SYNOPSIS OF RESEARCH REPORT [redacted]

(PROTOCOL MO18458 FOLLOW-UP)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	CSR MO18458 (Follow-up) – A single arm study to assess the efficacy and safety of bevacizumab in combination with irinotecan and infusional 5-fluorouracil/folinic acid regimens as first line treatment for patients with metastatic colorectal cancer. Report No. [redacted], July 2008.		
INVESTIGATORS / CENTERS AND COUNTRIES	31 centers in 5 countries (Australia 8, Italy 4, Canada 12, Spain 5, China 2). Principal investigator: [redacted], Italy, [redacted]		
PUBLICATION (REFERENCE)			
PERIOD OF TRIAL	April 1, 2005 to October 10, 2007 (first patient enrolled to last follow-up)	CLINICAL PHASE	IV
OBJECTIVES	Primary: • To determine the efficacy of bevacizumab in combination with irinotecan and infusional 5-fluorouracil plus folinic acid based regimens as compared with historical controls, based on progression-free survival. Secondary: • To evaluate the safety profile of bevacizumab in combination with irinotecan and infusional 5-fluorouracil plus folinic acid based regimens. • To determine the overall response rate, time to response, duration of response, and overall survival of bevacizumab in combination with irinotecan and infusional 5-fluorouracil plus folinic acid based regimens as compared with historical controls.		
STUDY DESIGN	Multicenter, open-label, single arm.		
NUMBER OF SUBJECTS	209 patients enrolled.		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Metastatic colorectal cancer Inclusion criteria: • No major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to treatment, or anticipation of the need for major surgery during the course of the study. Central venous access device (CVAD) for chemotherapy administration inserted within 2 days prior to study treatment start. • No prior chemotherapeutic treatment for mCRC. • Adequate organ function. • No clinical evidence of brain metastases. • ECOG performance status of 0 or 1. • Age ≥18 years.		

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TRIAL DRUG / STROKE (BATCH) No.	Bevacizumab batch numbers 400 mg vials: [redacted] 100 mg vials: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Bevacizumab (5 mg/kg iv infusion every 2 weeks) plus FOLFIRI regimen (irinotecan 180 mg/m^2, folinic acid 200 mg/m^2, 5-fluorouracil [5-FU] 400 mg/m^2 as intravenous bolus then 5-FU 2400 mg/m^2 as continuous infusion) until disease progression. Local practice modifications allowed for 5-FU/folinic acid administration.
REFERENCE DRUG / STROKE (BATCH)	-
CRITERIA FOR EVALUATION	
EFFICACY:	Primary: • Progression-free survival (PFS) Secondary: • Best overall response rate • Duration of response • Time to response • Overall survival • Disease control rate
SAFETY:	Adverse events, laboratory tests (hematology, serum chemistry, urinalysis), vital signs, ECOG performance status, ECG.
STATISTICAL METHODS	All statistical analyses are of a descriptive, exploratory nature; point estimates and confidence intervals but no p-values are presented.

METHODOLOGY:

After undergoing screening assessments and providing their informed consent, patients were enrolled on to the study to receive bevacizumab 5 mg/kg plus FOLFIRI every 2 weeks for a minimum of 6 weeks or until clear evidence of disease progression or unmanageable toxicity. In case of permanent discontinuation of either bevacizumab or chemotherapy for safety reasons, the other treatment component could be continued. Tumor measurements/assessments were made based on RECIST criteria using CT scan, MRI scan, X-ray, bone scan, ultrasound for soft tissue lesions and clinical examination until evidence of disease progression. A maximum of 5 target lesions per organ and 10 lesions in total were to be identified, recorded and measured at screening. All other lesions were to be recorded as non-target lesions. Post screening assessments were to be performed every 12 weeks for the first year and every 16 weeks thereafter until disease progression. In cases of clinical evidence of progression before the next scheduled assessment, an unscheduled tumor assessment was to be performed. In responding patients, the response had to be confirmed by a second assessment performed a minimum of 4 weeks after the first response had been recorded.

Adverse events were recorded on an ongoing basis. Special guidelines were to be followed in the case of hypertension, proteinuria and wound healing complications. Assessments including body weight, body temperature and pulse were performed every 4 weeks during the treatment period. Hematology and blood

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chemistry were performed before each chemotherapy treatment and thereafter at 4-weekly intervals. Urinalysis and blood pressure were to be assessed prior to each bevacizumab infusion. ECG assessments were made as clinically indicated and ECOG performance status was assessed every 12 weeks for the first year and every 16 weeks thereafter until progression.
On clear evidence of disease progression, bevacizumab had to be discontinued. On discontinuation of bevacizumab, a safety follow-up was to be performed 28 days after last dose to include: ECOG performance status, body weight, body temperature, pulse, hematology, blood chemistry, urinalysis and blood pressure, concomitant treatments and adverse events.
Survival follow-up for all patients (upon disease progression) was to continue until study closure. Visits were scheduled every 6 months and the following assessments were requested: survival, subsequent anti-cancer therapy, follow-up of events of hypertension, proteinuria and wound healing for up to 6 months, and follow-up of study drug-related unexpected serious adverse events until the event had resolved.

EFFICACY RESULTS:

The primary endpoint was PFS, defined as the time from the start of study medication to disease progression or death from any cause, based on investigator assessment. The ITT population was the primary population for the efficacy analyses; similar outcomes were obtained from the PP population. The median duration of PFS was 337 days (11.1 months).

