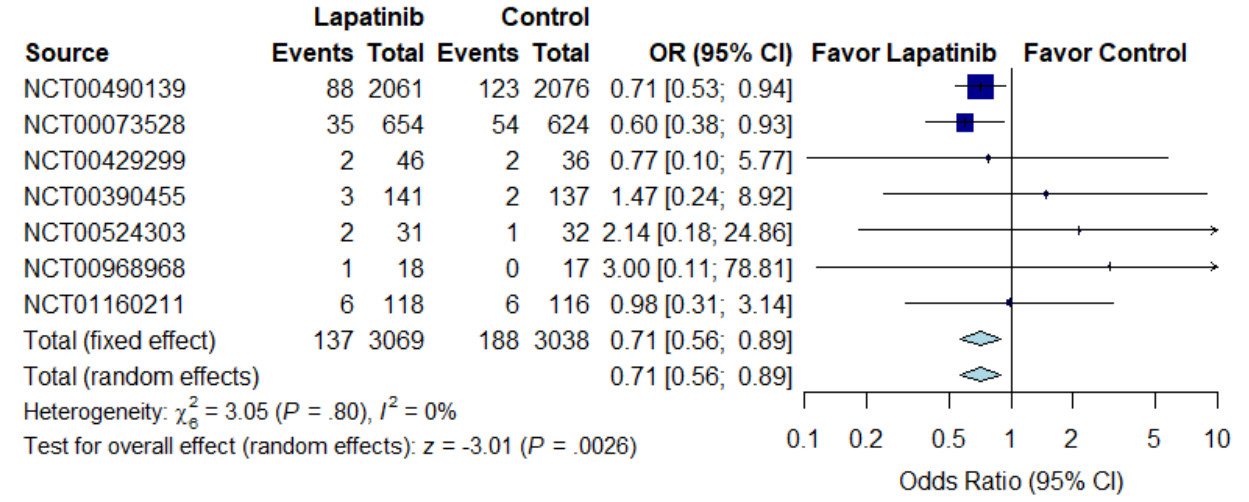


**Figure S5-3**. Effect of lapatinib on bone pain, when NCT00075270, NCT00486954, and NCT00281658 were excluded.

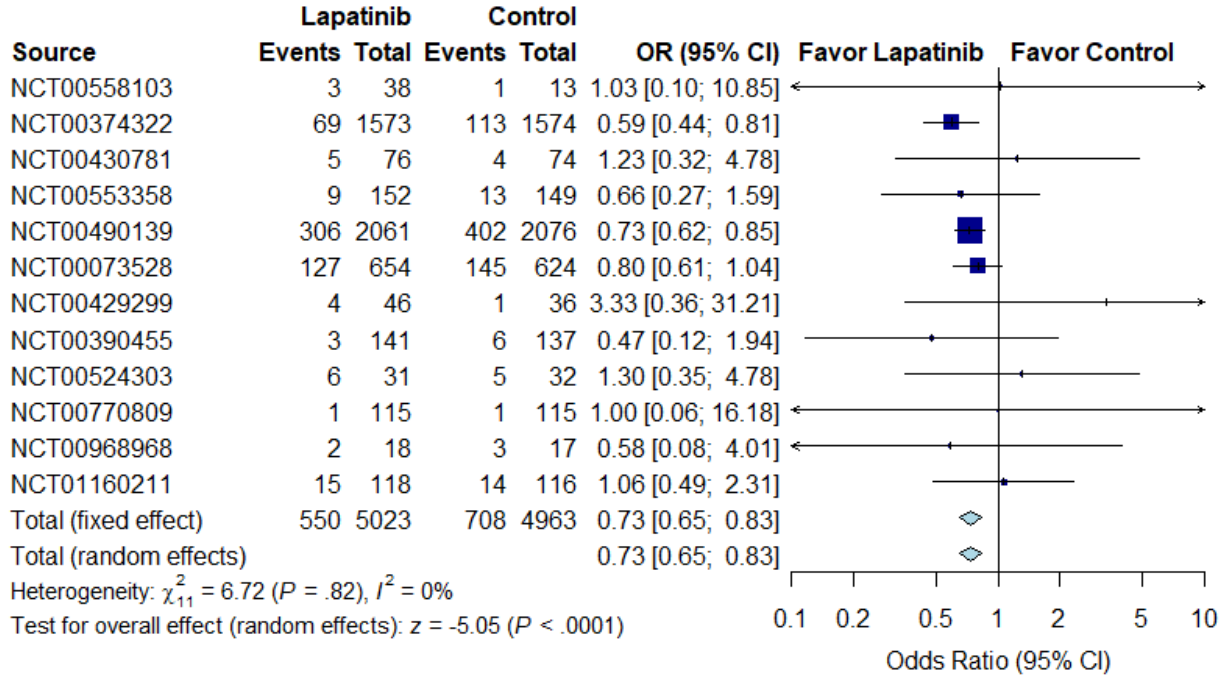


**Figure S5-4**. Effect of lapatinib on arthralgia, when NCT00075270, NCT00486954, and NCT00281658 were excluded.

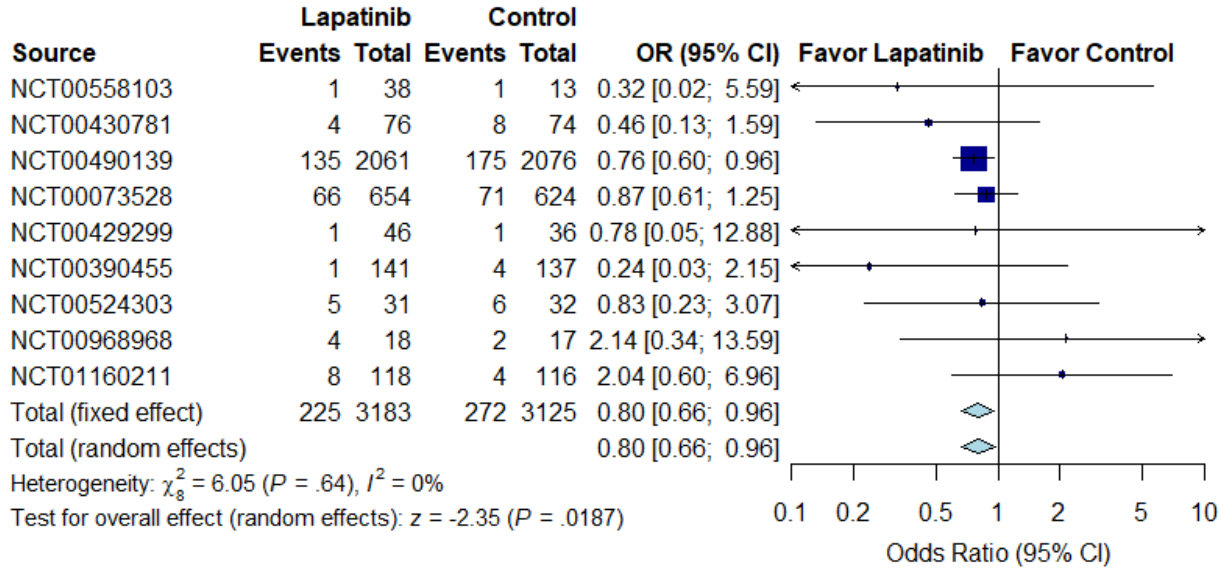


**Figure S5-5**. Effect of lapatinib on pain in extremity, when NCT00075270, NCT00486954, and NCT00281658 were excluded.

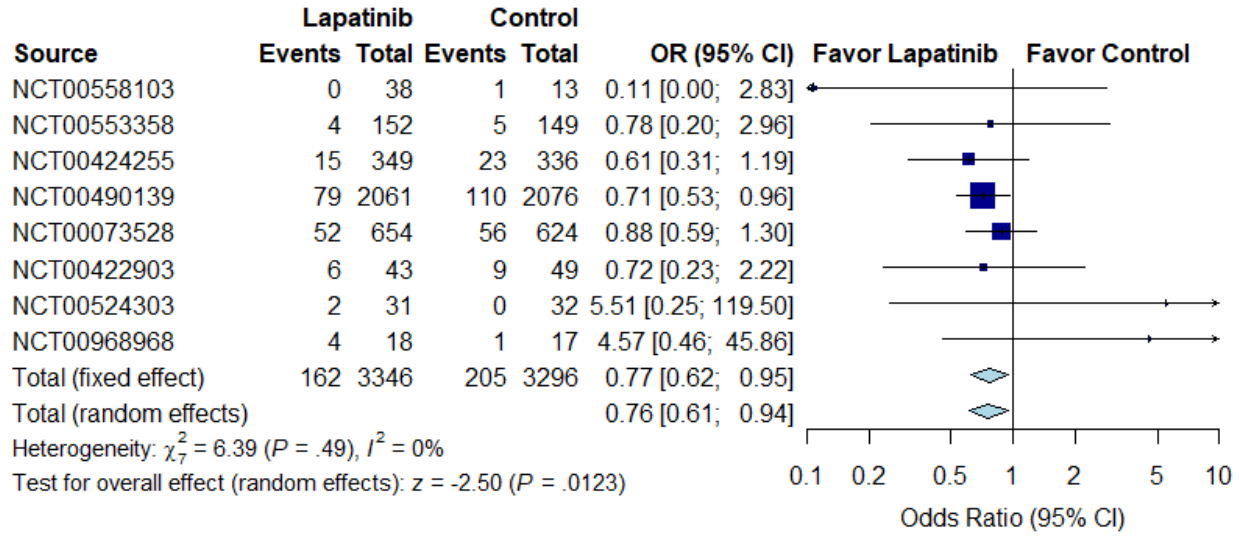


**Figure S5-6**. Effect of lapatinib on musculoskeletal pain, when NCT00075270, NCT00486954, and NCT00281658 were excluded.

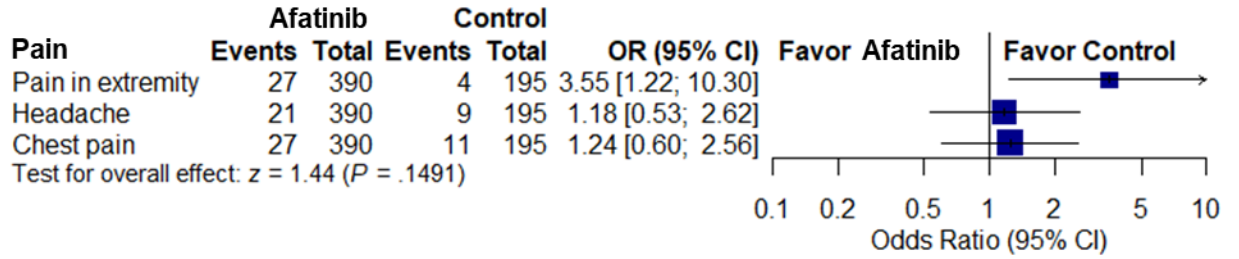


**Figure S6**. Effects of afatinib on various forms of pain. Data from NCT00656136.[1]

**Formula for Calculation of Odds Ratio (OR):**

| | Diseased | Healthy |
