SYNOPSIS OF RESEARCH REPORT
(PROTOCOL MO18024)

COMPANY: F. Hoffmann-La Roche LTD NAME OF FINISHED PRODUCT: Avastin ™ (RO 487-6646) NAME OF ACTIVE SUBSTANCE(S): Bevacizumab	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / DATE OF REPORT	*First-line Bevacizumab and Chemotherapy in Metastatic Cancer of the Colon or Rectum. First BEAT (Bevacizumab Expanded Access Trial) (MO18024)* 13 November 2008, Final report V1.0		
CENTERS AND COUNTRIES	376 centers in 41 countries were involved in this study.		
PUBLICATION (REFERENCE)	Safety and Efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: The BEAT study. Article in-progress.		
PERIOD OF TRIAL	First patient, 1st visit: 30 Aug 04 Last patient, last visit: 1 Oct 07 Last survival status: Dec 07	CLINICAL PHASE	III b
OBJECTIVES	Primary: To assess the safety profile of bevacizumab when combined with fluoropyrimidine-based chemotherapy (CTX) regimens as first-line treatment of metastatic cancer of the colon or rectum (mCRC). Secondary: To assess the effectiveness of bevacizumab as measured by time to disease progression (TTP), duration of survival (time to death [TTD] / overall survival [OS]). Progression free survival (PFS) and best response to study therapy were also studied as additional endpoints.		
STUDY DESIGN	Open-label, non-comparative, multicenter study		
NUMBER OF SUBJECTS	2000 patients were planned for enrollment. 1965 patients were screened and 1914 enrolled. 1914 patients were entered in the Intent-to-treat (ITT) population.		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients with histologically confirmed metastatic CRC, untreated with CTX for metastatic disease (prior adjuvant CTX for CRC was allowed), who were scheduled to start first-line fluoropyrimidine-based chemotherapeutic treatment.		
TRIAL DRUG	Bevacizumab (Avastin™, RO 487-6646)		
DOSE / ROUTE / REGIMEN / DURATION	Intravenous (i.v.) dose of 5mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks according to the CTX regimen. Standard CTX regimen chosen at the discretion of the investigator. Drug provided in 100 mg and 400 mg vials: concentrate for solution for i.v. infusion. Median treatment duration per patient was expected to be 10 months.		
REFERENCE DRUG	Not applicable.		
DOSE / ROUTE / REGIMEN / DURATION	Not applicable.		

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CRITERIA FOR EVALUATION	
EFFICACY:	The effectiveness of bevacizumab was assessed with the following variables: • Duration of survival, or TTD/OS (defined as the time period from the first bevacizumab administration [i.e. along with the start of first-line CTX] to date of death, irrespective of the cause of death). • TTP (defined as the time period from the first bevacizumab administration [i.e. along with the start of first-line CTX] to first occurrence of investigator-assessed disease progression). • PFS (time to progression or death, defined as the time period from the first bevacizumab administration [i.e. along with the start of first-line CTX] to investigator-assessed disease progression or death for any cause, whichever occurred first). • Best response to study therapy (investigator's assessment using either Response Evaluation Criteria in Solid Tumors [RECIST] or World Health Organization [WHO] criteria). • Best responses to first-line and second-line CTX.
PHARMACODYNAMICS:	Not applicable.
PHARMACOKINETICS:	Not applicable.
SAFETY:	The safety profile of bevacizumab when combined with fluoropyrimidine-based CTX regimens as first-line treatment was assessed via: • Incidence of all reported adverse events (AEs) or serious adverse events (SAEs) (irrespective of their relatedness). • Incidence of SAEs related to bevacizumab. • Incidence of the following specific AEs (all occurrences irrespective of suspected relationship with bevacizumab treatment): o gastrointestinal (GI) perforation o wound healing complication o hypertension o proteinuria o bleeding/haemorrhage o thromboembolism (arterial and venous thromboembolic event). • Incidence of other bevacizumab and/or CTX related toxicities as reported by the investigator. • Laboratory findings. • Eastern Cooperative Oncology Group (ECOG) performance status (at visits). • Vital signs (resting heart rate, blood pressure and body temperature) pre- and post-infusion.

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- Body weight before administrations of bevacizumab.
- Withdrawals due AEs.

Severity of AEs/laboratory results was assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events grading system(NCI CTCAE) (NCI CTCAE version 3.0, 2003).

STATISTICAL METHODS

METHODOLOGY:

The ITT population contained all patients who received at least one dose of bevacizumab. The analysis and reporting were based on this population. Subgroups of patients by type of first regimen of the first-line CTX were also considered.

Continuous measures were summarized with descriptive statistics including the mean, standard deviation, median, minimum and maximum values. Categorical measures were summarized using counts and percentages. Survival and disease progression information were assessed only at the end of the study and were descriptively summarized by Kaplan-Meier estimates. Overall response was summarized by response rates and 95% Pearson-Clopper confidence intervals (CI).

