Study protocol: systematic review and meta-analysis of randomized controlled trials in first-line treatment of squamous non-small cell lung cancer

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Abstract

Background: There is a high unmet need for effective treatments for patients with squamous non-small cell lung cancer (NSCLC). Eli Lilly and Company is conducting a phase III, randomized, multicenter, open-label study of gemcitabine plus cisplatin plus necitumumab (GC + N) versus gemcitabine plus cisplatin (GC) for the first-line treatment of patients with stage IV squamous NSCLC. Given GC is not the only treatment commonly used for the treatment of squamous NSCLC, this study was designed to compare the survival, toxicity, and quality of life outcomes of current treatment strategies for squamous NSCLC in the first-line setting.

Methods/Design: A systematic review and meta-analysis (including indirect comparisons) of treatments used in squamous NSCLC will be conducted to assess the clinical efficacy (overall and progression-free survival), health-related quality of life (HRQoL), and safety (grade 3–4 toxicity) of GC + N compared to other treatments used in squamous NSCLC. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines will be followed for all aspects of this study. A systematic literature review will be conducted to identify randomized controlled trials evaluating chemotherapy treatment in first-line NSCLC. Eligible articles will be restricted to randomized controlled trials (RCTs) among chemotherapy-naïve advanced NSCLC cancer patients that report outcome data (survival, toxicity, or quality of life) for patients with squamous histology. Following data extraction and validation, data consistency and study heterogeneity will be assessed. A network meta-analysis will be conducted based on the available hazard ratios for overall and progression-free survival, odds ratios for published toxicity data, and mean difference of HRQoL scales. Sensitivity analyses will be conducted.

Discussion: This is a presentation of the study protocol only. Results and conclusions are pending completion of this study.

Systematic review registration: PROSPERO CRD42014008968

Keywords: Non-small cell lung cancer, Chemotherapy, Non-squamous, Cancer, Meta-analysis, Network meta-analysis

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Background

Lung cancer is the leading cause of cancer-related deaths worldwide, accounting for 1.3 million deaths annually [1]. It is defined as cancer that forms in the tissues of the lung, usually in the cells lining air passages, and is divided into two main subtypes: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC is the predominant subtype form and accounts for about 85% of all lung cancers [2]; it is further divided by cell histology into adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma, with adenocarcinoma the currently predominant histology. Although the overall age-adjusted incidence rates for lung cancer are declining in many developed nations, lung cancer remains the leading cause of cancer-related deaths worldwide with an overall 5-year survival rate of about 15% [3], resulting in significant disease burden worldwide.

The treatment of lung cancer is based on the type and stage of tumor, as well as the patient’s general medical condition. For patients diagnosed with early stage disease (i.e., stages I and II), surgery offers the best option for survival and cure. Adjuvant chemotherapy is increasingly used in those with stage II disease and occasionally for those with stage IB, depending on the size of the tumor. For those with stage III lung cancer, chemoradiotherapy alone or in addition to surgery is used to treat patients; however, while treatment is administered with a curative intent, the 5-year survival for patients with regional disease is approximately 26%, which decreases to 3.9% for patients with metastatic disease [3]. Treatment for patients with advanced disease tends to be palliative, although extension in survival may be achieved. The standard first-line drug treatments for advanced NSCLC, neoadjuvant, adjuvant, or chemoradiotherapy, are generally based on the combination of a second- or third-generation cytotoxic drug with a platinum agent (cisplatin or carboplatin).

There are many drug therapies available for treatment of NSCLC; however, not all current therapies are suitable for use in tumors of all histologies. The results of clinical trials have indicated that drugs such as pemetrexed have greater efficacy among patients with adenocarcinoma than those with other NSCLC histologies (e.g., squamous cell carcinoma) [4]. Other newer agents, such as bevacizumab, are indicated for adenocarcinoma because of higher toxicities observed in patients with squamous histology [5]. Drugs such as erlotinib and gefitinib are not restricted by histology, but have greater efficacy among patients with epidermal growth factor receptor (EGFR) mutations [6,7]. The frequency of EGFR mutations in patients with squamous cell carcinoma, as opposed to those with adenocarcinoma, is very low [8]. Therefore, histology-specific treatment options are limited for patients with squamous cell carcinoma, which accounts for about 25% of all non-small cell lung cancers [9].

There is thus a high unmet need for effective treatments for patients with squamous NSCLC, as disease burden is large and there is currently a lack of targeted drug therapies for NSCLC squamous cell tumors. Eli Lilly and Company is currently developing necitumumab as a first-line treatment in patients with stage IV squamous NSCLC. The current phase III study (ClinicalTrials.gov identifier: NCT00981058) is a randomized, multicenter, open-label study of gemcitabine-cisplatin chemotherapy plus necitumumab (GC + N) versus gemcitabine-cisplatin (GC) chemotherapy alone in first-line treatment of patients with stage IV squamous NSCLC. The target patient population for this trial is comprised of male and female patients with histologically or cytologically confirmed, advanced squamous NSCLC, previously untreated for metastatic disease.

The purpose of this systematic literature review and meta-analysis is to compare survival, toxicity, and quality of life outcomes of current treatment strategies with necitumumab among patients with squamous NSCLC.

Methods/Design

This systematic literature review and meta-analysis (including indirect comparisons) will be conducted of treatments used in squamous NSCLC to assess the clinical efficacy, quality of life, and safety of GC + N compared to other treatments used in squamous NSCLC. To complete this objective, the following specific aims will be pursued:

1. To conduct a systematic literature review of randomized trials of all relevant treatments used for the first-line treatment of advanced squamous NSCLC;
2. To extract relevant data from the relevant published literature;
3. To perform indirect and direct comparisons of GC + N to all identified comparators for the following outcomes:
   3.1 Overall survival;
   3.2 Progression-free survival;
   3.3 Toxicity; and
   3.4 Quality of life

Search strategy

Searches will be conducted in PubMed, Ovid/MEDLINE, and Embase using free text and controlled vocabulary terms (MeSH). Studies published prior to 1995 will be excluded as NSCLC histology was not clearly differentiated at that time. Studies not published in English will be excluded. Comparisons will be made across all regimens and not just limited to “add-on” therapies.

Tables 1,
Table 1 PubMed search strategy

| Category            | Search | Query                                                                 | Items found |
|---------------------|--------|----------------------------------------------------------------------|-------------|
| Disease terms       | #1     | "carcinoma, non small cell lung/drug therapy" [MeSH Terms]           | 11,135      |
|                     | #2     | Randomized Controlled Trials as Topic [MeSH Major Topic]              | 12,361      |
|                     | #3     | "randomized controlled trials as topic" [MeSH Terms]                 | 85,095      |
|                     | #4     | Random Allocation [MeSH Terms]                                       | 76,843      |
|                     | #5     | double blind method [MeSH Terms]                                     | 118,616     |
|                     | #6     | "controlled clinical trial" [Publication Type]                       | 85,642      |
|                     | #7     | "randomized controlled trial" [Publication Type]                     | 344,749     |
|                     | #8     | "clinical trials as topic" [MeSH Terms]                              | 263,513     |
|                     | #9     | "clinical trial" [Publication Type]                                   | 709,361     |
|                     | #10    | ((#2 or #3 or (#4 and (#5 or #8 or #9)) or #6 or #7))               | 509,729     |
|                     | #11    | (randomization and control and clinical and trial)                   | 10,468      |
|                     | #12    | ((randomized and control and clinical trial) or (randomized and control and clinical and trial)) | 108,134     |
|                     | #13    | (((double or single or triple or treble) and (blind* or mask*) and (random*))) | 136,554     |
|                     | #14    | ((random and allocat*) and control* and trial)                       | 4,775       |
|                     | #15    | (#12 or #13 or #14)                                                  | 214,899     |
|                     | #16    | (#10 or #15)                                                        | 2,065       |
|                     | #17    | (#1 AND #16)                                                        |             |
| Exclusion terms     | #18    | Case report [Title/Abstract]                                        | 195,029     |
|                     | #19    | Review [Publication Type]                                            | 1,765,829   |
|                     | #20    | Letter [Publication Type]                                            | 794,012     |
|                     | #21    | "systematic review" [Title/Abstract]                                | 39,341      |
|                     | #22    | "clinical review" [Title/Abstract]                                  | 3,144       |
|                     | #23    | (#18 OR #19 OR #20 OR #21 OR #22)                                   | 2,734,788   |
|                     | #24    | (#17 NOT #23)                                                       | 1,579       |
| Year and language   | #25    | (#24 AND ("1995" [Date - Publication]: "2013" [Date - Publication])) AND English [Language] | 1,217       |

