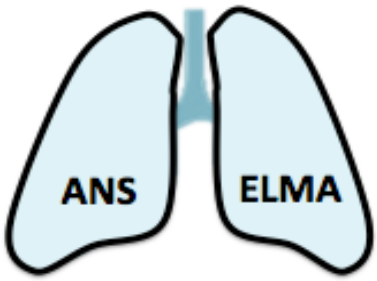

ANSELMA

ANtiangiogenic SEcond line Lung cancer Meta-Analysis

Antiangiogenic agents in advanced non-small cell lung cancer patients who failed first-line chemotherapy: an individual patient data meta-analysis

October 2016

Prospero registration number: CRD42016035670

SECRETARIAT

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1. Introduction and background

Erlotinib, docetaxel and pemetrexed are approved second-line therapies for advanced non-small cell lung cancer (NSCLC) patients [1]. Pemetrexed has shown to have a similar efficacy to docetaxel in second-line setting but with significantly better toxicity profile [2]. TITAN trial reported that erlotinib was equivalent to pemetrexed or docetaxel in refractory (progression during first-line chemotherapy) patients unselected for EGFR status [3]. In molecularly selected wild-type (wt) EGFR population, the TAILOR trial shown that docetaxel was superior to erlotinib as second-line therapy with respect to overall survival (OS) and progression free survival (PFS) [4]. However, in the subset analysis of EGFR-wt tumors, the DELTA trial failed to demonstrate a gain in OS for docetaxel *vs*. erlotinib [5], reinforcing erlotinib as a potential second-line treatment option independently of EGFR status. Currently, the efficacy of approved drugs for second-line treatment is limited with an objective response rate (RR) of less than 10%, median PFS of less than 4 months, and median OS of 7-9 months [6].

Avoiding immune destruction is a hallmark of cancer. The Immune checkpoint inhibitor anti-programmed death-1 nivolumab has reported to improved RR and OS as second line therapy in advanced NSCLC compared with docetaxel in two randomized phase III trials [7,8]. However, independently of the immune checkpoint inhibitor subtype (nivolumab [7,8], pembrolizumab [9], atezolizumab [10,11]), the overall response rate is approximately of 20% as monotherapy in second-line treatment with no standardized predictive marker, especially in squamous histology, for better selecting the patients.

Tumor angiogenesis is critical for tumor progression. The vascular endothelial growth factor (VEGF) promotes angiogenesis, and overexpression of the VEGF has been correlated with poor prognosis in NSCLC. Bevacizumab, a monoclonal antibody against the VEGF, significantly prolonged OS and PFS when added to first-line platinum-based chemotherapy in advanced NSCLC patients [12]. Recently two randomized phase III trials LUME-lung 1 [13] and REVEL trial [14] have proven to improve the outcome with nintedanib or ramucirumab combined with docetaxel over docetaxel alone as second-line therapy in advanced NSCLC, respectively. A recent network meta-analysis,

suggest that nintedanib plus docetaxel may offer the highest clinical benefit when used as second-line treatment, compared to pemetrexed, docetaxel or erlotinib alone, with similar results in PFS [15]. The main limitations of this study are its limitation to only one antiangiogenic drug and the limitation of any study based indirect comparisons that corresponds to a lower level of evidence that direct comparison. Also, a recent systematic review and meta-analysis of phase II/III of randomized clinical trials with 8 358 patients, reported a significant improvement in RR (RR 1.75, 95%CI: 1.55-1.98, p<0.00001), PFS (HR 0.80, 95% CI: 0.76-0.84, p<0.00001), and OS (HR 0.94, 95% CI: 0.89-0.99, p=0.03) in the group with antiangiogenic therapy plus standard second-line treatment compared with the group with standard second-line treatment alone. The benefit in OS was restricted to docetaxel combinations and to non-squamous histology [16]. These results suggest the efficacy of antiangiogenic agents in this subpopulation, but the analysis was based on subgroup analysis and not in the study of the interaction between control treatment (or histology) and treatment effect. The analysis by histology was not available for all the trials. However, some factors should be considered when assessing the real benefit of antiangiogenic therapies in second-line treatment of advanced NSCLC such as differences by histologic subtype, clinical criteria for patient selection (age, brain metastasis….), the best treatment partner for antiangiogenic therapies, and negative results with other antiangiogenic treatments such as vandetanib [17–19], sunitinib [20–22], sorafenib [23,24], aflibercept [25], and bevacizumab [26–28]; these factors are confounding about the real benefit of these therapies in second line. Also, new antiangiogenics therapies have been tested with very preliminary results [29,30]. Finally, one of the major challenges with antiangiogenic therapies is the identification of reliable predictive biomarkers to establish which patients are most likely going to benefit from antiangiogenic inhibitors, but although these agents are available for 10 years, no biomarker has been yet identified.

Given that the benefit of antiangiogenic therapies is not consistently positive and provides only a mild absolute clinical benefit which varies according to the type of histology and/or prognosis factors, without a real improvement in the quality of life of patients but with an incremental in the cost of treatment, a systemic review and meta-analysis of randomized controlled phase II/III trials

will be performed. Hazard ratio will be used for survival data. The main purpose of this meta-analysis will be to evaluate the OS of antiangiogenic therapies in second-line treatment of advanced NSCLC patients and the population that most benefit from such therapies.

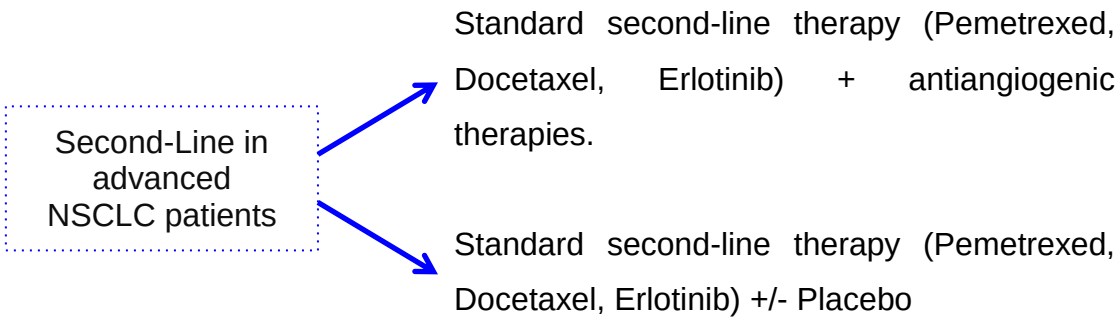
The meta-analysis will be based on individual patient data [31–33] and will use a similar methodology to that used in the Prophylactic Cranial Irradiation Overview [34], NSCLC meta-analysis [35,36], and Meta-Analysis of Radiotherapy in Lung Cancer [37]. A similar collaborative group comprising those involved in trials included in the project will be established and the meta-analysis will be conducted and reported on its behalf. Because of the potential difficulty to collect individual patient data on recent treatment, a summary data analysis may be performed as a first step. Both published and unpublished studies will be included in the meta-analysis since there is evidence that both investigators and journal editors are more likely to publish trials with positive results [38]. Basic survival and prognostic information will be collected for all patients randomized in each study because this allows a more reliable and flexible approach, a more sensitive analysis and avoids the potential bias of post-randomization exclusion [31–33]. Data on compliance and toxicity will be collected. Only individual patient data allow studying the variation of treatment effect according to clinical or biological factors.

2. Objectives

Assessment of the role of antiangiogenic therapies adjunction to the standard second-line therapy in advanced NSCLC patients by study the following questions:

2.1 Primary objective

Role of antiangiogenics on OS in patients with advanced NSCLC by comparing the two following second-line treatments: conventional second-line treatment plus placebo (or no supplementary treatment) vs. conventional second-line treatment plus antiangiogenic therapy based on the results of randomised phase II / III clinical trials.



2.2 Secondary objectives

- Effect of this combination on progression-free survival;
- Effect on objective response rate;
- Comparison on toxicity between the treatment arms (hematological toxicity, haemorrhagic-events, gastrointestinal disorders, renal toxicity, cardiovascular disorders, thromboembolic events and neurological disorders);
- Study the impact of previous antiangiogenic therapies (bevacizumab) on the efficacy and toxicity;
- Describe the compliance of treatment in the two arms
- Investigation of the interaction between the treatment effect in terms of survival and severe toxicity (grade ≥ 3) and the prognostic factors and patients characteristics (subgroups analyses):
    - Gender
    - Age
    - Ethnic origin
    - Performance status
    - Tobacco status
    - Brain metastases
    - Histologic subtype
    - Platinum sensitivity (free interval with the last cycle of platinum based chemotherapy)
    - Epidermal Growth Factor Receptor (*EGFR)* mutation if available and other molecular alterations (*ALK*, *KRAS*) if available

- Prior bevacizumab treatment in first-line
- Maintenance chemotherapy
- Other factors to be discussed: Body Mass Index (BMI), body surface, albumin level, lymphocyte/neutrophils ratio or lymphocytes </> 1 000.

3. Trial selection criteria

3.1 Inclusion criteria

All trials included in the meta-analysis must satisfy the following criteria:
Trials must:

- Be performed in advanced NSCLC patients who experienced a platinum-chemotherapy first-line failure.
- Compare the standard second-line treatment (pemetrexed, docetaxel, erlotinib) to standard second-line treatment plus antiangiogenic agent (monoclonal antibody or tyrosine kinase inhibitor against vascular pathway).
- Be randomized in a way, which precludes prior knowledge of treatment assignment.
- Have completed accrual before 31st December 2014.

