Meta-analysis of bevacizumab in advanced non-small-cell lung cancer

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1. INTRODUCTION AND BACKGROUND

Lung cancer is the leading cause of cancer death in the Western world[1], killing more than one million people worldwide each year. Approximately 85% of all cancers are non-small-cell lung cancer (NSCLC) and around 55% of patients are diagnosed with advanced or metastatic disease[2]. Overall survival (OS) of patients at 5 years is around 14%. The standard treatment for the patients with advanced disease is systemic chemotherapy containing a platinum agent. Although modest progress has been made with the use of chemotherapy in patients with metastatic non-small-cell lung cancer, additional treatment options are needed.

Vascular endothelial growth factor (VEGF) promotes tumor angiogenesis, which is critical for tumor progression[3]. In non–small-cell lung cancer (NSCLC), increased VEGF expression is common and associated with adverse clinical outcomes. Bevacizumab, a humanized monoclonal anti-VEGF antibody[4] has demonstrated significant clinical benefit in first- and second-line colorectal cancer and in first-line treatment of metastatic breast cancer, as well as renal cell cancer[5-8].

In a randomized, three-arm, phase II trial in advanced NSCLC comparing carboplatin and paclitaxel (CP) alone versus CP in combination with bevacizumab (7.5 or 15 mg/kg every 3 weeks), improved time to progression was observed in the bevacizumab 15 mg/kg arm[9]. Given the high rate of severe hemoptysis in the squamous cell carcinomas, further phase III trials excluded those tumors, along with tumors invading or abutting central blood vessels and brain metastasis. The Eastern Cooperative Oncology Group (ECOG) selected the 15 mg/kg dose for the open label phase III NSCLC trial E4599. In that trial the median survival was 12.3 months in the group assigned to chemotherapy (CP) plus bevacizumab, as compared with 10.3 months in the chemotherapy-alone group (hazard ratio for death, 0.79; P=0.003). The

median progression-free survival (PFS) in the two groups was 6.2 and 4.5 months, respectively (hazard ratio for disease progression, 0.66; p< 0.001), with corresponding response rates of 35% and 15% (p<0.001). Rates of clinically significant bleeding were 4.4% and 0.7%, respectively (p<0.001)[10].

More recently, the AVAiL trial evaluated bevacizumab (7.5 or 15 mg/kg) versus placebo in combination with cisplatin/ gemcitabine (CG), a commonly used and efficacious regimen in NSCLC. The primary endpoint PFS was significantly prolonged; the hazard ratios (HR) for PFS were 0.75 (median PFS, 6.7 v 6.1 months for placebo; p = 0.003) in the low-dose group and 0.82 (median PFS, 6.5 v 6.1 months for placebo; p = 0.03) in the high-dose group compared with placebo. Objective response rates were 20.1%, 34.1%, and 30.4% for placebo, low-dose bevacizumab, and high-dose bevacizumab plus CG, respectively[11]. More recently the OS results of the AVAiL trial were reported with a lack of survival benefit and a median survival in the placebo arm of 13.1 months, 13.6 months in the 7.5 mg/kg bevacizumab-arm and 13.4 months in the 15 mg/kg bevacizumab-arm[12].

Finally, an open--label Japanese randomized phase II using comparing CP alone versus CP in combination with bevacizumab (15 mg/kg every 3 weeks) was presented at ASCO 2009[13]. The primary endpoint PFS was significantly prolonged (HR 0.61, 95% confidence interval, 0.41-0.89, p=0.009).

In order to gain insight on the clinical value of bevacizumab combined with a platin-based backbone (i.e. efficacy, toxicity) we decided to perform a meta-analysis that combines the results from similar and unconfounded randomized clinical trials[14]. It has the advantage of taking into account all available data and of providing evidence based on a large number of patients.

The meta-analysis has been initiated by the Institut Gustave-Roussy in collaboration with trial investigators. This project will concern the 1st line systemic treatment of inoperable locally advanced (IIIB), recurrent or metastatic (IV) NSCLC or non-squamous NSCLC, involving the standard platinum based chemotherapy associated or not with bevacizumab.

In order to avoid publication bias, both published and unpublished randomized trials 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[15]. 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[16,17]. Updated follow-up information will be sought which will enable us to report on long-term survival and treatment effects.

A systematic review and meta-analysis will be performed, first based on summary data and in a second step, based on individual patient data using a methodology similar to the one used in the Prophylactic Cranial Irradiation Overview and the Lung Adjuvant Cisplatin Evaluation18,19. This protocol focuses on the summary data meta-analysis. Hazard ratio will be used for survival data and odds ratio for toxicity as in the Delbaldo et al. meta-analysis20.