2, and 3 detail the specific search strategies for PubMed, Ovid, and Embase, respectively.

The following is a list of the conference databases that will be searched:

- American Association for Cancer Research, AACR
- American College of Radiation Oncology
- American Society for Radiation Oncology, ASTRO
- American Society of Clinical Oncology, ASCO
- Asia Pacific Lung Cancer Conference, APLCC
- Asia Pacific Oncology Summit, APOS
- Asian Oncology Summit, AOS
- Atualizacoes em Oncologia
- Australian Lung Cancer Conference, ALCC
- Austrian Society of Haematology and Oncology, ASHO
- The Association for Cancer Surgery, BASO
- Biennial Congress of the European Association for Cancer Research, EACR
- British Thoracic Oncology Group Conference, BTOG
- Clinical Oncology Society of Australia, COSA
- Cancer Symposium of the Society of Surgical Oncology, CSSSO
- Chicago Supportive Oncology Conference, CSOC
- Clinical Interventional Oncology, CIO
- Congres National de la Societe Francaise de Radiotherapie Oncologique, SFRO
- Congress of the European Society for Medical Oncology, ESMO
- Congress of the European Society of Surgical Oncology, ESSO
- Congress of the International Society of Oncology and Biomarkers, ISOBM
- Educational Cancer Convention Lugano of the European School of Oncology, ECCLU
- European Lung Cancer Conference, ELCC
- European Multidisciplinary Cancer Congress
Table 2 Embase search strategy

| Category        | Search                        | Query                                                                 | Hits     |
|-----------------|-------------------------------|-----------------------------------------------------------------------|----------|
| Design terms    | #1 "randomized controlled trial (topic)"/exp | 37,931                                                               |          |
|                 | #2 "randomized controlled trial"/exp          | 337,523                                                             |          |
|                 | #3 "randomization"/exp              | 61,698                                                               |          |
|                 | #4 "double blind procedure"/exp       | 115,032                                                              |          |
|                 | #5 [controlled clinical trial]/lim     | 511,199                                                              |          |
|                 | #6 [randomized controlled trial]/lim    | 337,523                                                              |          |
|                 | #7 "clinical trial"/exp              | 961,450                                                              |          |
|                 | #8 "clinical trial (topic)"/exp        | 73,222                                                               |          |
|                 | #9  #1 OR #2 OR #3 OR #4 OR #5 OR #6   | 1,088,520                                                            |          |
|                 | #10 sing*: ab,ti OR doub*: ab,ti OR treb*: ab,ti OR tripl*: ab,ti AND (blind*: ab,ti OR mask*: ab,ti) | 174,394 |          |
|                 | #11 "placebo"/exp                   | 236,244                                                              |          |
|                 | #12 random* AND (clinical OR control*) AND trial OR (placebo* AND (randomly allocated* OR (allocated AND random*)) | 504,649 |          |
|                 | #13 (#7 OR #8) AND (#10 OR #11 OR #12) | 513,722                                                              |          |
|                 | #14 #9 OR #13                      | 705,098                                                              |          |
| Exclusion terms | #15 [conference review]/lim           | 3,863                                                                |          |
|                 | #16 "case report":ab,ti              | 256,868                                                              |          |
|                 | #17 [review]/lim                     | 2,026,389                                                            |          |
|                 | #18 [letter]/lim                     | 827,115                                                              |          |
|                 | #19 "phase 1 clinical trial"/exp     | 24,619                                                               |          |
|                 | #20 [short survey]/lim OR "historical article": ab,ti | 514,714 |          |
|                 | #21 "systematic review": ab,ti       | 78,920                                                               |          |
|                 | #22 "clinical review": ab,ti         | 3,904                                                                |          |
|                 | #23 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 | 3,628,070             |          |
|                 | #24 #14 NOT #23                      | 424,301                                                              |          |
| Rx terms        | #25 "drug therapy"/exp/mj            | 574,153                                                              |          |
|                 | #26 "treatment response"/exp/mj      | 2,763                                                                |          |
|                 | #27 "treatment outcome"/exp/mj       | 28,936                                                               |          |
|                 | #28 "drug efficacy"/exp/mj           | 153,753                                                              |          |
|                 | #29 "outcome assessment"/exp/mj      | 9,603                                                                |          |
|                 | #30 chemothera* OR ("drug"/exp/mj AND thesa*) OR antineoplastic* OR palliat* OR standar* NEAR/2 care OR support* NEAR/2 care OR "best supportive care" OR best?support* NEXT/2 care | 1,895,030 |          |
|                 | #31 "radiotherapy"/exp               | 367,367                                                              |          |
|                 | #32 #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 | 2,609,134             |          |
|                 | #33 #23 AND #31                      | 88,937                                                               |          |
| Disease terms   | #34 (llung$ OR pulmon$) NEAR/5 (adenocarcinom$ OR squamous OR "large cell" OR "non-small cell"); ab,ti | 44,817 |          |
|                 | #35 "lung non small cell cancer"/exp  | 52,027                                                               |          |
|                 | #36 metastatic: ab,ti                | 181,820                                                              |          |
|                 | #37 advanced: ab,ti                  | 320,393                                                              |          |
|                 | #38 stage 3: ab,ti                   | 61                                                                   |          |
|                 | #39 "Stage 3": ab,ti                 | 8,708                                                                |          |
|                 | #40 stage 4: ab,ti                   | 32                                                                   |          |
|                 | #41 "stage 4": ab,ti                 | 5,270                                                                |          |
|                 | #42 stage iii: ab,ti                 | 30                                                                  |          |
Eligibility assessment
To be eligible, published studies must meet the criteria outlined in Table 4. Briefly, eligible articles must report at least one of the following outcomes (overall survival, progression-free survival, quality of life, or toxicity) for patients with squamous NSCLC. Eligible articles must
report data from randomized controlled trials published since 1995. Abstracts of all potentially eligible citations will be reviewed and excluded if it can be definitively stated that no eligibility criterion is met. All other publications will be considered potentially eligible. Full-text articles of all potentially eligible citations will be obtained and

