



Non-interventional study

Avastin[®] in Metastatic Breast Cancer

ML 21165 / 2007

Clinical Study Report

Synopsis

Name of Sponsor Roche Pharma AG, D-79630 Grenzach-Wyhlen, Germany
Name of finished Product and active substance Avastin® (Bevacizumab)
Title of study Avastin® in metastatic breast cancer
Investigators and study centres The individual patient data in this observational study were collected at 495 centres throughout Germany. Principal Investigator: PD Dr. Marcus Schmidt, Klinik und Poliklinik für Geburtshilfe und Frauenkrankheiten, UNIVERSITÄTSMEDIZIN der Johannes-Gutenberg-Univ. Mainz Cf. Appendix I for a complete list of participating institutions
Publications Schmidt M, Schneeweiss A, Foerster FG et al.: Mature Results on Metastatic Breast Cancer Patients with Prolonged (≥ 1 Year) Exposure to First-Line Bevacizumab Combined with Paclitaxel from a Large Observation Study. San Antonio Breast Cancer Symposium 2013 (submitted) Schrader I, Foerster FG, Schneeweiss A et al.: Analysis according to prognostic factors in patients (pts) treated with first-line bevacizumab (BEV) combined with paclitaxel (PAC) for HER2-negative metastatic breast cancer (mBC) in a routine oncology practice study. J Clin Oncol 2012; 30 (suppl): 1077 Kümmel S, Schneeweiss A, Foerster F et al.: Prolonged (≥ 1 year) exposure to first-line bevacizumab combined with paclitaxel in patients with her2-negative metastatic breast cancer treated in a routine oncology practice study. San Antonio Breast Cancer Symposium 2011 (abstr. P1-14-04)

Foerster F, Aktas B, Geberth M et al.: First-Line Bevacizumab (Bev) Combined With Paclitaxel (pac) in Older Patients (pts) Treated for HER2-Negative Metastatic Breast Cancer (mBC) in a Routine Oncology Practice Study. Eur J Cancer 2011 (suppl), abstr. 5072

Klare P, Foerster F, Geberth M et al.: Efficacy and safety of first-line bevacizumab (Bev) combined with paclitaxel (Pac): An observational study in 786 patients (pts) with HER2-negative metastatic breast cancer (mBC). J Clin Oncol 2011; 29 (suppl): 1079

Geberth M, Foerster F, Klare P et al.: Efficacy and Safety of First-Line Bevacizumab (BEV) Combined with Paclitaxel (PAC) According to Age: Subpopulation Analysis of a Large, Multicenter, Non-Interventional Study in Patients (Pts) with HER2-Negative Metastatic Breast Cancer (MBC). San Antonio Breast Cancer Symposium 2009 (abstr. 6085)

Foerster F, Geberth M, Schumacher C et al.: First-line bevacizumab (bev) plus paclitaxel (pac) combination therapy: safety findings from a multicentre German non-interventional study in patients with metastatic breast cancer (MBC). Eur J Cancer 2009 (suppl), abstr. 5074

Studied period

Recruitment of observed patients: June 2007 – September 2009

Data base closure (for follow-up data): July 2012

Phase of development

Pharmacovigilance, non-interventional observation study

Objectives

The objective of this non-interventional study / postmarketing surveillance (according to § 67 Abs. 6 AMG) is the documentation of data concerning efficacy and safety of Avastin® (Bevacizumab) in the first line (chemo)therapy of metastatic breast cancer in current clinical practice.

The purpose of this investigation was to document and examine the application of Avastin® as a part of routine treatment in Germany. The implementation of this

study did not influence the physician regarding therapy, diagnostics and frequency of medical examination during and after the treatment.

In particular, the following questions/topics were prospectively specified:

- Are there any adverse effects of the drug and/or its routinely used combinations which have not been recorded before?
- Do the frequencies of adverse effects correspond to the hitherto known safety profile?
- Which dosages and regimens of application are used in routine practice?
- What are the causes for eventual treatment modifications or withdrawal?
- Can the positive therapy effects shown in the registration studies be reproduced in broad clinical practice?
- Which conventional prognostic factors are predictive for efficacy results in the treatment of metastatic breast cancer with Avastin combinations?
- What total accumulative doses of Avastin are administered?

Methodology

Each centre received a file titled 'Nicht-interventionelle Studie: AVASTIN® beim metastasierten Mammakarzinom' (Non-interventional study of AVASTIN® in metastatic breast cancer) for each patient in order to document the baseline characteristics, the treatment and its results.

The following information was to be documented:

- Demographic characteristics and medical history of the patients including histological and staging information
- Current sites of disease
- Previous treatment
- Relevant concomitant diseases
- Vital signs and standard hematology/blood chemistry
- Therapy with Avastin and concomitant antineoplastic medication
- Adverse drug reactions, serious adverse drug reactions
- Tumor response
- End of therapy / reasons
- Progression-free survival and overall survival

- Further-line antineoplastic therapy

The detailed observation period for each patient was until end of Avastin treatment or up to a maximum of one year. Thereafter, additional core data, especially on progression-free and overall survival status, were collected by fax forms.