Patients must:

- Have received previous systemic chemotherapy with or without bevacizumab. Patients can also have received other monoclonal antibodies, such as cetuximab, in combination with chemotherapy.
- Be suitable to receive second-line treatment and antiangiogenic therapy.
- Be randomized to receive conventional second-line treatment with or without antiangiogenic therapy.

3.2 Exclusion criteria

Trials to be excluded:

- Randomized trials without a conventional second-line treatment.

4. Trial Search and selection

Data from all published and published randomized trials making the above comparisons in advanced NSCLC will be sought using electronic database searching (Pubmed, Scopus, Wos, Embase, ClinicalTrials, Centerwatch, National Cancer Institute NIH, Cochrane) and manual searching (meeting proceedings, review, articles). The detail of initial search and its results are given in the **Appendix 1.** Other sources of clinical data such as clinicaltrials.gov have been consulted. Meta-analyses on this topic have been searched (above sources plus Prospero). Bibliography of randomized trials and meta-analysis publication has been systematically reviewed. Also, a trial flow chart has been created in the **Appendix 2**. Two persons performed trial selection with discussion by a third person in case of disagreement

5. Criteria of evaluation

5.1 Endpoints

The main endpoint will be **overall survival**, because of its importance and because the reliability of the measurement.

Secondary end-points such as progression-free survival, objective response rate will be considered. Observance and toxicity under standard second-line treatment and antiangiogenic therapy will be also studied, if possible.

5.2 Prognostic factors

The following prognostic factors and patients characteristics, if available, will be considered:

- Gender
- Age (<60 years *vs*. 60- 69 years *vs*. ≥70 years)
- Ethnic origin (Caucasia, Asian, other)
- Performance status (WHO, or equivalent, PS: 0 *vs*. 1 *vs*. 2)
- Tobacco status (smoker, never smoker, former smoker)
- Brain metastases (present/absent)

- Histologic subtype (adenocarcinoma *vs*. squamous *vs*. others)
- Duration of first-line chemotherapy until randomization
- Platinum sensitivity (free interval from the last cycle of platinum-based chemotherapy to the start of second line in 3 categories according to the available data).
- *EGFR* mutation status (positive/negative)
- *KRAS* mutation status (positive/negative)
- *ALK* rearrangement status (yes/not)
- Prior target therapy combined with chemotherapy such as bevacizumab or cetuximab or other target therapy in combination with chemotherapy
- Maintenance chemotherapy (yes/no)

6. Description of the included trials

The eligible trials are described in **Appendix 3 and 4**. In total, seventeen trials (8 randomized phase III trials and 9 randomized phase II trials) with 8 706 patients have been included in the meta-analysis. PFS and OS were the primary endpoint in 13 and in 4 of the 17 trials, respectively.

The **Appendix 3** describes the trials selected for the meta-analysis according the percentage of number of patients included, histologic subtype, treatments, the schedule and the median follow-up.

The **Appendix 4** describes the results (response rate (RR), PFS and OS) of the trials included in the meta-analysis.

The **Appendix 5** describes the ongoing trials excluded in this meta-analysis.

7. Data collection and quality control

7.1 Data collection

For the first step, on published information, two persons will extract the data independently from publication, clinicaltrials.gov or statistical reports. A specific form will be designed to extract the data. If possible, summary data (hazard ratio) on the effect of antiangiogenic therapies in second-line treatment on OS

and PFS by patients' subgroups defined by the above-mentioned prognostic factors and patients' characteristics will be extracted.

For all eligible trials, the main investigator will be asked to provide the following basic data for survival and prognostic factors for all randomized patients:

- Gender
- Age or date of birth
- Ethnic origin
- Performance Status
- Tobacco status
- Date of diagnosis
- Brain metastases at randomization
- Histology
- Dates of first and last administration (or day 1 last cycle, if last one not available) of first-line chemotherapy administration or delays between the first and last administration of the chemotherapy and the randomization.
- Type of first-line chemotherapy administered
- Prior target therapy (bevacizumab, cetuximab, other) combined with first first-line chemotherapy
- Maintenance chemotherapy
- Treatment allocated by randomization
- Date of randomization
- Date of chemotherapy start
- Number of chemotherapy cycles or months of target therapy received
- Number of months, or injection of antiangiogenic therapy received
- Post-discontinuation treatments
- Date of last follow-up
- Survival Status
- Cause of death
- Date of progression
- Severe toxicity (grade ≥ 3)
- Type of severe toxicity
- Epidermal Growth Factor Receptor (*EGFR)* mutation, *KRAS* mutation and *ALK* rearrangement if available (positive / negative),
- Body Mass Index (BMI),

- Albumin level
- Lymphocyte/neutrophils ratio or lymphocytes </> 1 000

Appendix 6 gives the suggested format and coding of the form to be sent to the Secretariat.

7.2 Quality control

For the summary data meta-analysis, the risk of bias of included trials will be appraised by two independent investigators according the latest version of the "Risk of bias assessment tool" developed by the Cochrane collaboration [39] with divergences resolved by consensus.

For the IPD meta-analysis all data will be checked for internal consistency and consistency with the trial protocol and published report. Range checks will be performed and extreme values will be checked with the trialists. Each trial will be analysed individually, and the resulting survival analyses and trial data will be sent to the trialists for verification [40].

This study follows the guidance provided by the Cochrane Working Group on the conduct of IPD meta-analysis [40] and PRISMA Statement on the reporting [33,41,42]

8. Statistical analysis plan

Trial characteristics will be reported in tabular form, information will include patient numbers, population description, treatment details, number of patients lost to follow-up and median follow-up. Median follow-up will be computed using the reverse Kaplan-Meier method [43].

The ultimate aim will be to obtain and analyse data from all randomized patients included in all relevant randomized trials on an intention-to-treat basis. With around 5 000 patients (or 2750 deaths) it would be possible to detect, with a power of 90%, an absolute improvement in survival from 40 % to 45 % at 1-years (two-sided log-rank test, type I error = 5%).

The main analysis will be performed on the endpoint of overall survival. Additional analyses will be performed on objective response rate, progression-free survival, if sufficient data are available. Compliance and severe acute toxicity rates will be also studied.

All analyses will include all randomized patients and will be carried out on an intention-to-treat basis that is patients will be analysed according to the treatment allocated, irrespective of whether they received that treatment. Survival analyses will be stratified by trial, and the log-rank expected number of deaths and variance would be used to calculate individual and overall pooled hazard ratios by the fixed-effect model [44]. Thus, the time to death for individual patients will be used within trials to calculate the hazard ratio, representing the overall risk of death for patients who were allocated standard treatment plus antiangiogenic compared with those who were allocated standard treatment. For comparing toxicity rates, overall pooled odds ratio stratified by trials will be calculated by a fixed-effect model.

The $\chi 2$ heterogeneity tests [45,46] will be used to test for gross statistical heterogeneity, the I^2 statistic [47] will be used as a measure of consistency among trials. Random effect will be used in case of unexplained heterogeneity. Stratified survival curves will be estimated for control and experimental groups using annual death rates and hazard ratios [48]. They will be used to calculate absolute benefit at 6-months, and 12-months with their 95% confidence intervals [48]. All p-values will be two-sided.

8.1 Analysis by trial level characteristics

The effect of antiangiogenic may vary across trials in the meta-analysis because the treatments might be applied in different ways. To explore this further, providing that there are sufficient data available, analyses are planned in which trials, or arms within trials, will be grouped according to the type of antiangiogenic to determine whether there is any difference in treatment effect among these groups.

Trial	N	Comparison
Monoclonal antibodies / proteins added to Chemotherapy		
REVEL	1 253	Docetaxel ± Ramucirumab
Herbst*	120	Docetaxel / Pemetrexed ± Bevacizumab
VITAL	913	Docetaxel ± Aflibercept
WJOG5910	100	Docetaxel ± Bevacizumab
Hosomi	160	Docetaxel ± Ramucirumab
Tyrosine kinase Inhibitors (TKI) added to Chemotherapy		
LUME Lung 1	1314	Docetaxel ± Nintedanib
LUME Lung 2	713	Pemetrexed ± Nintedanib
ZODIAC	1391	Docetaxel ± Vandetanib
Vandetanib phII**	127	Docetaxel ± Vandetanib
ZEAL	534	Pemetrexed ± Vandetanib
CALGB30704[+]	130	Pemetrexed ± Sunitinib
N0626	100	Pemetrexed ± Sorafenib
Antiangiogenic (monoclonal antibodies or TKI) added to TKI		
BeTaLung	636	Erlotinib ± Bevacizumab
SUN1087	960	Erlotinib ± Sunitinib
Sunitinib ph II	132	Erlotinib ± Sunitinib
LUN160	168	Erlotinib ± Sorafenib
ECOG1512[#]	125	Erlotinib ± Cabozantinib

* For the meta-analysis, the bevacizumab + erlotinib arm (n=39) has not been analysed.

** For the meta-analysis, the docetaxel + vandetanib 300 mg arm (n=44) has not been analysed.

[+] For the meta-analysis, the cabozantinib arm (n=47) has not been analysed.

[#] For the meta-analysis, the sunitinib arm (n=40) has not been analysed.

8.2 Analyses by patient level characteristics

Provided that there will be sufficient data available, we will investigate whether any observed treatment effect is consistent across well-defined patient subgroups. These analyses will be carried out on all trials with the available data and will be stratified by trial. If there are substantial heterogeneity and differences of effect between treatment categories, then subgroup analyses will be done within treatment categories. Depending of the data available, some characteristic may be considered as trial factor instead of patient factor (e.g. prior bevacizumab treatment given to all patient or non-depending of the trial). To avoid bias, only within trial information will be used for subgroup analyses, as described by Fisher et al [49].