| Category       | Search                                                                 | Query                                                                 | Hits  |
|----------------|------------------------------------------------------------------------|----------------------------------------------------------------------|-------|
| Design terms   | #1 Randomized Controlled Trials as Topic/                              | 100,690                                                              |       |
|                | #2 Randomized Controlled Trial/                                        | 382,290                                                              |       |
|                | #3 Random Allocation/                                                  | 80,788                                                               |       |
|                | #4 Double Blind Method/                                                | 129,303                                                              |       |
|                | #5 controlled clinical trial.pt.                                       | 88,866                                                               |       |
|                | #6 randomized controlled trial.pt.                                     | 382,290                                                              |       |
|                | #7 Clinical Trial/                                                     | 499,767                                                              |       |
|                | #8 clinical trial.pt.                                                  | 499,767                                                              |       |
|                | #9 Clinical Trials as Topic/                                           | 173,590                                                              |       |
|                | #10 1 or 2 or 3 or 4 or 5 or 6                                        | 631,570                                                              |       |
|                | #11 7 or 8 or 9                                                       | 602,541                                                              |       |
|                | #12 ((singl* or doub* or treb* or tripl*) and (blind* or mask*)).ab,ti.| 145,496                                                              |       |
|                | #13 Placebos/                                                          | 33,372                                                               |       |
|                | #14 ((random* and (clinical or control*) and trial) or (placebo* and ("randomly allocated" or (allocated and random*))).mp. | 457,488                                                              |       |
|                | #15 12 or 13 or 14                                                    | 513,100                                                              |       |
|                | #16 11 and 15                                                         | 264,991                                                              |       |
|                | #17 10 or 16                                                          | 645,804                                                              |       |
| Disease terms  | #18 ((lung* or pulmon*) and (adenocarcinom* or squamous or "large cell" or "non-small cell").ab,ti. | 59,093                                                               |       |
|                | #19 Carcinoma, Non-Small-Cell Lung/                                   | 34,861                                                               |       |
|                | #20 (metastatic or advanced or stage or "stage 3" or stage4 or "stage 4" or stagell or "stage III" or StageIV or "Stage IV" or Stage?III or "Stage ?III" or Stage?IV or "Stage ?IV" or "Stage III/IV" or "Stage ?III/IV" or "Stage III?IV?" or "Stage II/Stage IV" or "Stage ?II/Stage IV?" or "Stage III/Stage IV?" or Stage III/Stage IV or inoperable or in?operable or unresectable or non?resectable or "late/stage" or (metast* or advance*)).ab,ti. | 1,177,250   |       |
|                | #21 18 or 19                                                          | 66,533                                                               |       |
|                | #22 20 and 21                                                         | 34,403                                                               |       |
|                | #23 17 and 22                                                         | 3,600                                                                |       |
| Exclusion terms| #24 case report.ab,ti.                                                | 201,610                                                              |       |
|                | #25 review.pt.                                                        | 1,893,388                                                             |       |
|                | #26 letter.pt.                                                        | 817,960                                                              |       |
|                | #27 Clinical Trial, Phase Ipt.                                         | 15,867                                                               |       |
|                | #28 Historical Article/                                               | 298,058                                                              |       |
|                | #29 systematic review.ab,ti.                                          | 44,587                                                               |       |
|                | #30 clinical review.ab,ti.                                            | 3,354                                                                |       |
|                | #31 24 or 25 or 26 or 27 or 28 or 29 or 30                            | 3,184,956                                                             |       |
|                | #32 23 not 31                                                         | 2,702                                                                |       |
| Rx terms       | #33 drug therapy/ or treatment outcome/ or ("treatment" and "response").ab,ti. or ("drug" and "efficacy").ab,ti. or outcome assessment/ | 1,014,086                                                             |       |
|                | #34 32 and 33                                                         | 1,611                                                                |       |
| Final          | #35 limit 34 to yr = "1995 -Current"                                   | 1,464                                                                |       |
# Table 4 Eligibility criteria and screening matrix

| Eligibility criteria                                                                 | Ineligibility criteria                                                                 |
|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| **Patients**                                                                        | **Interventions**                                                                       |
| Male or female patients with histologically or cytologically-confirmed squamous NSCLC | Not first-line treatment with first-line defined as patients with no prior exposure to chemotherapy |
| Study participants must have not received chemotherapy treatment prior to first-line chemotherapy for NSCLC at the time of randomization in the study | Radiation therapy in the absence of concurrent chemotherapy in any treatment group |
| Interventions                                                                        | Study design                                                                             |
| The study assesses a chemotherapy treatment in each of the study arms                | Review articles, news, editorials, commentaries                                           |
| No limits are placed on the type of chemotherapy used                                | Time frame                                                                               |
| Outcomes                                                                            | 1995 to present                                                                          |
| One or more of the following outcomes must be quantitatively reported in the publication: overall survival, progression-free survival, toxicity, or quality of life |                                                                                         |
| At least one of the required outcome variables must be reported separately for patients with advanced or metastatic (stage III/IV) NSCLC that is of squamous histology |                                                                                         |
| Study design RCTs                                                                    | Study design Review articles, news, editorials, commentaries                             |
|                                                                                      | Time frame 1995 to present                                                               |

## Ineligibility criteria

### Interventions
- Not first-line treatment with first-line defined as patients with no prior exposure to chemotherapy
- Radiation therapy in the absence of concurrent chemotherapy in any treatment group

### Study design
- Review articles, news, editorials, commentaries

### Time frame
- Publication date prior to 1995

## Matrix for patients with "squamous histology"

| Squamous inclusion obvious in abstract? | Squamous results obvious in abstract? | Inclusion | Comments                  |
|----------------------------------------|---------------------------------------|-----------|---------------------------|
| Yes                                    | Yes                                   | Yes       |                           |
| No                                     | Yes                                   | Yes       |                           |
| Yes                                    | No                                    | Yes/No    | Need full text to determine the inclusion |
| No                                     | No                                    | Yes/No    | Need full text to determine the inclusion |

| Only non-squamous inclusion obvious in abstract? | Squamous results obvious in abstract? | Inclusion | Comments                  |
|--------------------------------------------------|---------------------------------------|-----------|---------------------------|
| Yes                                              | Yes                                   | Not possible case |                           |
| No                                               | Yes                                   | Yes       |                           |
| Yes                                              | No                                    | No        |                           |
| No                                               | No                                    | Yes/No    | Need full text to determine the inclusion |

| Abstract mentions just NSCLC as inclusion?      | Squamous results obvious in abstract? | Inclusion | Comments                  |
|-------------------------------------------------|---------------------------------------|-----------|---------------------------|
| Yes                                              | Yes                                   | Yes       |                           |
| No                                               | Yes                                   | Yes/No    | Need full text to determine the inclusion |
| Yes                                              | No                                    | Yes/No    | Need full text to determine the inclusion |
| No                                               | No                                    | Noise in the search | Need full text to determine the inclusion |
| Multiple cancers                                 | If mentions lung cancer                | Yes/No    | Need full text to determine the inclusion |
|                                                  | If does not mention any specific tumor types | Yes/No    | Need full text to determine the inclusion |
|                                                  | If only mentions breast cancer or other types and does not mention lung cancer | Noise in the search | Need full text to determine the inclusion |

## Matrix for "not first-line treatment"

| Condition                         | Line of treatment to be considered | Inclusion | Comments |
|------------------------------------|-----------------------------------|-----------|----------|
| Naive NSCLC patients               | 1st                               | Yes       |          |
| First- or front-line treatment     | 1st                               | Yes       |          |
| Untreated NSCLC patients           | 1st                               | Yes       |          |
| Metastatic chemo-naive NSCLC patients | 1st                         | Yes       |          |
| Chemo-naive NSCLC patients         | 1st                               | Yes       |          |
Table 4 Eligibility criteria and screening matrix (Continued)

| Second-line treatment | 2nd | No |
|-----------------------|-----|----|
| (Rx)-resistant NSCLC patients | 2nd | No |
| Recurrent or progressive disease | 2nd | No |
| (Rx)-responder/non-responder patients | 2nd | No |
| If no clear information on line of treatment | NA | Yes/No |

reviewed to determine final eligibility. The eligibility of both the abstracts and full-text articles will be assessed independently by two reviewers using the criteria and screening matrix presented in Table 4. If the two reviewers do not agree on the eligibility of an article, a third reviewer will serve as the tie breaker. Systematic reviews and other review articles will be scanned to ensure no eligible randomized controlled trials (RCTs) are missed.