The main purpose of this meta-analysis will be to evaluate the overall survival (OS) and the progression-free survival (PFS). During the collection of the individual patient data, an evaluation of the OS and PFS will be performed, based on the current summary available data. Toxicity profiles will be analyzed as well.

2. OBJECTIVES

Assessment of the role of bevacizumab adjunction to the standard chemotherapy treatment by studying the following questions:

MAIN QUESTION

Role on the overall survival of patients with NSCLC by comparing the two following first line treatments:

- Conventional chemotherapy plus placebo (or no supplementary treatment);
- Conventional chemotherapy plus bevacizumab.

SECONDARY QUESTIONS

- Effect of this combination on the progression-free survival;
- Effect on objective response rate;
- Comparison of toxicity between the treatment arms (hematological toxicity, hemorrhagic events, gastro-intestinal disorders, renal toxicity, cardiovascular disorders, thrombembolic events and neurological disorders);
- Study the impact of bevacizumab dose on efficacy and toxicity;
- Investigation of the interaction between the treatment effect and the prognostic factors and patients characteristics (subgroup analyses);
- Lastly to interpret the results, the rate of cross-over to bevacizumab and second line treatment by arm for each trial will be described.

3. TRIAL SELECTION CRITERIA

3.1. INCLUSION CRITERIA

All trials must meet the following criteria:

Trials must:

- be randomized in a way that precludes prior knowledge of treatment assignment;
- be unconfounded, i.e. trials should only differ on bevacizumab administration;
- the same chemotherapy should be administered in all arms;
- include patients with IIIB or IV stage or recurrent NSCLC.

Patients must:

- not have received prior systemic treatment;
- be suitable to receive chemotherapy and bevacizumab;
- be randomized to receive conventional chemotherapy or chemotherapy and bevacizumab;
- have agreed to participate to the trial.

3.2. EXCLUSION CRITERIA

- randomized trials without a conventional platinum based chemotherapy arm;
- prior systemic anticancer treatment;

4. TRIAL SEARCH

Data from all randomized trials investigating the above mentioned comparisons in NSCLC will be sought using electronic database searching and trial registers

(Medline, ClinicalTrial, Scopus…), hand searching (review, articles, meeting proceedings) and by contacting experts in the field. The detail of the initial search and its results are given in the **Appendix A.** Eligible trials will be independently selected by two persons with discussion with a third person in case of disagreement.

5. DESCRIPTION OF INCLUDED TRIALS

The eligible trials are described in the **Appendix B**.

In total, four randomized trials including more than 2,000 patients studied the role of bevacizumab in addition to the standard platinum based chemotherapy as first treatment in advanced or metastatic lung cancer.

6. CRITERIA OF EVALUATION

6.1. ENDPOINTS

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

Secondary endpoints such as progression–free survival, response rate, lung cancer mortality, non-lung cancer mortality will be also considered. The latter endpoint will be analyzed if the cause of death is available.

Observance, toxicity under chemotherapy + bevacizumab and under bevacizumab alone will be also studied, if possible.

6.2. PROGNOSTIC FACTORS

The following prognostic factors and patient characteristics, if available at least for the two largest trials, will be considered:

- Age
- Sex
- Histology
- Stage
- Performance status
- Race
- Body weight loss
- HTA
- Smoking status
- LDH before treatment
- Tumor location (central vs. non-central)

7. DATA COLLECTION AND QUALITY CONTROL

For the first step, on published information, the data will be extracted independently by two persons from publication or statistical reports. A specific form will be designed to extract the data. In case of disagreement between these two persons, discussion with a third person will be organized. Because of the availability of these reports, it will be possible to extract summary data (hazard ratio) on the effect of bevacizumab on overall survival and PFS by patients subgroups defined by the above mentioned prognostic factors and patient characteristics.