If there are insufficient numbers of patients within any patient category, categories will be combined. Chi-squared tests for interaction or trend will be used to test whether there is any evidence that a particular type of patients benefits more or less from antiangiogenic therapies.

The subgroups to be analysed will be as follows: gender, age, ethnic origin, performance status, tobaccos history, histologic subtype, brain metastases status, duration of first-line treatment, platinum sensitivity, *EGFR* mutation status, prior bevacizumab treatment, prior maintenance treatment.

8.3 Sensitivity analysis

The following sensitivity will be performed:

- Exclusion of trials including only Asian or old patients
- Exclusion any trials that are clear outliers or particular (trial alone in its category),
- Exclusion of small trials (<100 patients)
- Exclusion of trials with a median follow-up shorter than 12 months
- Exclusion of trials for which date of randomization and events are not available, as data checking will be incomplete in this case.

- Exclusion of trials considered of poor quality based on Cochrane scale for the summary data meta-analysis and after data checking for IPD meta-analysis

9. Working parties in the meta-analysis project

In order to complete the meta-analysis successfully, three groups with specific functions have been created: 1) the Secretariat, 2) the Advisory Board and 3) the ANSELMA Trialists' Collaborative Group (ANSELMA-CG).

The Secretariat is in charge of the coordination of the meta-analysis. It is responsible for completing the trial register and for inviting investigators to provide patient data. The Secretariat is also in charge of checking, processing and analyzing the data. Finally, the Secretariat is responsible for preparing reports and publications.

The Advisory Board is a small group of international experts that will support the Secretariat with medical and statistical expertise.

The Trialists' Collaborative Group (ANSELMA-CG) will include the investigators responsible for the trials included in the meta-analyses. The members of the Secretariat and the Advisory Board will also be included in this group. The investigator will be responsible for providing the Secretariat with data on patients. Both the investigators and the advisory board will be invited to discuss the reports prepared by the Secretariat.

9.1 Practical considerations

The Secretariat is located in the Biostatistics Department of Gustave Roussy. This Department will be responsible for liaising with trialists, running the main database. All data, updates and corrections should be sent there. The Secretariat will collect and check the data checking and perform the analysis.

All supplied data will remain confidential and will be used exclusively for these meta-analyses. **Appendix 7** provides the form to register in the meta-analysis.

10. Publication policy

The Secretariat will prepare the manuscript and will submit it for revision to all members of the group. Any publication arising from this project will be made in the name of the ANSELMA Collaborative Group and will associate members of the Secretariat, advisory board and trial investigators.

11. Acknowledgements

We thank Françoise Delassus for administrative support and Alexia Nerfié for the bibliography searches. We thank the Gustave Roussy thoracic oncology multidisciplinary committee for financial support.

12. Appendix 1

Trial search strategy (search equations)

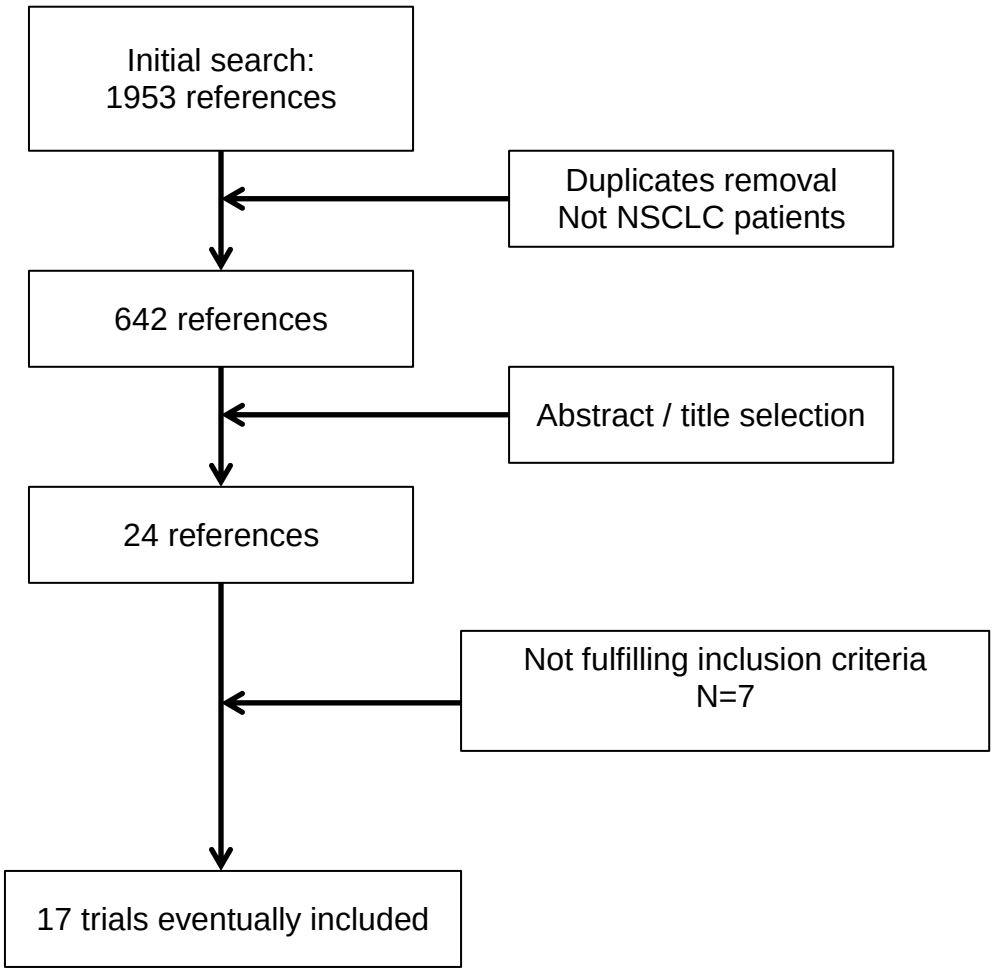
Database and date of research	Ref	Search equations
Pubmed Le 17/7/2015	23	(((((randomized[Title/Abstract] OR randomised[Title/Abstract] OR controlled[Title/Abstract] OR controled[Title/Abstract] AND trial*[Title/Abstract])))))) AND (((((((((("Lung Neoplasms"[Mesh]) AND (NSCLC OR "non-small cell lung cancer")) OR "Carcinoma, Non-Small-Cell Lung"[Mesh])) AND second line[Title/Abstract])) AND ((erlotinib[Title/Abstract] OR docetaxel[Title/Abstract] OR pemetrexed[Title/Abstract]) AND (bevacizumab[Title/Abstract] OR nintedanib[Title/Abstract] OR ramucirumab[Title/Abstract] OR vandetanib[Title/Abstract] OR sunitinib[Title/Abstract] OR aflibercept[Title/Abstract] OR antiangiogenic[Title/Abstract] OR sorafenib[Title/Abstract] OR cabozantinib[Title/Abstract])))) AND ("2005/01/01"[Date - Publication] : "3000"[Date - Publication]))
Scopus Le 17/7/2015	162	((TITLE-ABS-KEY (lung neoplasms) OR TITLE-ABS-KEY (nsclc) OR TITLE-ABS-KEY (non-small cell lung cancer)) AND TITLE-ABS-KEY (second line)) AND (TITLE-ABS-KEY (erlotinib) OR TITLE-ABS-KEY (docetaxel) OR TITLE-ABS-KEY (pemetrexed)) AND (TITLE-ABS-KEY (bevacizumab) OR TITLE-ABS-KEY (nintedanib) OR TITLE-ABS-KEY (ramucirumab) OR TITLE-ABS-KEY (vandetanib) OR TITLE-ABS-KEY (sunitinib) OR TITLE-ABS-KEY (aflibercept) OR TITLE-ABS-KEY (antiangiogen*) OR TITLE-ABS-KEY (sorafenib) OR TITLE-ABS-KEY (cabozantinib)) AND ((TITLE-ABS-KEY (randomized) OR TITLE-ABS-KEY (randomised) OR TITLE-ABS-KEY (controlled) OR TITLE-ABS-KEY (controled)) AND (TITLE-ABS-KEY (trial*) OR TITLE-ABS-KEY (study))) AND (PUBYEAR > 2004) AND (EXCLUDE (LANGUAGE , "German")) AND (EXCLUDE (LANGUAGE , "Turkish")) AND PUBYEAR > 2004
WOS Le 17/7/2015	82	((((((ts=lung neoplasm OR ts=NSCLC OR ts=non small cell lung cancer) AND (ts=second line)) AND (ts=erlotinib OR ts=docetaxel OR ts=pemetrexed)) AND (ts=bevacizumab OR ts=nintedanib OR ts=ramucirumab OR ts=vandetanib OR ts=sunitinib OR ts=aflibercept OR ts=antiangiogenic OR