Data extraction and verification
In a process similar to that used for assessing eligibility, two reviewers will independently extract the data elements listed in Table 5 from each eligible article. These data are extensive and it is not expected, nor is it required, that all studies will report all data fields included. However, attempts to collect as extensive of data as possible will be made to increase the potential range of sensitivity and descriptive analyses. In addition to the data extraction, two reviewers will also assess bias using the Cochrane Risk of Bias Tool and will measure study quality using the Physiotherapy Evidence Database (PEDro) scale (see the “Assessment of bias and study quality” section). Data from both reviewers will be compared. If any data element does not match, the reviewers will meet and attempt to resolve the discrepancies. In cases of non-resolution, a third reviewer will be consulted. All rules and decision criteria used in the data resolution process will be recorded for quality assurance and methodological consistency purposes. To further ensure the accuracy of the extracted data, a subset of 10% of all extracted articles will be verified by an individual not involved in the data extraction process. In cases of error detection, the full database will be reviewed to ensure accuracy.

Analysis plan
A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram will be developed based on the search strategy and eligibility assessment to show the flow of included and excluded studies. The descriptive statistics from each trial of patients with squamous cell carcinoma will be included and described. These variables will include treatment group, number of patients, mean age (standard deviation), number and percent male, number and percent with stage IV disease, overall survival, progression-free survival, toxicity, and quality of life.

A network diagram visually describing existing treatments for squamous NSCLC will be created after all eligible studies have been identified. However, some publications may not present data in a format that allows them to be included in the study despite otherwise meeting eligibility criteria (e.g., mixed populations not reported separately, mixed histologies not reported separately, mixed lines of therapy not reported separately). In the case of a disconnected network resulting from the absence of data for the appropriate patient population, authors of such articles will be contacted and asked to provide the needed data from their publications that would enable connection to the studied network.

The primary purpose of this study is to perform indirect and direct comparisons of GC+N versus all identified comparators for overall survival (OS) and progression-free survival (PFS). Individual hazard ratios (HR) or median time-to-event (median time) and 95% confidence intervals (90% or 99% confidence intervals will be converted to 95%) for overall survival will be included in the network meta-analysis using a Bayesian approach that ensures the preservation of randomization in the network [10]. The HR will be used as the primary unit of analyses to evaluate differences in effect size between treatment groups. Data for analysis will be extracted directly from the text of each eligible article, calculated from data included in the text, or extrapolated from the Kaplan-Meier plot according to the method of Parmar and colleagues [11]. Graphs and figures will be digitized using TechDig software and/or xyscan tool (Debian, Inc) if necessary, and digitized values will be extracted.

Heterogeneity will be explored by comparing the fixed and random effects models to ensure that the network has good properties. Additionally, heterogeneity will be explored by visual inspection of forest plots. The consistency assumption will be tested by examining network diagrams to identify any closed “loops” where inconsistencies can occur. When the network is complex with multiarm trials, the “node-splitting” approach defined by Dias and colleagues [12] will be used to identify
Table 5 Variables for data extraction

| Arm | Unique arm number. Unique number for the treatment arm is a grouping variable that is used to highlight which outcome is in the same group of subjects |
|-----|-------------------------------------------------------------------------------------------------------------------------------------|
| Number of study arms | 1, 2, 3 |
| Open label versus blinded | |
| Phase of study | 1, 2, 3, or unknown |
| Objectives | OS, PFS, RR, TPD, etc. |
| Patients randomized | Number of patients randomized to the arm. Number value |
| Arm description | Description of the treatment arm usually includes the drug name, dose, and frequency e.g., methotrexate 10 mg QW (once a week) |
| Sub arm analysis | Indicates if the analysis is in a subset of study arm. Yes, NA. Use all in case of AE or dropout data is reported for the randomized trial population |
| Arm comment | Comment referring to the arm. Comment in relevance to the understating of arm or NA |
| Study phase | Description of the specific phase within the overall study from which the data is derived. Lead-in, active, follow-up |
| Study phase description | Qualifies the "Study Phase" field with any additional information deemed necessary or helpful for that arm. e.g., open-label follow-up |
| Phase duration | Length of the study phase from which the data is derived for the arm. Time |
| Phase duration unit | Time unit for phase duration for the arm. Units |
| Phase comment | Comment concerning the study phase. Any comment that is relevant to the understanding of the phase or NA |
| Period | Used if necessary to separate crossover periods within a crossover trial. If the phase has multiple periods, the number of the period. Integer in sequence, or NA |
| Period description | Used to qualify the "Period" field with any additional information deemed necessary or helpful e.g., treatment A, titration, maintenance, NA |
| Period duration | Length of time of the period in a study phase from which the data is derived. Time, NA |
| Period duration unit | Time unit for period duration. Units, NA |
| Period comment | Comment concerning the period. Any comment that is relevant to the understanding of the period or NA |
| Repository | Description. Data entry standards |

Demographics and medical history information at baseline by study arm and overall—adjusted and unadjusted