To realize an individual patient data analysis, for each eligible trial, the main investigator will be asked to provide the following basic data for survival and prognostic factors for all randomized patients. The provisional data list to be collected includes:

- Date of birth or age
- Sex
- Race
- Performance status
- HTA
- Smoking status
- Body weight loss
- Histology
- Tumor localization
- Stage TNM for NSCLC (if not available stage: information on classification used),
- LDH before treatment
- Allocated treatment
- Date of randomization
- Date of chemotherapy start
- Number of chemotherapy received cycles
- Bevacizumab started / not started
- Date first day bevacizumab
- Date last day bevacizumab
- Total administered dose of bevacizumab
- Total number of injections with bevacizumab
- Second line treatment, and its starting date
- Date of last follow-up
- Survival status
- Cause of death
- Date of progression and second cancer
- Acute toxicity (neutropenia, thrombocytopenia, anemia, hemorrhagic events; gastro-intestinal disorders, including perforation; renal, cardiovascular

disorders, in particular hypertension and venous and arterial thrombo-embolic events; neurologic disorders)

+ Specification of toxicity grading used system

+ grade of toxicity

+ occurrence during chemotherapy (+/- bevacizumab) or during bevacizumab alone

- Whether excluded from trial analysis
- Reason for exclusion (if applicable)

Appendix C gives the suggested format and coding for the individual patient data to be sent to the Secretariat.

All data will be checked for consistency with the trial protocol, statistical report and publication.

For individual patient data (IPD), internal consistency of the data will be also checked. Range checks will be performed and extreme values will be checked with the trialists.

Whatever the type of data, each trial will be analyzed individually, and the resulting survival analyses and trial data will be sent to the trialists for verification.

8. STATISTICAL ANALYSIS PLAN

Trial characteristics will be reported in tabular form, information will include patient numbers, period of recruitment, methods of randomization, 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 when individual patient data will be available[21].

The ultimate aim will be to obtain and analyze data from all randomized patients included in all relevant randomized trials on an intention-to-treat basis. With more than 2,000 patients (or 1,500 deaths) it would be possible to detect, with a power of 90%, an absolute improvement in survival from 50 % to 56 % at 1-year (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 PFS. Proportion of patients who have received at least one administration of bevacizumab, proportion of patients who started treatment by bevacizumab alone after the end of chemotherapy, the percentage of the planned total dose of bevacizumab (only for IPD meta-analysis) and toxicity rates will be also studied.

All analyses will include all randomized patients and will be carried out on an intention-to-treat basis meaning that all patients will be analyzed according to the allocated treatment, whether they received or not that treatment. Survival analyses will be stratified by trial, and the hazard ratio of each trial will be extracted from publication or statistical report.

Once the IDP will be available, the log-rank expected number of deaths and variance will be used to calculate individual and overall pooled hazard ratios by the fixed-effect model[22]. 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 to whom conventional chemotherapy plus bevacizumab was allocated, compared with those whom only conventional chemotherapy was allocated. For comparing toxicity rates, overall pooled odds ratio stratified by trials will be calculated by a fixed-effect model.

The χ^2 heterogeneity test[18] will be used to test for gross statistical heterogeneity, the I^2 statistic[23] will be used as a measure of consistency among trials. In case of significant and unexplained heterogeneity, random effect model will be used. Stratified survival curves will be estimated for control and experimental groups, using annual death rates and hazard ratios[24] when IPD will be available. They will be used to calculate absolute benefit at 6 months and 12 months with their 95% confidence intervals[24.] All p-values will be two-sided.

8.1. 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 if possible on all trials and will be stratified by trial.

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 benefit more or less from bevacizumab.

The subgroups to be analyzed will be as follows (if data available):
Age (<65, 65+)
Sex (Male, Female)
Performance Status (0 vs. 1+)
Histology (Adenocarcinoma, Large Cell, Other) in NSCLC after exclusion of the small group of patients with squamous cell carcinoma included in the oldest trial
Tumor localization (central, yes/no)
Stage (IIIB, IV, recurrence)
Race (White, Other)
Body weight loss (≤ 5%, > 5%)
Smoking consumption (< 10 pack-years, ≥ 10 pack-years)
LDH (>ULN, ≥ ULN)
HTA (yes/no)

8.2. SENSITIVITY ANALYSES

Different hazard ratios will be used as a sensitivity analysis for the summary data meta-analysis:

- for overall survival, HR stratified on randomization factors instead of unstratified hazard ratio
- for PFS, HR calculated for the different definitions given for PFS
- for overall survival and PFS, HR excluding the squamous cell (randomized in one of the four trials) and HR excluding patients with CNS metastasis.

9. PRACTICAL CONSIDERATIONS

The Secretariat is located in the Biostatistics Department of the Institut 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 and perform the analysis. The secretariat will be supported by the trial representative in the different steps of the project.

All supplied data will remain confidential and will be used exclusively for this 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 associate members of the Secretariat and trial investigators.