		ts=cabozantinib OR ts=sorafenib)) AND ((ts=randomized OR ts=randomised OR ts=controled)) AND (ts=trial OR ts=study))) **Refined by:** [excluding] **LANGUAGES:** (GERMAN) Indexes=SCI-EXPANDED Timespan=2005-2015
Before manual deduplication	267	
After manual deduplication	204	
Embase Le 17/7/2015	155	(('non small cell lung cancer'/exp OR nsclc) AND ('erlotinib'/exp OR 'docetaxel'/exp OR 'pemetrexed'/exp) AND ('bevacizumab'/exp OR 'nintedanib'/exp OR 'ramucirumab'/exp OR 'vandetanib'/exp OR 'sunitinib'/exp OR 'aflibercept'/exp OR 'cabozantinib'/exp OR 'antiangiogenic agent'/exp) AND (('randomised controlled trial'/exp OR 'randomised controlled trial') OR ((controlled OR controled OR randomised OR randomized OR random) AND (trial OR 'study'/exp OR study))) AND (first AND line)) AND [embase]/lim NOT [medline]/lim AND (2006:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py)
Before deduplication manual	359	
After manual deduplication	333	
Clinical trials	78	NSCLC or 'non small cell lung cancer' | bevacizumab OR nintedanib OR ramucirumab OR vandetanib OR sunitinib OR aflibercept OR cabozantinib OR antiangiogeni | erlotinib OR docetaxel OR pemetrexed | Phase 2, 3 | received from 01/01/2005 to 07/01/2015 | updated from 01/01/2005 to 07/01/2015
Centerwatch http://www.centerwatch.com/clinical-trials/listings/	26	Therapeutic Areas: . Non-Small Cell Lung Cancer Clinical Trials Phase 2/3
National Cancer institute NIH http://www.cancer.gov/about-cancer/treatment/clinical-trials/search	9	Cancer type = lung cancer, non small cell Stage = all Location = type of trial = treatment drug : any drugs shown :bevacizumab nintedanib ramucirumab vandetanib sunitinib aflibercept cabozantinib keywords : second line Trial phase : III II
Cochrane 29/7/2015	50	#1 MeSH descriptor: [Lung Neoplasms] explode all trees #2 NCLCC or non-small cell lung cancer # 3 #1 and #2 #4 erlotinib or docetaxel or pemetrexed #5 bevacizumab or nintedanib or ramucirumab or vandetanib or sunitinib or aflibercept or sorafenib or antiangiogen* or cabozantinib #6 #4 and #5 #7 #3 and #6 #8 randomised or controlled or controled or randomized #9 stud* or trial*

		#10 #8 and #9 #11 #7 and #10
Asco	205	NSCLC "non-small cell lung cancer" erlotinib docetaxel pemetrexed (any words) in title, controlled randomised controled randomized (any words) in title or abstract, and bevacizumab nintedanib ramucirumab vandetanib sunitinib aflibercept sorafenib cabozantinib antiangiogen* (any words) in full text, from Jan 2005 through Aug 2015.

13. Appendix 2

Trial Flow Chart



14. Appendix 3

The table below lists the trials eligible for the meta-analysis

Trial Name [Ref] **Trial phase (Ph)** NCT reference	**Inclusion Period**	**N**	**Histology** **%ADC** **% Sq** **% Others**	**Treatment**	**Treatment Dose**	**Follow up**
REVEL [14] **Ph III** NCT 01168973	2010-2013	1 253	75% 25%	Docetaxel + Ramucirumab Docetaxel + Placebo (Lilly)	-Docetaxel 75 mg/m^2 iv d1 -Ramucirumab 10 mg/kg iv d1 21 day cycle	9.5 mo
LUME-Lung 1 [13] **Ph III** NCT 00805194	2008-2011	1 314	50% 50% 0%	Docetaxel + Nintedanib Docetaxel + Placebo (Bohringer)	-Docetaxel 75 mg/m^2 d1 -Nintedanib 200mg BID orally d2 21 day cycle	7.1 mo
LUME-Lung 2 [50] **Ph III** NCT 00806819	NR	713	95% 0% 5%	Pemetrexed + Nintedanib Pemetrexed + Placebo (Bohringer)	-Pemetrexed 500 mg/m^2 iv d1 -Nintedanib 200mg BID orally d2 21 day cycle	NR

Trial Name [Ref] **Trial phase (Ph)** NCT reference	**Inclusion Period**	**N**	**Histology** **%ADC** **% Sq** **% Others**	**Treatment**	**Treatment Dose**	**Follow up**
ZODIAC [17] **Ph III** NCT 00312377	2006-2008	1 391	60% 25% *15%*	Docetaxel + Vandetanib Docetaxel + Placebo (Astra-Zeneca)	-Docetaxel 75 mg/m^2 iv d1 -Vandetanib 100mg/d orally d1 21 day cycle	12.8 mo
ZEAL [19] **Ph III** NCT 00418886	2007-2008	534	65% 20% *15%*	Pemetrexed + Vandetanib Pemetrexed + Placebo (Astra-Zeneca)	-Pemetrexed 500 mg/m^2 iv d1 -Vandetanib 100mg/d orally d1 21 day cycle	6 mo
Vandetanib [18] **Ph II** NCT00047840	2003-2004	127	50% 29% *21%*	Docetaxel + Vandetanib 100 Docetaxel + Vandetanib 300 Docetaxel (Astra-Zeneca)	-Docetaxel 75 mg/m^2 iv d1 -Vandetanib 100 / 300 mg/d orally d1 21 day cycle	NR
VITAL [25] **Ph III** NCT 00532155	2007-2010	913	83% 7% *10%*	Docetaxel + Aflibercept Docetaxel + Placebo (Sanofi)	-Docetaxel 75 mg/m^2 iv d1 -Aflibercept 6 mg/kg iv d1 21 day cycle	23 mo
BeTa Lung [28] **Ph III** NCT 00130728	2005-2008	636	75% 4% *21%*	Erlotinib + Bevacizumab Erlotinib + Placebo (Roche)	-Erlotinib 150 mg/d orally d1 -Bevacizumab 15 mg/kg iv d1 21 day cycle	19 mo

Trial Name [Ref] **Trial phase (Ph)** NCT reference	**Inclusion Period**	**N**	**Histology** **%ADC** **% Sq** **% Others**	**Treatment**	**Treatment Dose**	**Follow up**
Herbst [27] **Ph II** NCT 00095225	2004-2005	120	80% 0% 20%	Docet / Pem + Placebo Docet / Pem + Bevaciz. Erlotinib + Bevacizumab (Roche)	-Docetaxel 75 mg/m^2 iv d1 -Pemetrexed 500 mg/m^2 iv d1 -Bevacizumab 15 mg/kg iv d1 -Erlotinib 150 mg/d orally d1 21 day cycle	15.8 mo
SUN1087 [20] **Ph III** NCT 00457392	2007-2009	960	53% 28% *19%*	Erlotinib + Sunitinib Erlotinib + Placebo (Pfizer)	-Sunitinib 37.5 mg /d orally d1 -Erlotinib 150 mg/d orally d1 28 day cycle	21.3 mo
CALGB 30704 [22] **Ph II** NCT 00698815	2008-2011	130	64% 13% *23%*	Pemetrexed + Sunitinib Sunitinib (S) Pemetrexed (P) (Pfizer)	-Pemetrexed 500 mg/m^2 iv d1 -Sunitinib 37.5 mg/d orally d1 21 day cycle	36 mo
Sunitinib [21] **Ph II** NCT 00265317	2007-2009	132	50% 25% *25%*	Erlotinib + Sunitinib Erlotinib + Placebo (Pfizer)	-Sunitinib 37.5 mg /d orally d1 -Erlotinib 150 mg/d orally d1 28 day cycle	17.7 mo

Trial Name [Ref] **Trial phase (Ph)** NCT reference	**Inclusion Period**	**N**	**Histology** **%ADC** **% Sq** **% Others**	**Treatment**	**Treatment Dose**	**Follow up**
LUN160 [24] **Ph II** NCT 00600015	2008-2009	168	70%* 30%	Erlotinib + Sorafenib Erlotinib + Placebo (Bayer)	-Sorafenib 400 mg BID orally d1 -Erlotinib 150 mg/d orally d1 28 day cycle	7 mo
ECOG1512 [30] **Ph II** NCT 01708954	2013-2014	125	100% 0% 0%	Erlotinib Cabozantinib Cabozantinib + Erlotinib (Activebiochem)	-Cabozantinib 40 mg/d orally combo. -Cabozantinib 60 mg/d orally mono. -Erlotinib 150 mg/d orally d1 28 day cycle	8.5 mo
WJOG5910 [51] **Ph II**	2011-2013	100	94% 0% 6%	Docetaxel + Bevacizumab Docetaxel	-Docetaxel 60 mg/m2 iv d1 -Bevacizumab 15 mg/kg d1 21 day cycle	11.2 mo
Hosomi [52] **Ph II** NCT 01703091	NR	157	88% 12% 0%	Docetaxel + Ramucirumab Docetaxel	-Docetaxel 60 mg/m2 iv d1 -Bevacizumab 10 mg/kg d1 21 day cycle	12 mo
N0626 [53] **Ph II** NCT 00454194	NR	100	100% 0% 0%	Pemetrexed + Sorafenib Pemetrexed	-Sorafenib 400 mg BID orally d1 -Pemetrexed 500 mg/m2 iv d1 21 days cycle	13.6 mo

* Non-squamous
ADC: adenocarcinoma. Sq: Squamous. Combo: combination arm. Mono: monotherapy. NR not reported.