| Age | Mean (or median) age in years of patient population or treatment arm population. Age in years or NR if not mentioned specifically or clearly in the trial |
| Percent female | Percent of females in the patient population or treatment arm population. Percent or NR if not mentioned specifically or clearly in the trial |
| Weight | Mean body weight of the patient or treatment arm population. Weight in kg, normalize if needed or NR if not mentioned specifically or clearly in the trial |
| Height | Mean height of the patient or treatment arm population. Height in cm, normalize if needed or NR if not reported |
| BMI | Mean body mass index of the treatment arm population. BMI in kg/m², normalize if needed or NR if not reported in the trial |
| DBP | Mean (or median) diastolic blood pressure. mmHg |
| SBP | Mean (or median) systolic blood pressure. mmHg |
| Inclusion | Description of treatment arm or sub-arm inclusion criteria under the trial protocol. e.g., for sub-group females only, or NR if not mentioned specifically or clearly in the trial |
| Exclusion | Description of treatment arm or sub-arm exclusion criteria under the trial protocol. e.g., for sub-group exclusion of females with child-bearing potential, or NR if not mentioned specifically or clearly in the trial |
| Variable | Description | Note |
|----------|-------------|------|
| Ethnic white | Percent of the ethnic population who are whites or Caucasian in the trial | Percent or NR if not mentioned specifically or clearly in the trial |
| Ethnic black | Percent of the ethnic population who are black in the trial | Percent or NR if not mentioned specifically or clearly in the trial |
| Ethnic Hispanic | Percent of the ethnic population who are Hispanic in the trial | Percent or NR if not mentioned specifically or clearly in the trial |
| Ethnic Asian | Percent of the ethnic population who are Asian in the trial | Percent or NR if not mentioned specifically or clearly in the trial |
| Ethnic other | Percent of the ethnic population who are other in the trial | Percent or NR if not mentioned specifically or clearly in the trial |
| Primary disease | Primary disease being studied | |
| Percent current smokers | Percent of the population who are current smokers | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent previous smokers | Percent of the population who are previous smokers | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent adenocarcinoma type | Percent subjects with NSCLC adenocarcinoma type | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent squamous cell carcinoma type | Percent subjects with NSCLC squamous cell carcinoma type | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent non-squamous | | |
| Percent NSCLC stage 0/II | Percent subjects with NSCLC stage 0 or I or II | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent NSCLC stage III | Percent subjects with NSCLC stage III | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent NSCLC stage IV | Percent subjects with NSCLC stage IV | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent NSCLC stage III/IV total | Total percent of subjects with NSCLC stages III or IV | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent ECOG status 0 | Percent subjects with Eastern Cooperative Oncology Group performance status scale 0 | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent ECOG status 1 | Percent subjects with Eastern Cooperative Oncology Group performance status scale 1 | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent ECOG status 0/1 total | Percent subjects with Eastern Cooperative Oncology Group performance status scales 0 or 1 | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent Karnofsky status ≥80 | Percent subjects with Karnofsky’s index of performance status ≥80% | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent WHO performance status 0/1 | Percent subjects with WHO performance status scale 0 or 1 | Percent or NR if not mentioned specifically or clearly in the trial |
| Num of metastatic lymph nodes | Mean or median number of metastatic lymph nodes | NR if not mentioned specifically or clearly in the trial |
| Percent metastatic L-node positive | Percent subjects who are lymph node positive or with metastatic lymph nodes | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent bone metastasis | Percent subjects with bone metastasis | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent brain metastasis | Percent subjects with brain metastasis | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent liver metastasis | Percent subjects with lung metastasis | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent other metastasis | Percent subjects with other metastatic organs | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent metastatic organ sites | Percent subjects with one metastatic organ or site involved | Percent or NR if not mentioned specifically or clearly in the trial |
| | Percent subjects with two metastatic organs or sites involved | Percent or NR if not mentioned specifically or clearly in the trial |
Table 5 Variables for data extraction (Continued)

| Variable | Description | Data entry standards |
|----------|-------------|----------------------|
| Percent metastatic organ sites 2 | Percent subjects with three or more metastatic organs or sites involved | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent metastatic organ sites >3 | Percent subjects with baseline hemoglobin levels <11.5 g/dl | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent hemoglobin <11.5 g/dl | Percent subjects with baseline hemoglobin levels <11.5 g/dl | Percent or NR if not mentioned specifically or clearly in the trial |
| Patient demographic comments | Any pertinent demographic comments that are not dealt by other variables | Any comment that may be relevant to the understanding of the demographic characteristics of the patient population |
| Percent previous surgery | Subjects with previous treatment for NSCLC as complete or partial surgery. Procedures include wedge resection (removal of part of a lobe), segmentectomy (removal of an anatomic division of a particular lobe of the lung), lobectomy (one lobe), bilobectomy (two lobes), or pneumonectomy (whole lung) | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent previous radiotherapy | Percent subjects with previous radiotherapy as treatment for NSCLC | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent previous chemotherapy | Percent subjects with previous chemotherapy as treatment for NSCLC | Percent or NR if not mentioned specifically or clearly in the trial |
| Comorbidities | Any pertinent demographic comments that are not dealt by other variables | Any comment that may be relevant to the understanding of the demographic characteristics of the patient population |
| Percent comorbidities | Percent subjects with baseline hemoglobin levels <11.5 g/dl | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent previous platinum | Percent subjects with previous platinum treatment | Percent or NR if not mentioned specifically or clearly in the trial |
| Percent no previous treatment | Percent subjects with no treatment for NSCLC | Percent or NR if not mentioned specifically or clearly in the trial |
| Previous treatment comments | Comments regarding the previous treatment | Any comment that may be relevant to the understanding of the previous NSCLC treatment in this record, NA if no comments |

Pharmacological therapy information

| Repository | Description | Data entry standards |
|------------|-------------|----------------------|
| Primary NSCLC therapy | Name of primary drug therapy used in this arm at that time point | NSCLC drug, e.g., cisplatin, docetaxel |
| Primary NSCLC dose | Randomized daily dose at time of outcome. Please note that this is the dose the patients were receiving when the observation is made (not the first randomized dose). If the treatment is switched at the time of observation, record the prior treatment the patients were getting just before the observation was made | Total daily dose at the time of observation |
| Primary NSCLC dose achieved | Average daily dose during assessment period or for the total treatment period | Average daily dose achieved. Specifically useful for dose titration and crossover trials, NA for the fixed dose trials as both dose achieved and total daily dose do not vary |
| Primary NSCLC dose unit | Unit of total daily or average dose achieved | Unit, NR if not reported |
| Primary NSCLC dose freq/cycle | | e.g., d1, d8 |
| Primary Rx days of administration | | e.g., 10 min i.v. infusion |
| Primary therapy duration and route of administration | | |
| Primary NSCLC Rx cycle duration | | |
| Primary NSCLC Rx number of cycles | | |
| Primary NSCLC formulation | Special treatment formulation | Only specialized formulations like IR, CR, SR |
| Primary NSCLC therapy status | Indicates whether the observation refers to the first, continuing or last dose of the therapy | Start = first dose starts on at this time, continuing = treatment is continuing at this time, end = |
Table 5 Variables for data extraction (Continued)

| Variable                                    | Description                                                                 | Data entry standards                                                                                  |
|----------------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Primary NSCLC dose comments                  | Comment regarding the dosing of primary NSCLC treatment at that time point   | Any comment that may be relevant to the understanding the dosing of the primary treatment in this record, NA if no comments |
| Combo NSCLC therapy                          | Name of secondary NSCLC therapy used in this arm in addition to the primary treatment at that time point | NSCLC drug, e.g., PTH NA if no secondary NSCLC therapy                                                |
| Combo NSCLC dose                             | Randomized daily dose of the secondary NSCLC therapy at time of outcome. Refer to the dose description of primary NSCLC dose | Total daily dose at the time of observation, NR if not reported and NA if no secondary NSCLC therapy |
| Combination NSCLC dose achieved              | Average daily dose of the secondary NSCLC therapy during assessment period or for the total treatment period | Average daily dose achieved. Specifically useful for dose titration and crossover trials, NA for the fixed dose trials as both dose achieved and total daily dose do not vary |
| Combination NSCLC dose unit                  | Unit of total daily or average dose achieved for the secondary NSCLC therapy | Unit, NR if not reported or NA if no secondary NSCLC therapy                                           |
| Combination NSCLC dose reg freq/cycle        | Frequency of secondary NSCLC therapy being administered                      | QD, BID, etc., NA if no secondary NSCLC therapy                                                       |
| Combination Rx days of administration        | Referred to in e.g., d1, d8                                                  |                                                                                                       |
| Combination Rx duration and route of administration | Referred to in e.g., 10 min i.v. infusion                                    |                                                                                                       |
| Combination NSCLC Rx cycle duration          |                                                                              |                                                                                                       |
| Combination NSCLC Rx number of cycles        |                                                                              |                                                                                                       |
| Combination NSCLC dose comment               | Comment regarding the dosing of secondary NSCLC therapy at that time point   | Any comment that may be relevant to the understanding the dosing of the secondary treatment in this record, NA if no comments |
| Concomitant medications                      | Baseline or by treatment arm                                                 | Baseline or by treatment arm for radiation therapy                                                   |