Parameter (Median value)	**Overall population Bv5+FOLFIRI n = 209 (Median value)**	**Subgroup Bv5+FOLFIRI n = 156 (Median value)**	**Subgroup Bv5+FOLFIRI modified n = 53 (Median value)**
Progression-free survival	337 days **11.1 months**	342 days **11.2 months**	310 days **10.2 months**
Overall survival	676 days **22.2 months**	676 days **22.2 months**	641 days **21.1 months**
Overall response rate	111 (53.1%)	83 (53.2%)	28 (52.8%)
Complete response	8 (3.8%)	6 (3.8%)	2 (3.8%)
Partial response	103 (49.3%)	77 (49.4%)	26 (49.1%)
Stable disease	68 (32.5%)	49 (31.4%)	19 (35.8%)
Progressive disease	16 (7.7%)	12 (7.7%)	4 (7.5%)
Missing	14 (6.7%)	12 (7.7%)	2 (3.8%)
Duration of response	274 days **9.0 months**	260 days **8.5 months**	291 days **9.6 months**
Time to response	137 days **4.5 months**	-	-
Disease control rate	181 (86.6%)	-	-

SAFETY RESULTS:

The safety data were generally in line with observations in previous studies of bevacizumab in cancer patients. Overall, gastrointestinal disorders were the most frequently reported events, particularly diarrhea and nausea, which occurred in 79% and 77% of patients, respectively. Other gastrointestinal events which occurred in over 20% of the patients were vomiting (55%), constipation (50%), abdominal pain (37%), stomatitis (32%) and dyspepsia (22%).
Adverse events other than gastrointestinal disorders, observed at an incidence of more than 20%, were: fatigue (58%), alopecia (46%), neutropenia (43%), anorexia (40%), epistaxis (39%), mucosal inflammation (37%), headache and hypertension (both 27%), insomnia and dyspnea (both 22%).
For adverse events of CTCAE grade 3-5, 81% of patients experienced 463 events. Overall, gastrointestinal disorders (35%) and blood and lymphatic disorders (35%) were the most frequently reported groups of

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events. Neutropenia was the most common single grade 3-5 event and was recorded in 29% of patients; febrile neutropenia was observed in 6% of patients. Other events of grade 3 or above that were recorded in over 5% of patients included diarrhea (12%), fatigue (10%), vomiting, pulmonary embolism and deep vein thrombosis (7% for each event) and nausea (6%).

A total of 79% of patients experienced 331 adverse events of special interest to bevacizumab. The most frequently reported groups of events were events of bleeding (53%), hypertension (28%) and venous thromboembolic events (24%). The incidence of wound healing complications was 7%. The incidence of proteinuria, fistula/abscess, gastrointestinal perforation and congestive heart failure was low (2-3%) (see table below).

There were 7 patients who died due to an adverse event. No particular pattern was seen in the types of events that resulted in death.

Laboratory tests did not show new clinically relevant safety signals. The most common hematological grade 3-4 abnormalities were low neutrophil counts observed in 45% of patients (in this study, neutropenia was the most common single grade 3-5 adverse event and was recorded in 29% of patients; febrile neutropenia in 6% of patients). For clinical chemistry laboratory parameters, the most common grade 3-4 abnormalities were high uric acid (27%) and high gamma-GT (18%). All other grade 3-4 events for laboratory parameters occurred at an incidence of 10% or less.

No notable changes in vital signs, ECG or ECOG performance status were observed during the study.

Safety Parameter	**Bv5 + FOLFIRI (n = 209)**
Any adverse event	209 (100%)
NCI-CTC grade 3, 4, 5 adverse event	170 (81%)
Adverse event leading to death [b]	7 (3%)
Serious adverse event	108 (52%)
AE leading to discontinuation (any study drug)	51 (24%)
Adverse events of special interest	166 (79%)
Hypertension	58 (28%)
Proteinuria	7 (3%)
Wound healing complication	15 (7%)
Gastrointestinal perforation	5 (2%)
Venous thromboembolic events	51 (24%)
Arterial thromboembolic events	9 (4%)
Bleeding	111 (53%)
Congestive heart failure	4 (2%)
Fistula/abscess	6 (3%)

CONCLUSIONS:

This study demonstrates that the addition of bevacizumab to irinotecan with infusional 5-FU/folinic acid (FOLFIRI) provides clinically meaningful benefit to patients with previously untreated metastatic colorectal cancer, and is in this regard in line with results reported with bevacizumab administered with a chemotherapy regimen employing a bolus administration of 5-FU/folinic acid with irinotecan (IFL regimen) in the pivotal study AVF2107g.

The overall safety profile was favorable, consistent with previous observations in metastatic colorectal cancer patients receiving bevacizumab, and no new safety signals were observed. The pattern and incidence of common adverse events includes both the established side effects of FOLFIRI (neutropenia, diarrhea) as well as bevacizumab-associated toxicities, such as bleeding/hemorrhage, hypertension, proteinuria and

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thromboembolic events. Of note, was the decreased incidence of grades 3-5 diarrhea and grades 3-5 hypertension when compared with an IFL regimen.
It can therefore be concluded that the combination of bevacizumab with FOLFIRI is as safe and efficacious as the combination of bevacizumab with the IFL regimen.