15. Appendix 4

Clinical results of clinical trials selected for the meta-analysis

Trial	N	Treatments compared	Response Rate (%)	Progression-free Survival (median in months) Hazard Ratio (HR)	Overall Survival (median in months) Hazard Ratio (HR)
REVEL [14] NCT 01168973	1 253	Docetaxel + Ramucirumab Docetaxel + Placebo	23 14 p<0.001	4.5 *vs*. 3.0 HR 0.76 (0.67-0.86) p<0.001	10.5 *vs*. 9.1* HR 0.85 (0.75-0.98) p=0.0253
LUME-Lung 1 [13] NCT 00805194	1 314	Docetaxel + Nintedanib Docetaxel + Placebo	4.4 3.3 p=0.30	3.4 *vs*. 2.7* HR 0,79 (0.68-0.92) p=0.0019	10.1 *vs*. 9.1 HR 0.94 (0.83-1.05), p=0.27 ADC: 12.6 *vs*. 9.3, p=0.0359 ADC 9mo: 10.9 *vs.* 7.9, p=0.007
LUME-Lung 2 [50] NCT 00806819	713	Pemetrexed + Nintedanib Pemetrexed + Placebo	9.1 8.3 p=0.7279	4.4 *vs*. 3.6* HR 0.83 (0.70-0.99) p=0.0435	12.0 *vs*. 12.7 HR 1.01 (0.85-1.21) p=0.8940

Trial	N	Treatments compared	Response Rate (%)	Progression-free Survival (median in months) Hazard Ratio (HR)	Overall Survival (median in months) Hazard Ratio (HR)
ZODIAC [17] NCT 00312377	1 391	Docetaxel + Vandetanib Docetaxel + Placebo	17 10 p=0.0001	4.0 *vs*. 3.2* HR 0.79 (0,70–0,90) p<0·0001	10.3 *vs*. 9.9 HR 0·95, (0.84–1.07) p=0·371
ZEAL [19] NCT 00418886	534	Pemetrexed + Vandetanib Pemetrexed + Placebo	19 8 p=0.001	4.40 *vs*. 2.98* HR 0.86 (0.69 - 1.06) p=0.108	10.5 *vs*. 9.2 HR, 0.86 (0.65 - 1.13) p=0.219
Vandetanib [18] NCT00047840	127	Docetaxel (D) + Vandetanib 100 Docetaxel+ Vandetanib (V) 300 Docetaxel	26 18 12	4.68* 4.25 3.0 V100 *vs*. D HR 0.64 (0.38-1.05) p=0.074 (two-sided) V300 vs. D HR 0.83 (0.50-1.36) p=0.461 (two-sided	13.1 7.9 13.4 V100 *vs*. D HR 0.91 (0.55-1.52) p=0.723 (two-sided) V300 vs. D HR 1.28 (0.78-2.10) p=0.334 (two-sided)

Trial	N	Treatments compared	Response Rate (%)	Progression-free Survival (median in months) Hazard Ratio (HR)	Overall Survival (median in months) Hazard Ratio (HR)
VITAL [25] NCT 00532155	913	Docetaxel + Aflibercept Docetaxel + Placebo	23 8.9 p=0.001	5.2 *vs*. 4.1 HR 0.82 (0.72-0.94) p=0.0035	10.1 *vs*. 10.4* HR 1.01 (0.87-1.17) p=0.90
BeTa Lung [28] NCT 00130728	636	Erlotinib + Bevacizumab Erlotinib + Placebo	13^{+} 6	3.4 *vs*. 1.7 HR 0.62 (0.52-0.75) p<0.0001	9.3 *vs*. 9.2* HR 0.97 (0.80-1.18) p=0.76
Herbst [27] NCT 00095225	120	Docet / Pem + Placebo (CT) Docet / Pem + Bevaciz. (CTB) Erlotinib + Bevacizumab (EB)	12.2 12.5 17.9 p=NS	3* 4.8 4.7, p=NS CT *vs*. CTB HR 0.66 (0.38-1.16) CT *vs*. EB: HR 0.72 (0.42-1.23)	8.6 12.6 13.7, p=NS CT *vs*. CTB HR 0.71 (0.41-1.21) CT *vs*. EB HR 0.78 (0.46-1.31)
SUN1087 [20] NCT 00457392	960	Erlotinib + Sunitinib Erlotinib + Placebo	10.6 6.9 p=0.047	3.6 *vs*. 2.0 HR 0.81 (0.70-0.94) p= 0.023	9 *vs*. 8.5* HR 0.922 (0.8-1.06) p=0.1388

Trial	N	Treatments compared	Response Rate (%)	Progression-free Survival (median months) Hazard Ratio (HR)	Overall Survival (median months) Hazard Ratio (HR)
CALGB 30704 [22] NCT 00698815	130	Pemetrexed + Sunitinib Sunitinib (S) Pemetrexed (P)	22 17 14 p=0.34	P+S *vs*. P* 3.7 vs. 4.9 HR 1.3 (0.9-2.1) p=0.18	P+S *vs*. P 6.7 vs. 10.5 HR 2 (1.2-3.2) p=0.03
Sunitinib [21] NCT 00265317	132	Erlotinib + Sunitinib Erlotinib + Placebo	4.6 3.0 p=0.624	2.8 *vs*. 2.0* HR 0.90 (0.67-1.2) p= 0.321	8.2 *vs*. 7.6 HR 1.07 (0.71-1.61) p=0.62
LUN160 [24] NCT 00600015	168	Erlotinib + Sorafenib Erlotinib + Placebo (Bayer)	8 11 P=0.555	3.4 *vs*. 1.9* HR 0.86 (0.60-1.23) p=0.196	7.6 *vs*. 7.2 HR 0.89 (0.59-1.34) p=0.290

Trial	N	Treatments compared	Response Rate (%)	Progression-free Survival (median months) Hazard Ratio (HR)	Overall Survival (median months) Hazard Ratio (HR)
ECOG1512 [30] NCT 01708954	125	Erlotinib (E) Cabozantinib (C) Cabozantinib + Erlotinib (EC) (Activebiochem)	3 14 8	1.9* 4.2 4.7 E *vs*. C HR 0.38 (0.27-0.55), p=0.0004 E *vs*. EC HR 0.35 (0.23-0.52), p=0.005	4.1 9.2 13.3 E *vs*. C HR 0.59 (0.42-0.84) p=0.03 E *vs*. EC HR 0.44 (0.30-0.66) p=0.004
WJOG5910[a] [51]	100	Docetaxel + Bevacizumab Docetaxel	36 26 p=0.387	4.4 vs. 3.4* HR 0.71 (0.47-1.09) p= 0.058	13.1 vs. 11 HR 0.74 (0.46-1.19) p=0.11
Hosomi [52] NCT 01703091	157	Docetaxel + Ramucirumab Docetaxel	28.9 18.5	5.2 vs. 4.2* HR 0.83 (0.59-1.16)	15.15 vs. 14.65 HR 0.86 (0.56-1.32)

Trial	N	Treatments compared	Response Rate (%)	Progression-free Survival (median months) Hazard Ratio (HR)	Overall Survival (median months) Hazard Ratio (HR)
N0626 [53] NCT 00454194	100	Pemetrexed + Sorafenib Pemetrexed	NR	3.4 vs. 4.1* p=0.22[b]	9.4 vs. 9.7 p=0.49

* Primary End-Point. ADC: adenocarcinoma. Sq: Squamous. ADC 9mo: patients with adenocarcinoma histology who progressed within 9 months after start of first-line treatment. W: weeks. [+] not compared statistically. NS: non significant. [a] All patients have already received bevacizumab plus platinum-based doublet as first-line treatment. [b] In pemetrexed + Sorafenib arm, patients without previous bevacizumab treatment the PFS was 2.8 *vs*. 5 mo for those with previous bevacizumab exposure (p=0.06)

16. Appendix 5

Appendix 5: describes the ongoing trials excluded from the meta-analysis.

The phase III ULTIMATE trial (NCT01763671) compares the efficacy of paclitaxel-bevacizumab (wPB) with docetaxel (DOC) as second- or third-line treatment in 166 non-squamous NSCLC patients. The trial is ongoing but the recruiting has been completed and results have been presented in ASCO 2016 (the adjusted hazard ratio (HR) for PFS was 0.62 (IC95%: 0.44-0.86, p=0.005). Median PFS was 5.4 months for wPB *vs.* 3.9 months for DOC. Efficacy was observed regardless of number of previous lines (1 line: HR 0.56, IC95% [0.39-0.89], p=0.01; 2 lines: HR 0.56, IC95% [0.30-1.04], p=0.07). ORR was 22.5% with wPB and 5.5% with DOC (p=0.006). No difference in OS was observed (median wPB 9.9 months, DOC 10.8 months, adjusted HR 1.15, p=0.49). No differences in Grade 3-4 adverse events) [54]. However, this study was not included initially because results will be obtained after the inclusion period. Despite the fact that the trial does not compare the same chemotherapy in both treatment arms, chemotherapeutic agents have the same mechanism of action, therefore, this trial could be included in the future analysis.