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11. Appendix A: Trials search strategy

Base	Research strategy	Results
PubMed MEDLINE	("bevacizumab"[Substance Name] OR "bevacizumab"[All Fields] OR "avastin"[All Fields]) AND ("Carcinoma, Non-Small-Cell Lung"[Mesh] OR (NSCLC OR (Non-Small-Cell[Title/Abstract] AND Lung[Title/Abstract]))) AND ((("random allocation"[MeSH Terms] OR "randomized"[All Fields]) AND ("clinical trials as topic"[MeSH Terms] OR "trial"[All Fields])) OR Randomized Controlled Trial[ptyp])	61 references
SCOPUS	(TITLE-ABS-KEY(bevacizumab AND (randomized OR randomised) AND trial) AND TITLE(non-small-cell AND lung))	96 references
The Cochrane Library	Bevacizumab AND Non-Small-Cell Lung Cancer	No reference
ClinicalTrials.gov	Avastin OR Bevacizumab | "Non-small Cell Lung Cancer" | Phase II III CLOSED Avastin OR Bevacizumab | Closed Studies | "Non-small Cell Lung Cancer" | Phase II III OPEN Avastin OR Bevacizumab | Open Studies | "Non-small Cell Lung Cancer" | Phase II III	89 references 39 references 50 references
ASCO's comprehensive database of abstracts	lung in Abstract Body and randomized in Abstract Body	100 references

Hand search: proceeding of the World Conference on Lung Cancer: 2005, 2007.

12. Appendix B: trials description

Study	Number of patients randomized	Inclusion period	Histology	Bevacizumab dose	CT dose	Patients characteristic
JO19907 (phase II)	160*	2007-2008	NSCLC Non squamous	arm 1: 15 mg/kg D1 arm 2: none	Carboplatin (AUC=6) D1 Paclitaxel 200 mg/m² D1 6 cycles	stage IIIB / IV or recurrent PS 0-1
AVAiL	1043 (3 arms)	2005 - 2006	NSCLC Non squamous	arm 1: 7.5 mg/kg D1 arm 2: 15 mg/kg D1 arm 3: placebo D1	Cisplatin 80 mg/m² D1 Gemcitabine 1250 mg/m² D1,8 6 cycles	stage IIIB / IV or recurrent PS 0-1
ECOG 4599	878	2001 - 2004	NSCLC Non squamous	arm 1: 15 mg/kg D1 arm 2: none	Carboplatin (AUC=6) D1 Paclitaxel 200 mg/m² D1 6 cycles	stage IIIB / IV or recurrent PS 0-1
Johnson (phase II)	99 (3 arms)		NSCLC	arm 1: 7.5 mg/kg D1 arm 2: 15 mg/kg D1 arm 3: placebo D1	Carboplatin (AUC=6) D1 Paclitaxel 200 mg/m² D1 6 cycles	stage IIIB / IV or recurrent PS 0-2

** Randomization 2:1*

13. Appendix C: suggested coding

Concern individual patient data meta-analysis.

Please provide data on all patients randomised. You may complete data forms (provided on request) or supply your data as a computer printout, on floppy disk (formatted for PC) or by email.

Data can be in almost any format (ASCII, Excel, Dbase, etc.), but please indicate which format has been used. It would be helpful if you used the coding suggested, however you may code the data in the way that is most convenient for you. Please supply us with full details of the data coding system used.

If sending data via email, please encrypt the data and let us know how it has been encrypted in a separate email.

Variable	Format/Coding
Patient Identifier	Type character **(Preferably not name)** - Width 15
Date of Birth	Type date - Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format
Or Age at randomization	Type numeric - Width 3 Code age in years, unknown = 999
Sex	Type numeric - Width 1 1=male, 2=female, 9=unknown
Race	Type numeric - Width 1 1=white, Asian=2, other=3, 9=unknown
*Performance Status (**Karnofsky**)*	Type numeric – Width 3 Code 10-100, 999=unknown
*Performance Status (**WHO/ECOG**)*	Type numeric - Width 1 Code 1-4, 9=unknown
HTA	Type numeric - Width 1 0=no,1= yes, 9=unknown
Smoking status	Type numeric – Width 1 1=current smoker, 2= past smoker, 3=never smoked
Number of pack-years	Type numeric – Width 2 Code 0 if no smoker, 99=unknown
Body weight loss	Type numeric – Width 1 1=≤ 5%, 2=6-10%, 3=>10%
Histology	Type numeric – Width 1 1=adenocarcinoma, 2=squamous cell, 3=mixed, 4=large cell undifferentiated, 5=NSC unspecified, 6=small cell, 7=other, 9=unknown,