**Radiation therapy information**

| Variable                          | Description                                                                 | Data entry standards |
|-----------------------------------|-----------------------------------------------------------------------------|----------------------|
| Radiation therapy type            |                                                                             |                      |
| Radiation therapy comments        |                                                                             |                      |

**Assessment characterization**

| Variable                          | Description                                                                 | Data entry standards |
|-----------------------------------|-----------------------------------------------------------------------------|----------------------|
| Assessment                        | Common name for assessment that this record refers to, e.g., PANSS          | As in the assessments and conventions sheet |
| Assessment short form             | Code for the assessment                                                     | As in the assessments and conventions sheet |
| Assessment comment                | Any comment that describes the nature of the assessment                     | e.g., plasma glucose level, NA if no comments |
| Assessment location               | Location from where the assessment value is taken or extracted from the manuscript | Table number, figure number, page number |
| Assessment category               | Describes what the assessment value represented is, whether it is absolute, change from baseline (CFB), percent change from baseline (PCFB), or fraction of randomized patients with the event, count in case of tender or swollen joint counts | Absolute, CFB, PCFB, Frac, or Count |
| Assessment Stat parameter         | The summary parameter of the assessment value                               | Mean, median, percent, NR if not reported |
| Stat population                   | Statistical population for which the efficacy/safety analyses were done and value reported | ITT, OC, completers, randomized, PPP (per protocol population: define), NR if not reported |
| Missing data treatment            | Method used for handling with missing observations in computing the summary parameter | LOCF (last observation carried forward), none, NR if not reported |
Table 5 Variables for data extraction (Continued)

| Repository                      | Description                                                                 | Data entry standards                                                                 |
|---------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Scale lower limit               | Scale lower limit                                                           | The lower limit of the scale for the assessment, NA if not applicable                  |
| Scale upper limit               | Scale upper limit                                                           | The upper limit of the scale for the assessment, NA if not applicable                  |
| Assessment categories or words  | Scale category description                                                  | Category that is associated with each point of the scale                               |
| Total levels                    | Total categories/points in the scale                                         | The total number of categories associated with each point of the scale, e.g., 0 to 4 point scale |
| Total symptoms                  | Total symptoms in the scale                                                 | The total number of symptoms associated with the respective assessment, NA if not applicable |
| Total score lower limit         | Lower limit of the scale, this is calculated as the number of levels multiplied with the lowest possible scale Integer value, NA if not applicable |
| Total score upper limit         | Upper limit of the scale, this is calculated as the number of levels multiplied with the highest possible scale Integer value, NA if not applicable |
| Assessment level                | For ordered categorical data “scales.” Indicates which level in the categorical scale the assessment is referring to Integer level from 1 to number of levels, if fractional responder type, enter responder threshold value, eg., ≥5% weight loss from baseline for total body weight assessment, etc., NA if not applicable |
| PROs                            | Scale, mean value, SD by group, time point                                |                                                                                       |

Time, assessment, and baseline value information

| Repository                      | Description                                                                 | Data entry standards                                                                 |
|---------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Assessment visit                | Clinical visit at which the assessment is done                              | Visit 1 (usually baseline) is the first visit in the active phase. Lead in visits start at −1 and count backwards, NR if not reported |
| Assessment time reported        | Time at which the assessment is done during the study and as reported in the manuscript | Visit 1 = baseline = time 0 and the lead in assessment time starts at −1 and count backwards |
| Assessment time unit reported   | Unit for reported assessment time                                           | Time unit as reported                                                                  |
| Assessment time range reported  | In case if the assessment values are average over a time interval           | e.g., weeks 2 through 28 enter 2–28                                                   |
| Assessment time normalized      | Normalized time in days at which the assessment is done during the study and as reported in the manuscript | The normalized time value using the normalized unit as days, e.g., 4 weeks = 28 days |
| Assessment time unit normalized | Unit for standard assessment time                                           | Days is the standard unit                                                              |
| Assessment value                | Assessment value reported at that time point                               | Assessment value as reported                                                           |
| Assessment unit                 | Assessment unit as reported                                                 | Assessment unit as reported, NA if not applicable                                       |
| Assessment SE                   | SE of reported assessment value                                             | SE as reported, NR if not reported                                                    |
| Assessment SD                   | SD of reported assessment value                                             | SD as reported, NR if not reported                                                    |
| Assessment CI type              |                                                                                |                                                                                       |
| Assessment lower CI             |                                                                                |                                                                                       |
| Assessment upper CI             |                                                                                |                                                                                       |
| Assessment value normalized     | Assessment value converted into normalized assessment units                 | Still insert value here, report if normalized units are the same as the reported units |
| Assessment value norm           | Normalized assessment value units                                           | See assessments and conventions sheet for normalized assessment standard               |
| Assessment SE normalized        | Standard error of normalized assessment value                               | SE in the same units as normalized assessment, may need to be calculated from SD and N; if not provided, NA |
| Assessment SD normalized        | Standard deviation of normalized assessment value                           | SD in the same units as normalized assessment, may need to be calculated from SE and N; if not provided, NA |
Table 5 Variables for data extraction (Continued)

| Assessment CI type normalized | Number of patients assessed at that time point and the value derived. Integer value, but for responders and dropouts, this value is calculated from the percentages reported in the trial. |
| Assessment lower CI normalized | |
| Assessment upper CI normalized | |
| Assessment number | |
| Assessment value comment | Comment pertaining to the assessment value that cannot be dealt by other variables. e.g., the assessment value is the mean of last 7 days of before each clinical visit, etc. |
| Hazard ratio | 95% confidence intervals, progression-free survival, and overall survival—adjusted and unadjusted. |
| Baseline visit | Clinical visit at which the baseline assessment is done. Visit 1 = baseline = time 0, NR if not reported. |
| Baseline time | Time at which the baseline assessment is done. Visit 1 = baseline = time 0. |
| Baseline time unit | Unit for reported baseline time. Time unit as reported. |
| Baseline time normalized | Normalized time in days at which the baseline is done during the study and as reported in the manuscript. The normalized time value using the normalized unit as days, e.g., −4 weeks = −28 days. |
| Baseline time unit normalized | Unit for standard baseline time. Days is the standard unit. |
| Baseline value | Absolute baseline value for that assessment. Absolute baseline value. |
| Baseline value unit | Assessment unit as reported. Assessment unit as reported, NA if not applicable. |
| Baseline SE | SE of the absolute baseline value. SE as reported, NR if not reported. |
| Baseline SD | SD of the absolute baseline value. SD as reported, NR if not reported. |
| Baseline CI type | |
| Baseline lower CI | |
| Baseline upper CI | |
| Baseline value normalized | Baseline value converted into normalized baseline units. Still insert value here report if normalized units are the same as the reported units. |
| Baseline value unit normalized | Normalized baseline value units. See assessments and conventions sheet for normalized assessment standard. |
| Baseline SE normalized | Standard error of normalized baseline value. SE in the same units as normalized baseline, may need to be calculated from SD and N; if not provided, NA. |
| Baseline SD normalized | Standard deviation of normalized baseline value. SD in the same units as normalized baseline, may need to be calculated from SE and N; if not provided, NA. |
| Baseline CI type normalized | |
| Baseline lower CI normalized | |
| Baseline upper CI normalized | |
| Baseline N | Number of patients from which the baseline value is derived. Integer. |
| Baseline value comment | Comment pertaining to the baseline value that cannot be dealt by other variables. e.g., the baseline value is the mean of last 7 days of the run in period. |