17. Appendix 6

Appendix 6 gives the suggested format and coding of the form to be sent to the Secretariat

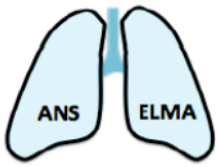
Variable	Format / Coding
Patient identifier	10 characters
Date of birth or age	dd/mm/yyyy, 99999999=Unknown 2 digits, 99=Unknown
Sex	1=Male, 2=Female, 9=Unknown
Weight (kg)	3 digits, 999=Unkown
Height (cm)	3 digits, 999=Unkown
Race and ethnicity	1=Black, 2=Asian, 3=White, 4=Other
Performance Status	For Karnofsky index use 3 digits, for WHO or ECOG index use 2 blanks and one digit
Smoking status *if yes, pack-years*	0=Never, 1=Former, 2=Current, 9=Unknown 3 digits, 999=Unkown
Date of diagnosis	dd/mm/yyyy, 99999999=Unknown
Histology	1=Adenocarcinoma, 2=squamous cell carcinoma, 3=Other NSCLC, 4=Other, if other NSCLC or other specify
Brain metastasis at randomization	0=No, 1=Yes
Absolute neutrophil count (/mm^3)	5 digit, 99999=Unknown
Lymphocytes (/mm3)	5 digit, 99999=Unknown
Albumin (g/L)	2 digits, 99=Unknown
Date of first administration of 1^{st} line chemotherapy or delays between the first administration of chemotherapy and randomization (specify unit, if possible in days)	dd/mm/yyyy, 99999999=Unknown 3 digits, 999=Unknown

Variable	Format / Coding
Date of last administration of 1st line chemotherapy (or day 1 last cycle, if not available) or delays between its last administration and randomization (specify unit, if possible in days)	dd/mm/yyyy, 99999999=Unknown 3 digits, 999=Unknown
Number of previous line(s) of treatment for advanced disease (include treatment for locally advanced disease; then number of line may be ≥ 1)	1 digit
Platinum-based chemotherapy	0=No, 1=Yes
if yes,	1=cisplatin, 2=carboplatin
Taxanes-based chemotherapy	0=No, 1=Yes
Chemotherapy without platinum or taxanes	0=No, 1=Yes
Prior target therapy in first-line	0=No, 1=Yes
If yes, date of last dose of targeted therapy	1=Bevacizumab, 2=Cetuximab, 3=Other, if other specify dd/mm/yyyy, 99999999=Unknown
Maintenance chemotherapy	0=No, 1=Yes
Treatment allocated	1=No antiangiogenic therapy 2=Antiangiogenic therapy
Date of randomization	dd/mm/yyyy, 99999999=Unknown
Number of chemotherapy cycles received	2 digits, 99=Unkown
or months of target therapy received	2 digits, 99=Unkown
Number of months of antiangiogenic therapy received	2 digits, 99=Unkown
or number of injections of antiangiogenic therapy received	2 digits, 99=Unkown
Post-discontinuation treatments	0=No, 1=Yes
Date of last follow-up	dd/mm/yyyy, 99999999=Unknown
Survival status	0=Alive, 1=Dead
Cause of death	0=Alive, 1=Cancer, 2=Toxicity of evaluated treatment (chemotherapy, gefitinib, antiangiogenic), 3=Other (including death related to further line of treatment), 9=Unknown
Progression	0=No, 1=Yes

Variable	Format / Coding
Date of progression	dd/mm/yyyy, 99999999=Unknown
Severe (grade 3, 4 or 5) toxicity, any type	0=No, 1=Yes
Nauseas (grade 3, 4 or 5)	**0=No, 1=Yes**
Vomiting (grade 3, 4 or 5)	0=No, 1=Yes
Asthenia (grade 3, 4 or 5)	0=No, 1=Yes
Neutropenia (grade 3, 4 or 5)	0=No, 1=Yes
Anaemia (grade 3, 4 or 5)	0=No, 1=Yes
Thrombocytopenia (grade 3, 4 or 5)	0=No, 1=Yes
HTA (grade 3, 4 or 5)	0=No, 1=Yes
Renal Failure (grade 3, 4 or 5)	0=No, 1=Yes
Proteinuria (grade 3, 4 or 5)	0=No, 1=Yes
Perforation (grade 3, 4 or 5)	0=No, 1=Yes
Pulmonary bleeding (grade 3, 4 or 5)	0=No, 1=Yes
Gastrointestinal bleeding (grade 3, 4 or 5)	0=No, 1=Yes
Pulmonary emboli (grade 3, 4 or 5)	0=No, 1=Yes
Deep vein thrombosis (grade 3, 4 or 5)	0=No, 1=Yes
CNS Ischemic event (grade 3, 4 or 5)	0=No, 1=Yes
Cardiac ischemic event (grade 3, 4 or 5)	0=No, 1=Yes
Arrhythmia (grade 3, 4 or 5)	0=No, 1=Yes
Other severe toxicities (grade 3, 4 or 5)	0=No, 1=Yes
Epidermal Growth Factor Receptor (EGFR) mutation	0=No, 1=Yes (activating), 2=Yes (resistant)
KRAS mutation	0=No, 1=Yes
ALK rearrangement	0=No, 1=Yes
Excluded from your analysis	0=No, 1=Yes
If yes, reasons for exclusion	text

18. Appendix 7

Appendix 7 provides the form to register in the meta-analysis.



ANtiangiogenic on Second line in Lung cancer Meta-Analysis

Trial / Protocol number _____

Trial Publication _____

_____

Name of Investigator _____

Address _____

_____

Telephone _____ Fax _____

Email _____

Are you willing to take part in the Meta-analysis? yes ☐ no ☐

Are the details of your trial correct? yes ☐ no ☐

Is the most recent publication cited in the publication list? yes ☐ no ☐

If no, please give correct details _____

_____

Do you know of any other relevant trials not listed in the protocol? yes ☐ no ☐

If yes, please provide details _____

_____

Is a copy of the trial protocol enclosed? yes ☐ no ☐

If different from above, please give details of the appropriate contact for the collection of trial data:

Name _____

Address _____

_____

Telephone _____ Fax _____

Email _____

Did the trial have a target for patient accrual? yes ☐ no ☐ Target: _____

Did the trial reach its target accrual? yes ☐ no ☐

Date trial opened |__|__| |__|__| |__|__|__|__| Date trial closed |__|__| |__|__| |__|__|__|__|

ANtiangiogenic on Second line in Lung cancer Meta-Analysis

What method was used to conceal randomisation?

Sealed envelope ☐ Central telephone ☐ Other ☐

What method of randomisation was used in this trial?

Simple ☐ Permuted Blocks ☐ Minimisation ☐ Other ☐

What, if any, stratification factors were used? _____

What proportions was the trial designed to have in each arm? (e.g.1:1) _____

Please list treatments used in the arms of your trial (including local treatment and drugs given):

Arm 1: _____

Arm 2: _____

Arm 3: _____

Arm 4: _____

Which TNM or staging classification was used? _____

Which performance status was used? WHO ☐ ECOG ☐ Karnofsky ☐ Other ☐

Which classification was used for toxicity?

Acute: WHO ☐ NCI-CTC ☐ Other ☐ Specify: _____

Do some of the data requested be never available?

yes ☐ no ☐

If yes, please specify: _____

_____

Any data supplied will remain the property of the trialist(s) who supplied it. These data will remain confidential and will not be used, circulated or distributed in any way that allows access to individual patient data.

Permission for use of the IPD for methodological Research

I agree that an anonymised version of the trial data that I supplied for the meta-analysis can be used in other methodological research projects:

☐ Yes ☐ No

Signed _____ Date _____

Please return to Jean-Pierre Pignon – Institut Gustave Roussy
39, rue Camille Desmoulins – 94805 Villejuif cedex France
- Fax 33 1 42 11 52 58 – e-mail : jpignon@igr.fr

References

[1] M. Reck, S. Popat, N. Reinmuth, D. De Ruysscher, K.M. Kerr, S. Peters, ESMO Guidelines Working Group, Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 25 Suppl 3 (2014) iii27-39. doi:10.1093/annonc/mdu199.

[2] N. Hanna, F.A. Shepherd, F.V. Fossella, J.R. Pereira, F. De Marinis, J. von Pawel, U. Gatzemeier, T.C.Y. Tsao, M. Pless, T. Muller, H.-L. Lim, C. Desch, K. Szondy, R. Gervais, null Shaharyar, C. Manegold, S. Paul, P. Paoletti, L. Einhorn, P.A. Bunn, Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy, J. Clin. Oncol. 22 (2004) 1589–1597. doi:10.1200/JCO.2004.08.163.

[3] T. Ciuleanu, L. Stelmakh, S. Cicenas, S. Miliauskas, A.C. Grigorescu, C. Hillenbach, H.K. Johannsdottir, B. Klughammer, E.E. Gonzalez, Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study, Lancet Oncol. 13 (2012) 300–308. doi:10.1016/S1470-2045(11)70385-0.

[4] M.C. Garassino, O. Martelli, M. Broggini, G. Farina, S. Veronese, E. Rulli, F. Bianchi, A. Bettini, F. Longo, L. Moscetti, M. Tomirotti, M. Marabese, M. Ganzinelli, C. Lauricella, R. Labianca, I. Floriani, G. Giaccone, V. Torri, A. Scanni, S. Marsoni, TAILOR trialists, Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial, Lancet Oncol. 14 (2013) 981–988. doi:10.1016/S1470-2045(13)70310-3.

[5] T. Kawaguchi, M. Ando, K. Asami, Y. Okano, M. Fukuda, H. Nakagawa, H. Ibata, T. Kozuki, T. Endo, A. Tamura, M. Kamimura, K. Sakamoto, M. Yoshimi, Y. Soejima, Y. Tomizawa, S.I. Isa, M. Takada, H. Saka, A. Kubo, Randomized phase III trial of erlotinib versus docetaxel as second- Or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and erlotinib lung cancer trial (DELTA), Journal of Clinical Oncology. 32 (2014) 1902–1908. doi:10.1200/JCO.2013.52.4694.

[6] K. Hotta, Y. Fujiwara, K. Kiura, N. Takigawa, M. Tabata, H. Ueoka, M. Tanimoto, Relationship between response and survival in more than 50,000 patients with advanced non-small cell lung cancer treated with systemic chemotherapy in 143 phase III trials, J Thorac Oncol. 2 (2007) 402–407. doi:10.1097/01.JTO.0000268673.95119.c7.