Tumor localization	Type numeric - Width 1 1=central,2= no central, 9=unknown
Tumour stage used	Type numeric - Width 1 1=AJCC, 2=1986 ISS, 3=1997 UICC
If possible, provide complete TNM, if not possible provide stage	
T :	0 to 4, 5=X, 6=in situ, 9=unknown
N	0 to 3, 4=X, 9=unknown
M	0, 1, 2=X, 9=unknown
If AJCC used *Tumour Stage AJCC* or *TNM*	Type numeric - Width 1 1=stage I, 2=stage II, 3=stage III, 4=metastatic, 9=unknown Type numeric - Width 1 for T, 1 for N, 1 for M
If ISS used *Tumour Stage 1986 ISS* or *TNM*	Type numeric - Width 1 1=stage I, 2=stage II, 3=stage IIIA, 4=stage IIIB, 5=stage IV, 9=unknown Type numeric - Width 1 for T, 1 for N, 1 for M
If 1997 staging used *Tumour Stage 1997 UICC* or *TNM*	Type numeric - Width 1 1=stage IA, 2=stage IB, 3=stage IIA, 4=stage IIB, 5=stage IIIA, 6=stage IIIB, 7=stage IV, 9=unknown Type numeric - Width 1 for T, 1 for N, 1 for M
LDH	Type numeric - Width 1 1=>Upper Limit Normal, 2= $\leq$ ULN,
Allocated Treatment	Type numeric - Width 1 Code = 1= chemotherapy, 2 = chemotherapy + bevacizumab
Date of Randomisation	Type date - Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format
Chemotherapy start	Type numeric - Width 1 0=not started chemotherapy,1=started chemotherapy, 9=unknown
Date of chemotherapy start	Type date - Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format
Number of chemotherapy received cycles	Type numeric - Width 1
Start of bevacizumab	Type numeric - Width 1 0=no,1= yes, 9=unknown
Date of bevacizumab start	Type date - Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format

Date of bevacizumab end	Type date - Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format
Total bevacizumab dose (mg/kg)	Type numeric - Width 3
Total number of injection of bevacizumab	Type numeric - Width 2
Second line treatment	Type numeric - Width 1 0=no,1= yes, 9=unknown
Date of start of second line treatment	Type date - Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format
Cross-Over to bevacizumab (control group only)	Type numeric - Width 1 0=no,1= yes, 9=unknown
Date of cross-over to bevacizumab	Type date - Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format
Date of Death / *Last Follow-up*	Type date – Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format
Survival Status	Type numeric – Width 1 0=alive, 1=dead
Cause of Death	Type numeric – Width 1 1=lung cancer, 2=treatment related, 3=other, 9=unknown
Progression	Type numeric – Width 1 0=no progression, 1= progression, 9=unknown
Date of Progression	Type date – Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format
Second Malignancy status	Type numeric – Width 1 0=no second malignancy , 1= second malignancy, 9=unknown
Date of Second Malignancy	Type date – Width 8 or 6 Code date in dd/mm/yyyy (recommended) or dd/mm/yy format
Acute toxicity scale used	Type numeric - Width 1 1=RTOG, 2=CTC – NCI, 3=WHO, 4=Other
Highest grade of anemia	Type numeric - Width 1 Code 0 to 5 , 9=unknown
Highest grade of neutropenia	Type numeric - Width 1

	Code 0 to 5, 9=unknown
Highest grade of thrombocytopenia	Type numeric - Width 1 Code 0 to 5, 9=unknown
Highest grade of hemorrhage	Type numeric - Width 1 Code 0 to 5, 9=unknown
Highest grade of gastro-intestinal disorder	Type numeric - Width 1 Code 0 to 5, 9=unknown
Highest grade of digestive perforation	Type numeric - Width 1 Code 0 to 5, 9=unknown
Highest grade of renal disorder	Type numeric - Width 1 Code 0 to 5, 9=unknown
Highest grade of cardiovascular disorder	Type numeric - Width 1 Code 0 to 5, 9=unknown
Highest grade of hypertension	Type numeric - Width 1 Code 0 to 5, 9=unknown
Highest grade of thrombo embolic event	Type numeric - Width 1 Code 0 to 5, 9=unknown
Highest grade of neurologic disorder	Type numeric - Width 1 Code 0 to 5, 9=unknown
Excluded	Type numeric - Width 1 0=included in analysis, 1=excluded from analysis, 9=unknown
Reason for Exclusion	Type character - Width 25