Reference specifications

| Repository | Description | Data entry standards |
|------------|-------------|----------------------|
| Ref code   | Numerical code assigned for the literature citation. Maps the record to the assessment details. | Integer |
| Protocol or trial number | Protocol ID or the number of the trial report. | As reported, NA if not applicable |
| Date modified | Date of initial entry or subsequent modification of the data point. | mm/dd/yy format |
| Modified by | Initials of curator. | |
Table 5 Variables for data extraction (Continued)

| Variable | Description |
|----------|-------------|
| Modification comment | Any comment that is relevant to modification by the curator Initial entry if new record, brief statement of change(s) |
| Copyright status | Provided by the client or procured by the service provider Client provided or yes in case the manuscript is procured by the service provider |
| Author | Authors of publication As reported |
| Journal | Journal name Standard abbreviated forms can be used, generally as in the PubMed |
| Publication year | Year of the publication Integer |
| Title | Title of the study |
| Volume | Volume number of the publication e.g., 180 |
| Pages | Page numbers of the publication e.g., 1–24 |
| Trial name alias | Trial name that trial is commonly refers to NR if not reported |
| Inclusion description | Provide description of inclusion criteria Can be cut and paste from PDF, can be placed in an attached note |
| Exclusion description | Provide description of exclusion criteria Can be cut and paste from PDF, can be placed in an attached note |
| Study design | Brief description of the study design Parallel-fixed arm, dose escalation, effect titration, crossover, etc. |
| Location of the trial | Geographical location where the study is conducted Primary nationalities list |
| Number of countries | Number of countries the study is conducted Integer |
| Number of centers | Number of centers the study is conducted Integer |
| Trial start date | Date when the trial started mmddyy format |
| Trial end date | Date when the trial completed mmddyy format |
| Placebo-controlled or active comparator | Was there a control group and was it placebo PBO control/active comparator |
| Active comparator therapy | If this was an active comparator trial what was the comparator therapy e.g., PTH |
| Percent randomized to placebo | Percent of subjects in the trial who are randomized to placebo Integer |
| Add-on/washout study | Was the study drug added on to standardized background Rx, was background Rx washed out prior to starting primary Rx, or was standardized background therapy withdrawn once primary RX started Add-On, Washout, Replacement, None |
| Study blind | Was the trial blinded for the treatment phase Yes, double blind |
| Number of arms | Number of treatment arms the patients are randomized to Integer |
| Arm description | Codes and description for arms 0 = placebo and others in sequence |
| Dose descriptions | Brief descriptions of the treatment drugs and the respective doses along with regimens received 0 = placebo, 1 = metformin 10 mg QW… |
| Dose ranging within study | Does the trial contain at least two primary treatment arms where different dose strengths were administered Yes, No. Placebo does not count as a dose strength |
| Primary longitudinal data | Were multiple time values reported for the primary assessment endpoint Yes, No. |
| Active phase trial duration | What was the duration of the active phase of the trial Time, units, i.e., 3 weeks |
| Steady state effect achieved? | Does it appear that effect stabilized over time for primary endpoints Yes, No. Not clear |
| Was there a lead-in phase? | Was there a standardized lead-in phase in the study other than a simple screening visit Yes, No |
| Lead-in phase duration | If so, what was the duration If yes, time, units, i.e., 6 months. If no, 0 |
| Was there a follow-up phase? | Was there a standardized follow-up phase that at least some patients were enrolled in after the active phase ended Yes, No |
inconsistencies. Density plots of the posterior samples from models based on direct, indirect, and mixed evidence will be compared. In addition, the heterogeneity parameters (variance and standard deviation) and goodness of model fit measures (residual deviance and deviance information criterion (DIC), a Bayesian criterion for model comparison) between the direct and indirect models will be compared.

OS and PFS data will be analyzed using a log transformation of the HR and treating this as a continuous outcome. For studies with median time information, we will also use log transformation of the median time and treat this as a continuous outcome in sensitivity analyses. HRs are preferred summary statistics to median time per Michiels and colleagues [13], and hence, the analysis will utilize HR data for the primary outcome measure.

Ideally, the literature will provide values for log (HR) and the standard error (SE) for log (HR). If the SE for log (HR) is not available, an attempt will be made to estimate the missing value from the SE for median time, assuming an exponential distribution of survival time and log (HR) = −log (median time ratio). Alternatively, an estimate of the SE for log (HR) will be made on the basis of the number of subjects with events as specified below:

1. “MedianTime” will be converted into log (median time);
2. The SE for log (median time) is estimated as (log (upper confidence limit) − log (lower confidence limit))/2/quantile (confidence level) if a treatment arm has non-missing value for all three variables;
3. If confidence limit is missing, then the number of subjects with events can be used to estimate the standard error for log (median time) as 1/sqrt(n) for a treatment arm.

Individual odds ratios and/or toxicity rates for each grade 3–4 toxicity from each study will be included, respectively, in an NMA using a Bayesian approach that ensures the preservation of randomization in the network. Odds ratios will be calculated for studies reporting toxicity rates. Prior to creating the odds ratios, we will ensure that similar versions of toxicity scaling criteria have been used. Data for analysis will be directly extracted from the text of the article or calculated from data in the text.

A network meta-analysis of GC + N to all identified comparators will be conducted for health-related quality of life (HRQoL) measures (including EQ-5D and the Lung Cancer Symptom Scale (LCSS)) during and following therapy. The most common quality of life instruments as reported across studies will be analyzed. Initial analyses will be limited to those quality of life outcomes for which GC + N data are available. For each identified measure, a standardized mean difference in quality of life outcomes from each study will be included. For each identified measure, data will be assessed according to the guidelines for that particular instrument and then pooled across studies to determine the standardized mean difference.

A meta-regression will be conducted using the key covariates of patient age and stage of disease (percent of patients with stage IV), as these variables have prognostic value in squamous NSCLC. Additional covariates may be identified following the literature review and will be considered for inclusion in post hoc analyses to control for potential bias.
Sensitivity analyses
We anticipate that some studies will not report all relevant data. In order that such studies can still be included in the analysis, we may consider imputing missing data using established methods as appropriate [14]. If imputation is made, the Bayesian model as described above will be used as the primary analysis and will be compared with analyses including the imputed values. Sensitivity analyses may be conducted to examine the effect of this method using an approach proposed by Carpenter and colleagues [15], which entails imputing missing data under a missing at random assumption, and then reweighting the imputed data to allow for non-random selection. Sensitivity analyses as outlined for OS and PFS will also be conducted for HRQoL; however, the use of disparate HRQoL instruments or assessment time points may result in an inability to evaluate the study endpoint. Sensitivity analyses will be performed to assess the robustness of the findings. At a minimum, the following analyses will be conducted if there are at least three studies available for analysis:

1. Repeat the meta-analysis using a frequentist approach;
2. HR only (primary aim) versus HR or median time;
3. By geographical site of study enrollment;
   a. e.g., Western versus Eastern hemispheres
   b. e.g., Americas versus Europe versus Asia
4. Limit to patients with stage IV disease;
5. Direct comparisons only;
6. By excluding phase II trials;
7. By age—studies with a mean age over the age of 70;
8. Limiting the analysis to high-quality studies (≥6) as determined by the PEDro scale;
9. Removing studies considered to be biased according to the Cochrane Risk of Bias Tool.