[7] J. Brahmer, K.L. Reckamp, P. Baas, L. Crinò, W.E.E. Eberhardt, E. Poddubskaya, S. Antonia, A. Pluzanski, E.E. Vokes, E. Holgado, D. Waterhouse, N. Ready, J. Gainor, O. Arén Frontera, L. Havel, M. Steins, M.C. Garassino, J.G. Aerts, M. Domine, L. Paz-Ares, M. Reck, C. Baudelet, C.T. Harbison, B. Lestini, D.R. Spigel, Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer, N. Engl. J. Med. 373 (2015) 123–135. doi:10.1056/NEJMoa1504627.

[8] H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, J.R. Brahmer, Nivolumab versus

Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer, N. Engl. J. Med. (2015). doi:10.1056/NEJMoa1507643.
[9] E.B. Garon, N.A. Rizvi, R. Hui, N. Leighl, A.S. Balmanoukian, J.P. Eder, A. Patnaik, C. Aggarwal, M. Gubens, L. Horn, E. Carcereny, M.-J. Ahn, E. Felip, J.-S. Lee, M.D. Hellmann, O. Hamid, J.W. Goldman, J.-C. Soria, M. Dolled-Filhart, R.Z. Rutledge, J. Zhang, J.K. Lunceford, R. Rangwala, G.M. Lubiniecki, C. Roach, K. Emancipator, L. Gandhi, KEYNOTE-001 Investigators, Pembrolizumab for the treatment of non-small-cell lung cancer, N. Engl. J. Med. 372 (2015) 2018–2028. doi:10.1056/NEJMoa1501824.
[10] Vansteenkiste J, Fehrenbacher L, Spira A, Mazieres J, Park K, Smith D, Artal A, Atezolizumab monotherapy vs docetaxel in 2L/3L non-small cell lung cancer: Primary analysis for efficacy, safety and predictive biomarkers from a randomized Phase II study (POPLAR), Ann Oncol 2015. (n.d.).
[11] Besse B, Johnson M, Janne P, Garassino M, Eberhardt WE, Peters S, Toh CK, Kurata T, li Z, Kowanetz M, Mocci S, Sandler A, Rizvi NA, Phase II, single-arm trial (BIRCH) of atezolizumab as first-line or subsequent therapy for locally advanced or metastatic PD-L1-selected non-small cell lung cancer, Ann Oncol 2015. 16LBA (n.d.).
[12] J.-C. Soria, A. Mauguen, M. Reck, A.B. Sandler, N. Saijo, D.H. Johnson, D. Burcoveanu, M. Fukuoka, B. Besse, J.-P. Pignon, meta-analysis of bevacizumab in advanced NSCLC collaborative group, Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer, Ann. Oncol. 24 (2013) 20–30. doi:10.1093/annonc/mds590.
[13] M. Reck, R. Kaiser, A. Mellemgaard, J.-Y. Douillard, S. Orlov, M. Krzakowski, J. von Pawel, M. Gottfried, I. Bondarenko, M. Liao, C.-N. Gann, J. Barrueco, B. Gaschler-Markefski, S. Novello, LUME-Lung 1 Study Group, Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial, Lancet Oncol. 15 (2014) 143–155. doi:10.1016/S1470-2045(13)70586-2.
[14] E.B. Garon, T.-E. Ciuleanu, O. Arrieta, K. Prabhash, K.N. Syrigos, T. Goksel, K. Park, V. Gorbunova, R.D. Kowalyszyn, J. Pikiel, G. Czyzewicz, S.V. Orlov, C.R. Lewanski, M. Thomas, P. Bidoli, S. Dakhil, S. Gans, J.-H. Kim, A. Grigorescu, N. Karaseva, M. Reck, F. Cappuzzo, E. Alexandris, A. Sashegyi, S. Yurasov, M. Pérol, Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial, Lancet. 384 (2014) 665–673. doi:10.1016/S0140-6736(14)60845-X.
[15] S. Popat, A. Mellemgaard, K. Fahrbach, A. Martin, M. Rizzo, R. Kaiser, I. Griebsch, M. Reck, Nintedanib plus docetaxel as second-line therapy in patients with non-small-cell lung cancer: a network meta-analysis, Future Oncology. 11 (2015) 409–420.
[16] J. Sheng, Y. Yang, Y. Ma, B. Yang, Y. Zhang, S. Kang, T. Zhou, S. Hong, T. Qin, Z. Hu, W. Fang, Y. Huang, L. Zhang, The efficacy of combining antiangiogenic agents with chemotherapy for patients with advanced non-small cell lung cancer who failed first-line chemotherapy: A systematic review and meta-analysis, PLoS ONE. 10 (2015). http://www.embase.com/search/results?subaction=viewrecord&from=export&id

=L604922939.
[17] R.S. Herbst, Y. Sun, W.E. Eberhardt, P. Germonpre, N. Saijo, C. Zhou, J. Wang, L. Li, F. Kabbinavar, Y. Ichinose, S. Qin, L. Zhang, B. Biesma, J.V. Heymach, P. Langmuir, S.J. Kennedy, H. Tada, B.E. Johnson, Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial, Lancet Oncol. 11 (2010) 619–626. doi:10.1016/S1470-2045(10)70132-7.
[18] J.V. Heymach, B.E. Johnson, D. Prager, E. Csada, J. Roubec, M. Pesek, I. Spasova, C.P. Belani, I. Bodrogi, S. Gadgeel, S.J. Kennedy, J. Hou, R.S. Herbst, Randomized, placebo-controlled phase II study of vandetanib plus docetaxel in previously treated non-small-cell lung cancer, J.Clin.Oncol. 25 (2007) 4270–4277.
[19] R.H. Boer, ? Arrieta, C.H. Yang, M. Gottfried, V. Chan, J. Raats, F. Marinis, R.P. Abratt, J. Wolf, F.H. Blackhall, P. Langmuir, T. Milenkova, J. Read, J.F. Vansteenkiste, Vandetanib plus pemetrexed for the second-line treatment of advanced non-small-cell lung cancer: a randomized, double-blind phase III trial, J.Clin.Oncol. 29 (2011) 1067–1074.
[20] G.V. Scagliotti, M. Krzakowski, A. Szczesna, J. Strausz, A. Makhson, M. Reck, R.F. Wierzbicki, I. Albert, M. Thomas, J.E. Miziara, Z.S. Papai, N. Karaseva, S. Thongprasert, E.D. Portulas, J. Pawel, K. Zhang, P. Selaru, L. Tye, R.C. Chao, R. Govindan, Sunitinib plus erlotinib versus placebo plus erlotinib in patients with previously treated advanced non-small-cell lung cancer: a phase III trial, J.Clin.Oncol. 30 (2012) 2070–2078.
[21] H.J. Groen, M.A. Socinski, F. Grossi, E. Juhasz, C. Gridelli, P. Baas, C.A. Butts, E. Chmielowska, T. Usari, P. Selaru, C. Harmon, J.A. Williams, F. Gao, L. Tye, R.C. Chao, G.R. Blumenschein Jr., A randomized, double-blind, phase II study of erlotinib with or without sunitinib for the second-line treatment of metastatic non-small-cell lung cancer (NSCLC), Ann Oncol. 24 (2013) 2382–2389. doi:10.1093/annonc/mdt212.
[22] R.S. Heist, X. Wang, L. Hodgson, G.A. Otterson, T.E. Stinchcombe, L. Gandhi, M.A. Villalona-Calero, P. Watson, E.E. Vokes, M.A. Socinski, CALGB 30704 (Alliance): A randomized phase II study to assess the efficacy of pemetrexed or sunitinib or pemetrexed plus sunitinib in the second-line treatment of advanced non-small-cell lung cancer, J Thorac.Oncol. 9 (2014) 214–221. doi:10.1097/JTO.0000000000000071.
[23] H.A. Wakelee, J.-W. Lee, N.H. Hanna, A.M. Traynor, D.P. Carbone, J.H. Schiller, A double-blind randomized discontinuation phase-II study of sorafenib (BAY 43-9006) in previously treated non-small-cell lung cancer patients: eastern cooperative oncology group study E2501, J Thorac Oncol. 7 (2012) 1574–1582. doi:10.1097/JTO.0b013e31826149ba.
[24] D.R. Spigel, H.A. Burris, F.A. Greco, D.L. Shipley, E.K. Friedman, D.M. Waterhouse, R.C. Whorf, R.B. Mitchell, D.B. Daniel, J. Zangmeister, J.D. Bass, J.D. Hainsworth, Randomized, double-blind, placebo-controlled, phase II trial of sorafenib and erlotinib or erlotinib alone in previously treated advanced non-small-cell lung cancer, J.Clin.Oncol. 29 (2011) 2582–2589.
[25] R. Ramlau, V. Gorbunova, T.E. Ciuleanu, S. Novello, M. Ozguroglu, T. Goksel, C. Baldotto, J. Bennouna, F.A. Shepherd, G.S. Le, A. Rey, V. Miller, N. Thatcher, G. Scagliotti, Aflibercept and Docetaxel versus Docetaxel alone after platinum failure in patients with advanced or metastatic non-small-cell lung cancer: a randomized, controlled phase III trial, J.Clin.Oncol. 30 (2012) 3640–