Number of patients

Planned: 1000

Analysed: 1049 (865 in the subgroup treated in combination with paclitaxel, according to the approved label)

Diagnosis of main criteria of inclusion

Patients with metastatic breast cancer without cytostatic pre-treatment in the palliative setting.

Additional selection criteria (to qualify for inclusion in the observation study):

Inclusion criteria:

- Age \geq 18 years
- Histologically confirmed metastatic breast cancer without cytostatic pre-treatment in the palliative setting

Exclusion criteria:

- Contraindications for Avastin[®] according to SmPC

The sites were selected by the gynecology sales force of Roche Pharma AG.

Test product, dose and mode of administration

Avastin[®] (Bevacizumab), monoclonal antibody against VEGF, intravenous administration.

According to the nature of a non-interventional study, there were no stringent dosage requirements (recommended dosed 10 mg/ kg body weight).

Duration of treatment

According to the nature of a non-interventional study, there were no fixed recommendations for treatment duration. In general, and if possible, the chemotherapy/antibody combination was to be administered until diagnosis of

disease progression.

Criteria for evaluation: Efficacy, safety

Efficacy criteria are tumor response, progression-free survival, and overall survival. The toxicity of the treatment regimen was assessed according to NCI CTC categories and severity grades, with a special focus on major adverse reactions particularly associated with Avastin treatment (gastrointestinal perforation, arterial thrombotic event, reversible posterior leukoencephalopathy). In addition, detailed data were collected on adverse reactions with presumed causal relationship to the antibody.

Statistical methods

Due to the observational character of this study, descriptive and explorative statistical methods were predominantly used, providing means, standard deviations, medians, quartiles, ranges, rates, and confidence intervals. Prognostic factors for long-term endpoints were assessed with Kaplan-Meier estimations and the logrank test.

Summary – Efficacy results

The disease and treatment course from a total of 1049 metastatic breast cancer patients without cytotoxic pre-treatment in the palliative setting was reported in this non-interventional observation study. Overall, 495 physicians/centres across Germany participated in the project, registering patients mainly between mid-2007 and mid-2009. The main data analysis report focuses on the subgroup of 865 patients, in which Avastin was combined with paclitaxel alone, according to the approved label of the drug in Germany.

According to the structure of the case report form, Avastin treatment was routinely recorded for one year (for longer periods in a limited number of about 10% of the patients), but could, of course, be administered beyond that limit in case of continued response of the disease. The long-term prognosis was recorded by several follow-up assessments of the patients' status after completing the form files covering the first year.

In general, the efficacy end point data reported from the three large pivotal studies on Avastin added to first-line chemotherapy in advanced breast cancer were confirmed by the results from this observational study. The most reliable and

mature parameter is progression-free survival, based on observed events in 715/865 patients (83%). The slightly lower median PFS compared to the ECOG-2100 study might reflect the less-selected population in this observational trial (Tab.).

Tab. Major efficacy endpoints in the bevacizumab phase III trials in breast cancer (1st line) and in this study

	ECOG-2100	AVADO	RIBBON-1*	this study
n (with bevacizumab)	347	495	415	865
Response rate [%]	37	60	51	62**
PFS, median [months]	11.8	9.5	9.2	9.6
OS, median [months]	26.7	30.5	27.5	21.6

* Subgroup with taxane/anthracycline backbone only

** Best response, all sources

The high response rate in the present study is probably due to the less restricted response definition, when compared to pivotal randomized trials. In particular, the confirmation of a remission after a defined time period was not required. Based on 524 recorded death dates, i.e. available in more than 60% of the observed cases, the estimated median overall survival of 21.6 months is within the expected range of an unselected metastatic breast cancer population, it is about half a year shorter than the medians observed in the pivotal studies. However, this may be at least in part be explained by the distinctly higher age (median 58 years compared to 54-56), and the lack of other restrictions such as absence of certain concomitant diseases, ECOG performance status below 2 etc.

Summary – Safety results

No major unexpected findings were detected with respect to the safety of the drug and its combination with paclitaxel. In general routine practice, adverse events of special interest occurred with the expected frequencies: gastrointestinal perforation in 1%, arterial thrombotic events in 2% (1% causally related to Avastin), and one case of reversible posterior leukoencephalopathy. Severe (grade 3 to 4) hypertension was recorded in 5% of the patients.

Summary – Conclusions

In summary, the efficacy and safety experience, as reported from the international pivotal clinical trials, seems to translate into the routine practice treatment of an unselected breast cancer patient population in Germany, when treated with a first-line Avastin/paclitaxel combination.