Assessment of bias and study quality
The risk of bias will be appraised using the Cochrane Risk of Bias Tool (www.cochrane-handbook.org). This tool was developed specifically to assess the internal validity of RCTs. It consists of the following seven criteria: 1) randomization generation, 2) allocation concealment, 3) blinding of outcome assessors, 4) blinding patients and personnel, 5) incomplete outcome data (i.e., withdrawals), 6) selective outcome reporting, and 7) other risks of bias. The final item will include fraudulent results, other methodological flaws in the RCTs, and the potential for bias.

To assess publication bias, the fail-safe N will be calculated. If the number of unpublished trials that may invalidate the findings is less than five, it will be noted in the conclusions as a potential limitation of the findings. If the number of unpublished trials to invalidate the findings is five or greater, it will be noted in the results. Furthermore, funnel plot analyses will also be conducted to provide a visual representation demonstrating where unpublished data may exist. This is planned to help guide the interpretation of the study findings and the direction of bias.

Quality of selected trials for inclusion in the review will be assessed. The PEDro quality scale, an 11-item scale designed for rating the methodological quality of randomized controlled trials [16], will be used to evaluate the quality of selected trials. Here the two reviewers will independently assess studies for methodological validity prior to inclusion. Identified studies that meet the inclusion criteria will then be grouped according to the class of statin used in the trial. High quality scores will be defined as a PEDro score ≥6 and low quality scores will be defined as a PEDro score <6.

Missing data are expected in the majority of data fields collected in this meta-analysis. In cases of missing data, heterogeneity will be tested on all outcome variables to ensure that studies are comparable. Forest plots will be created for OS, PFS, toxicity, and quality of life endpoints. In the case of non-overlapping confidence intervals, the research team will discuss the need for post hoc subgroup analyses.

Discussion
The study design for this systematic review and meta-analysis is presented here to follow PRISMA standards. Industry-sponsored or industry-led studies are increasingly under scrutiny regarding transparency and risk of bias [17]. This study protocol has been designed prior to any knowledge of the study data or outcomes from existing published literature and is being disseminated in an attempt to provide the scientific community with the ability to evaluate the methods and plans of our study before it is conducted. The study protocol has been designed to meet PRISMA standards [18,19] and is being disclosed so that our methods can be retrieved and evaluated against the final analyses and interpretation of findings.

While it is almost impossible to fully anticipate the limitations of the data once they are obtained, this study has been designed in an attempt to pre-specify all primary analyses and sensitivity analyses to demonstrate the stability in results that may be discovered. However, it is possible that there will not be sufficient data to achieve all the pre-specified study aims or to complete all planned analyses. There are also possible limitations in the network connections. Unlike patients diagnosed with lung cancers of non-squamous histology, those with squamous NSCLC have not benefited from the same depth and breadth of research conducted to identify optimal treatment strategies. Therefore, via our search criteria, we are casting a wide net in the hopes of finding studies that not only investigate, but also report, outcomes for this histological subgroup.
Our ultimate goal is to provide reliable and trustworthy data regarding the comparative efficacy of necitumumab against other possible options for care so that decision makers can come to their own conclusions regarding the value of this molecule currently in development.

Competing interests
All study authors disclose that they are employees of Eli Lilly and Company.

Authors’ disclosures
AD participated in the study design, development of the study protocol, drafting of the analysis plan, and writing of the manuscript and will be responsible for data and eligibility review. JB conceived of the study design, review of the study protocol, and substantive input to the manuscript. FN developed the study protocol analysis plan and will be responsible for final analyses. LZ developed the study protocol analysis plan and will be responsible for final analyses. SA will be responsible for data and eligibility review. LB and JT conceived of the study design and development and will be responsible for final analyses. ZC developed the study protocol analysis plan and will be responsible for final analyses. LH conceived of the study design, development of the study protocol, writing of the manuscript, and drafting of the analysis plan. LA participated in the study design, development of the study protocol, and will be responsible for data and eligibility review. All authors reviewed study protocol, writing of the manuscript, and drafting of the analysis plan. LH conceived of the study design, development of the study protocol, writing of the manuscript, and drafting of the analysis plan and will be responsible for data and eligibility review. All authors reviewed and approved the final version of the manuscript.

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References
1. ALA: Lung Cancer Fact Sheet - American Lung Association. 2013 [http://www.lung.org/lung-disease/lung-cancer/resources/facts-figures/lung-cancer-fact-sheet.html]
2. CancerCare: Lung Cancer 101. 2013 [http://www.lung.org/find_information/publications/163-lung_cancer_101/268-types_and_staging]
3. SEER: “Cancer Statistics.” Cancer of the Lung and Bronchus. 2013 [http://seer.cancer.gov/statfacts/html/lungb.html]
4. Scaglioni G, Hanna N, Fossella F, Sugarman K, Blatter J, Peterson P, Simms L, Shepherd FA: The differential efficacy of pemetrexed according to NSCLC histology: a review of two phase III studies. Oncologist 2009, 14(3):255–263.
5. Johnson DH, Fesherbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, Langer CJ, DeVore RF, Gauldreaul J, Darmico LA, Holmgren E, Kabbinavar F: Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004, 22(11):2184–2191.
6. AstraZeneca: Iressa. Gefinitib. 2014 [http://www.iressa.com]
7. Genentech: Erlotinib Tablets. 2013 [http://www.tarceva.com]
8. Gahr S, Steoer R, Geissinger E, Ficker JH, Brueckl VM, Gschwendtner A, Gutenboehner S, Fuchs FS, Reiker RJ, Hortmann A, Rueinmele P, Dietmaier W: EGFR mutational status in a large series of Caucasian European NSCLC patients: data from daily practice. Br J Cancer 2013, 109(7):1821–1828.
9. Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA: SEER Cancer Statistics Review, 1975–2010. Bethesda: N.C. Institute; 2013.
10. Shen W, Zhu B, Han B, Natanegea F: Bayesian Network Meta-Analysis for Health Technology Assessment and Evaluation for Investigative Treatment. In ICSSS/ISBS Joint Statistical Conference: 9–12 June 2013. Washington, DC: 2013.
11. Parmar MK, Torri V, Stewart L: Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998, 17(24):2815–2834.
12. Dias S, Welton NJ, Caldwell DM, Ades AE: Checking consistency in mixed treatment comparison meta-analysis. Stat Med 2010, 29(7–8):922–944.
13. Michiels S, Peddiosi P, Burdett S, Syz N, Stewart L, Pignon JP: Meta-analysis when only the median survival times are known: a comparison with individual patient data results. Int J Technol Assess Health Care 2005, 21(1):119–125.
14. Little JH, Pillai V: Systematic Reviews and Meta-Analysis. New York: Oxford University Press; 2008.
15. Carpenter J, Rucker G, Schwarzer G: Assessing the sensitivity of meta-analysis to selection bias: a multiple imputation approach. Biometrics 2011, 67(3):1066–1072.
16. de Morton NA: The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. Aust J Physiother 2009, 55(2):129–139.
17. Lundh A, Simondon S, Lewchin J, Bussio OA, Bero L: Industry sponsorship and research outcome. Cochrane Database Syst Rev 2012, 12, MR000033.
18. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009, 339:b2700.
19. Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009, 339:b2535.

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