3647.
[26] A.A. Adjei, S.J. Mandrekar, G.K. Dy, J.R. Molina, A.A. Adjei, D.R. Gandara, K.L.A. Ziegler, P.J. Stella, J. Rowland, S.E. Schild, R.G. Zinner, Phase II trial of pemetrexed plus bevacizumab for second-line therapy of patients with advanced non-small-cell lung cancer: NCCTG and SWOG study N0426, Journal of Clinical Oncology. 28 (2010) 614–619. doi:10.1200/JCO.2009.23.6406.
[27] R.S. Herbst, V.J. O'Neill, L. Fehrenbacher, C.P. Belani, P.D. Bonomi, L. Hart, O. Melnyk, D. Ramies, M. Lin, A. Sandler, Phase II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non small-cell lung cancer, J Clin Oncol. 25 (2007) 4743–4750. doi:10.1200/JCO.2007.12.3026.
[28] R.S. Herbst, R. Ansari, F. Bustin, P. Flynn, L. Hart, G.A. Otterson, G. Vlahovic, C.H. Soh, P. O'Connor, J. Hainsworth, Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BeTa): a double-blind, placebo-controlled, phase 3 trial, Lancet. 377 (2011) 1846–1854.
[29] B.A. Hellerstedt, G. Edelman, N.J. Vogelzang, H.M. Kluger, C.A. Yasenchak, X. Shen, D.A. Ramies, M.S. Gordon, P. Lara, Activity of cabozantinib (XL184) in metastatic NSCLC: Results from a phase II randomized discontinuation trial (RDT), ASCO Meeting Abstracts. 30 (2012) 7514.
[30] J.W. Neal, S.E. Dahlberg, H.A. Wakelee, S.C. Aisner, M. Bowden, D.P. Carbone, S.S. Ramalingam, Cabozantinib (C), erlotinib (E) or the combination (E+C) as second- or third-line therapy in patients with EGFR wild-type (wt) non-small cell lung cancer (NSCLC): A randomized phase 2 trial of the ECOG-ACRIN Cancer Research Group (E1512), ASCO Meeting Abstracts. 33 (2015) 8003.
[31] J.P. Pignon, C. Hill, Meta-analyses of randomised clinical trials in oncology, Lancet Oncol. 2 (2001) 475–482. doi:10.1016/S1470-2045(01)00453-3.
[32] L.A. Stewart, M.K. Parmar, Meta-analysis of the literature or of individual patient data: is there a difference?, Lancet. 341 (1993) 418–422.
[33] L.A. Stewart, M. Clarke, M. Rovers, R.D. Riley, M. Simmonds, G. Stewart, J.F. Tierney, PRISMA-IPD Development Group, Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement, JAMA. 313 (2015) 1657–1665. doi:10.1001/jama.2015.3656.
[34] A. Aupérin, R. Arriagada, J.P. Pignon, C. Le Péchoux, A. Gregor, R.J. Stephens, P.E. Kristjansen, B.E. Johnson, H. Ueoka, H. Wagner, J. Aisner, Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group, N. Engl. J. Med. 341 (1999) 476–484. doi:10.1056/NEJM199908123410703.
[35] NSCLC Meta-analyses Collaborative Group, R. Arriagada, A. Auperin, S. Burdett, J.P. Higgins, D.H. Johnson, T. Le Chevalier, C. Le Pechoux, M.K.B. Parmar, J.P. Pignon, R.L. Souhami, R.J. Stephens, L.A. Stewart, J.F. Tierney, H. Tribodet, J. van Meerbeeck, Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data, Lancet. 375 (2010) 1267–1277.

doi:10.1016/S0140-6736(10)60059-1.
[36] A. Aupérin, C. Le Péchoux, E. Rolland, W.J. Curran, K. Furuse, P. Fournel, J. Belderbos, G. Clamon, H.C. Ulutin, R. Paulus, T. Yamanaka, M.-C. Bozonnat, A. Uitterhoeve, X. Wang, L. Stewart, R. Arriagada, S. Burdett, J.-P. Pignon, Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer, J. Clin. Oncol. 28 (2010) 2181–2190. doi:10.1200/JCO.2009.26.2543.
[37] A. Mauguen, C. Le Péchoux, M.I. Saunders, S.E. Schild, A.T. Turrisi, M. Baumann, W.T. Sause, D. Ball, C.P. Belani, J.A. Bonner, A. Zajusz, S.E. Dahlberg, M. Nankivell, S.J. Mandrekar, R. Paulus, K. Behrendt, R. Koch, J.F. Bishop, S. Dische, R. Arriagada, D. De Ruysscher, J.-P. Pignon, Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis, J. Clin. Oncol. 30 (2012) 2788–2797. doi:10.1200/JCO.2012.41.6677.
[38] C.B. Begg, J.A. Berlin, Publication bias and dissemination of clinical research, J. Natl. Cancer Inst. 81 (1989) 107–115.
[39] Higgins JPT, Green S, Cochrane handbook for systemic reviews of interventions. Version 5.1.0 (updated March 2011)., The Corchrane Collaboration 2011. www.cochrane-handbook.org (n.d.).
[40] L.A. Stewart, M.J. Clarke, Practical methodology of meta-analyses (overviews) using updated individual patient data. Cochrane Working Group, Stat Med. 14 (1995) 2057–2079.
[41] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, PRISMA Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Ann. Intern. Med. 151 (2009) 264–269, W64.
[42] D. Moher, L. Shamseer, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, P. Shekelle, L.A. Stewart, PRISMA-P Group, Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement, Syst Rev. 4 (2015) 1. doi:10.1186/2046-4053-4-1.
[43] M. Schemper, T.L. Smith, A note on quantifying follow-up in studies of failure time, Control Clin Trials. 17 (1996) 343–346.
[44] S. Yusuf, R. Peto, J. Lewis, R. Collins, P. Sleight, Beta blockade during and after myocardial infarction: an overview of the randomized trials, Prog Cardiovasc Dis. 27 (1985) 335–371.
[45] Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group, BMJ. 311 (1995) 899–909.
[46] J. Bourhis, J. Overgaard, H. Audry, K.K. Ang, M. Saunders, J. Bernier, J.-C. Horiot, A. Le Maître, T.F. Pajak, M.G. Poulsen, B. O'Sullivan, W. Dobrowsky, A. Hliniak, K. Skladowski, J.H. Hay, L.H.J. Pinto, C. Fallai, K.K. Fu, R. Sylvester, J.-P. Pignon, Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group, Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis, Lancet. 368 (2006) 843–854. doi:10.1016/S0140-6736(06)69121-6.
[47] J.P.T. Higgins, S.G. Thompson, Quantifying heterogeneity in a meta-analysis, Stat Med. 21 (2002) 1539–1558. doi:10.1002/sim.1186.
[48] Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group, Lancet. 339 (1992) 71–85.

[49] D.J. Fisher, A.J. Copas, J.F. Tierney, M.K.B. Parmar, A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners, J Clin Epidemiol. 64 (2011) 949–967. doi:10.1016/j.jclinepi.2010.11.016.
[50] N.H. Hanna, R. Kaiser, R.N. Sullivan, O.R. Aren, M.J. Ahn, B. Tiangco, Z. Zvirbule, C.H. Barrios, A. Demirkazik, B. Gaschler-Markefski, I. Voccia, J. Barrueco, J.H. Kim, Lume-lung 2: A multicenter, randomized, double-blind, phase III study of nintedanib plus pemetrexed versus placebo plus pemetrexed in patients with advanced nonsquamous non-small cell lung cancer (NSCLC) after failure of first-line chemotherapy, ASCO Meeting Abstracts. 31 (2013) 8034.
[51] M. Takeda, T. Yamanaka, T. Seto, H. Hayashi, K. Azuma, M. Okada, S. Sugawara, H. Daga, T. Hirashima, K. Yonesaka, Y. Urata, H. Murakami, H. Saito, A. Kubo, T. Sawa, E. Miyahara, N. Nogami, K. Nakagawa, Y. Nakanishi, I. Okamoto, Bevacizumab beyond disease progression after first-line treatment with bevacizumab plus chemotherapy in advanced nonsquamous non-small cell lung cancer (West Japan Oncology Group 5910L): An open-label, randomized, phase 2 trial, Cancer. (2016). doi:10.1002/cncr.29893.
[52] K. Yoh, Y. Hosomi, K. Kasahara, K. Yamada, T. Takahashi, N. Yamamoto, M. Nishio, Y. Ohe, T. Koue, T. Nakamura, S. Enatsu, P. Lee, D. Ferry, T. Tamura, K. Nakagawa, A randomized, double-blind, phase II study of ramucirumab plus docetaxel vs placebo plus docetaxel in Japanese patients with stage IV non-small cell lung cancer after disease progression on platinum-based therapy, Lung Cancer. 99 (2016) 186–193. doi:10.1016/j.lungcan.2016.07.019.
[53] J.R. Molina, G.K. Dy, N.R. Foster, K.L. Allen Ziegler, A. Adjei, K.M. Rowland, M. Aubry, P.J. Flynn, S.J. Mandrekar, S.E. Schild, A.A. Adjei, North Central Cancer Treatment Group (, A randomized phase II study of pemetrexed (PEM) with or without sorafenib (S) as second-line therapy in advanced non-small cell lung cancer (NSCLC) of nonsquamous histology: NCCTG N0626 study, ASCO Meeting Abstracts. 29 (2011) 7513.
[54] A.B. Cortot, C. Audigier-Valette, O. Molinier, S. Le Moulec, F. Barlesi, G. Zalcman, P. Dumont, D. Pouessel, C. Poulet, P.J. Souquet, S. Hiret, A. Dixmier, P.-A. Renault, A. Langlais, M.P. Lebitasy, F. Morin, D. Moro-Sibilot, B. Besse, French Cooperative Thoracic Intergroup (IFCT), Weekly paclitaxel plus bevacizumab versus docetaxel as second or third-line treatment in advanced non-squamous non-small cell lung cancer (NSCLC): Results from the phase III study IFCT-1103 ULTIMATE., ASCO Meeting Abstracts. 34 (2016) 9005.