All safety parameters were analyzed and presented in terms of listings and summary tables. AEs were displayed in standard frequency tables. For laboratory parameters, shift tables of changes in NCI CTCAE grades were provided, with worst changes displayed. Descriptive summary tables of change from baseline over time were provided for vital sign parameters and ECOG status.

EFFICACY RESULTS:

The mean follow-up time in this study was 20.4 ±10.9 months.

Overall median TTD/OS was 22.7 months (95% CI: 21.7, 23.8) in the ITT population.

Overall median TTP was 11.3 months (95% CI: 10.8, 11.7), and overall median duration of PFS was 10.8 months (95% CI: 10.4, 11.3) in the ITT population. The overall response rate to study therapy was 45.1% (861 patients; 95% CI: 42.9%, 47.4%), with a complete response rate of 10.2% (195 patients) and a partial response rate of 34.9% (666 patients).

The best response to first-line CTX (ITT population) was a complete response in 201 patients (10.5%) and a partial response in 656 patients (34.3%). The majority of complete or partial responses were seen with the first regimen of first-line CTX. Second-line CTX was received by 952 patients in the ITT population and the best response to second-line CTX was a complete response in 5 patients (0.3%) and a partial response in 94 patients (4.9%).

PHARMACODYNAMIC RESULTS:

Not applicable.

PHARMACOKINETIC RESULTS:

Not applicable.

SAFETY RESULTS:

Overall, 1872 patients (97.8%) had AEs of any CTCAE grade. Of these, 850 patients (44.4%) experienced an AE of CTCAE grade 3, 261 patients (13.6%) of CTCAE grade 4 and 68 patients (3.6%) of CTCAE grade 5. Bevacizumab-related AEs (any CTCAE grade) were observed in 1235 patients (64.5%) and CTX-related AEs for 1794 patients (93.7%). The most commonly reported AEs overall were fatigue (59.1%), haemoglobin decreased (54.2%), nausea (52.1%) and diarrhoea (51.1%). The most commonly reported CTX-related AEs were fatigue (50.6%), nausea (49.1%), diarrhoea (48.0%) and haemoglobin decreased

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(44.2%), whereas the most commonly reported bevacizumab-related AEs were hypertension (22.9%), epistaxis (17.8%), fatigue (14.7%) and proteinuria (9.4%).
There were a total of 1133 deaths (59.2%) during this trial: 925 patients (81.6%) died due to disease progression, 48 patients (4.2%) of an AE and one patient (0.1%) had a fatal SAE. 20 patients (1.8%) died due to AEs and fatal SAEs related to bevacizumab. 631 patients (33.0%) had at least one SAE. 205 patients (10.7%) had at least one SAE which was related to bevacizumab, and 126 patients (6.6%) had at least a SAE resulting in death. The most commonly reported SAEs were diarrhoea (3.6%), pyrexia (2.5%) and intestinal obstruction (2.2%). Among the bevacizumab-related SAEs the most common were pulmonary embolism (1.5%), deep vein thrombosis (1.3%), diarrhoea (0.5%) and hypertension (0.5%). Generally, the incidence of SAEs was similar across the CTX treatment subgroups.
Overall, the reported events of special interest for bevacizumab therapy classed as SAEs or CTCAE Grade 3–5 AEs were thromboembolic events (8.6%, of which 7.7% were venous thromboembolic events and 1.5% were arterial thromboembolic events), hypertension (5.3%), bleeding (3.4%), GI perforation (1.9%), proteinuria (1.1%), and wound healing complications (1.1%).
SAEs or CTCAE Grade 3–5 AEs for infusion site reaction (as a generic name) were also reported for the preferred terms: application site reaction (0.1%), infusion site reaction (0.5%), injection site pain (0.1%), and catheter-related infection (0.4%)..
The majority of patients had no changes from baseline in CTCAE grades for laboratory parameters, and more than a half of abnormal laboratory values were of grade 1 or 2. However, a higher proportions of patients had increases in CTCAE grade from screening for haemoglobin (most commonly 1 grade: 536/1878), leukocytes (most commonly 1 [357/1872] or 2 [251/1872] grades), neutrophils (most commonly 1 [212/1837], 2 [227/1837], or 3 [213/1837] grades), platelets (most commonly 1 grade: 389/1851), and high glucose (most commonly 1 grade: 36/139). For proteinuria, the most common worst change from baseline was an increase of +1 which occurred in 20.5% of the patients. CTCAE grade 4 neutrophils were recorded for 4.5% of patients, with 1.5% of patients reporting an SAE of neutropenia.

CONCLUSIONS:

The safety and efficacy of first-line bevacizumab plus standard chemotherapy regimens in this study are consistent with results from previous phase III trials, thereby supporting the benefits of bevacizumab as first-line treatment for metastatic CRC.