|---|---|---|
| Exposed | $\boldsymbol{D_E}$ | $\boldsymbol{H_E}$ |
| Not exposed | $\boldsymbol{D_N}$ | $\boldsymbol{H_N}$ |

**OR = $(D_E/H_E)/(D_N/H_N) = (D_E H_N)/(D_N H_E)$**

For synthesis of the data from multiple trials, the detailed procedure of the random-effects model[2] used to calculate the weight of each trial used in the meta-analysis can be found in reference.[3]

**References**


1 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).

2 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* | Y | Y | Y | Y | Y |
| *Arthralgia* | Y | Y | Y | Y | Y |
| *Musculoskeletal pain* | Y | Y | Y | Y | Y |
| *Headache* | Y | Y | Y | Y | Y |
| *Pain in extremity* | Y | Y | Y | Y | Y |
| *Myalgia* | Y | Y | Y | Y | Y |
| *Overall* | Y | Y | Y | Y | Y |

### 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* | Y | N | Y | Y | Y |

# ROBIS analysis

| | | | | | |
|---|---|---|---|---|---|
| *Arthralgia* | Y | N | Y | Y | Y |
| *Musculoskeletal pain* | Y | N | Y | Y | Y |
| *Headache* | Y | N | Y | Y | Y |
| *Pain in extremity* | Y | N | Y | Y | Y |
| *Myalgia* | Y | N | Y | Y | Y |
| *Overall* | Y | N | Y | Y | Y |

**3. Data collection and study appraisal**

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

**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* | Y | Y | Y | Y | Y | Y |

# ROBIS analysis

| | | | | | | |
|---|---|---|---|---|---|---|
| *Arthralgia* | Y | Y | Y | Y | Y | Y |
| *Musculoskeletal pain* | Y | Y | Y | Y | Y | Y |
| *Headache* | Y | Y | Y | Y | Y | Y |
| *Pain in extremity* | Y | Y | Y | Y | Y | Y |
| *Myalgia* | Y | Y | Y | Y | Y | Y |
| *Overall* | Y | Y | Y | Y | Y | Y |

## 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 |