SYNOPSIS OF RESEARCH REPORT ML18147 (PROTOCOL1056834)

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

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Final Clinical Study Report – ML18147 – A randomized, open-label phase III Intergroup study: Effect of adding bevacizumab to cross over fluoropyrimidine-based chemotherapy (CTx) in patients with metastatic colorectal cancer and disease progression under first-line standard CTx/bevacizumab combination. Report No. 1056834, December 2013.
INVESTIGATORS / CENTERS AND COUNTRIES	220 sites located in 15 countries in Europe and Saudi Arabia.
PUBLICATION (REFERENCE)	Bennouna J, et al. Lancet Oncol. 2013;14:29-37. Kubicka S, et al. Ann Oncol. 2013;24:2342-2349.
PERIOD OF TRIAL	First Patient Entered: 01 February, 2006 Data cut-off/LPLV: 31 May, 2013
CLINICAL PHASE	III
OBJECTIVES	The primary objective of Study ML18147 was as follows: • To assess overall survival (OS) for patients treated with bevacizumab in combination with fluoropyrimidine/irinotecan- or fluoropyrimidine/oxaliplatin-based chemotherapy regimens versus patients treated with fluoropyrimidine/irinotecan- or fluoropyrimidine/oxaliplatin-based chemotherapy regimens alone, after progression under first-line treatment with bevacizumab in combination with standard chemotherapy The secondary objectives of Study ML18147 were as follows: • To compare progression-free survival (PFS) (after first progression) overall and on treatment • To evaluate overall response rate (ORR) • To evaluate OS from the time of starting first-line therapy between the two treatment arms • To compare the safety profile in the two treatment arms. As reported in the primary CSR (based on a clinical cut-off of 31 May 2011), the ML18147 study met its primary endpoint of OS (from randomization) and secondary endpoint of PFS. The HR for OS was 0.81 (95% CI: 0.69, 0.94, p-value = 0.0062). Median OS was 11.2 months for the Chemo + Bev arm, and 9.8 months for the Chemo arm. The purpose of this final CSR is to provide updated safety information from Study ML18147, describing cumulative

	clinical safety data collected up to a clinical cut-off date of 31 May 2013, corresponding to the end of study.
STUDY DESIGN	Prospective, randomized, open-label, multinational, controlled, Phase III trial to examine the effect of adding bevacizumab (2.5 mg/kg IV per week equivalent dose) to fluoropyrimidine-based chemotherapy in patients with histologically confirmed metastatic colorectal cancer (mCRC) and disease progression following treatment with a first-line bevacizumab-containing regimen and within three months of last bevacizumab administration. Eligible patients were randomized 1:1 to receive second-line therapy with fluoropyrimidine/irinotecan-based chemotherapy or fluoropyrimidine/ oxaliplatin−based chemotherapy (crossover chemotherapy depending on first-line chemotherapy) with (Arm A) or without (Arm B) bevacizumab. Randomization was stratified by first-line PFS (≤ 9 months vs. > 9 months), first-line chemotherapy (irinotecan-based vs. oxaliplatin-based), time from last dose of bevacizumab (≤ 42 days vs. > 42 days), ECOG PS (0/1 vs.2). Study treatment was given until disease progression, unacceptable toxicity, or patient refusal.
NUMBER OF SUBJECTS	820 patients were enrolled (411 patients randomized to the Chemo arm and 409 patients randomized to the Chemo + Bev arm).
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients with a histological confirmed diagnosis of metastatic CRC and disease progression previously treated with first-line therapy (bevacizumab and fluoropyrimidine/oxaliplatin-based or bevacizumab and fluoropyrimidine/irinotecan-based chemotherapy)
TRIAL DRUG / STROKE (BATCH) No.	**Chemo + Bev** (Arm A): Bevacizumab: Provided as 100 mg vials containing a 25 mg/mL concentrate solution. Chemotherapy: All established second-line fluoropyrimidine/irinotecan- and fluoropyrimidine/oxaliplatin-based regimens commonly used in clinical practice were permitted as partnering chemotherapy and were provided locally
DOSE / ROUTE / REGIMEN / DURATION	Bevacizumab: 2.5 mg/kg IV per week dose equivalent (either 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks) Chemotherapy: Clinical use and administration followed the respective product/prescribing information.
REFERENCE DRUG / STROKE (BATCH) No.	**Chemo** (Arm B) See above for chemotherapy
DOSE / ROUTE / REGIMEN / DURATION	See above for chemotherapy
CRITERIA FOR EVALUATION	
SAFETY:	Safety parameters relevant to this final CSR included treatment-emergent adverse events (including serious AEs and AEs of special interest [AESI] to bevacizumab), deaths, biochemistry and hematology laboratory parameters, vital signs, and ECOG performance status. Reported events were coded according to MedDRA v16.0. The intensity of AEs and laboratory parameters were graded according to NCI CTCAE v3.0.

STATISTICAL METHODS	No formal statistical analyses were conducted for safety data. All safety analyses were considered descriptive.

METHODOLOGY

Safety Data Reporting and Analysis Relevant to Final End-of-Study Analysis:

All patients had AEs evaluated at baseline and on an ongoing basis (before each cycle) during the treatment period and at a 28-day safety follow-up visit after the last dose of study treatment. After completion of the end-of-treatment assessments, patients were followed during the post-treatment follow-up period at 3-month intervals for SAEs related to bevacizumab (reported indefinitely) and new non-serious AEs related to study drug (reported up to 6 months after last dose of study treatment).

Following the fifth protocol amendment (Protocol v6.0), reporting periods were extended for all new AEs (90 days after last dose of study treatment) and new AESIs to bevacizumab (6 months after last dose of study treatment).

SAFETY RESULTS

An overview of the safety data reported during Study ML18147 up to the data cut-off date for the end of study, 31 May 2013 is shown in Table 1.

Table 1 Summary of Overall Safety in Study ML18147 (Safety Population; 31 May 2013 Cut-off)

Parameter	Chemo n = 409	Chemo + Bev n = 401
Patients with:		
Any AE	403 (98.5%)	394 (98.3%)
Serious AE	137 (33.5%)	130 (32.4%)
Grade ≥ 3	236 (57.7%)	256 (63.8%)
AE leading to death (Grade 5)	15 (3.7%) [a]	14 (3.5%) [a]
AE leading to discontinuation of any treatment	37 (9.0%)	63 (15.7%)
AE leading to discontinuation of chemotherapy	37 (9.0%)	53 (13.2%) [b]
AE leading to discontinuation of bevacizumab	N/A	58 (14.5%) [c]
Adverse events of special interest:		
Any AESI	87 (21.3%)	165 (41.1%) [e]
Any AESI, [d] Grade ≥ 3	24 (5.9%)	46 (11.5%)
Hypertension, Grade ≥ 3	5 (1.2%)	6 (1.5%)
Proteinuria, Grade ≥ 3	0	3 (0.7%)
Bleeding/hemorrhage, Grade ≥ 3	1 (0.2%)	8 (2.0%)
Abscesses and fistulae (non-GI), Grade ≥ 3	0	1 (0.2%)
GI perforation, Grade ≥ 3	3 (0.7%)	8 (2.0%)
Congestive heart failure, Grade ≥ 3	2 (0.5%)	0
Venous thromboembolic events, Grade ≥ 3	12 (2.9%)	19 (4.7%)
Arterial thromboembolic events, Grade ≥ 3	2 (0.5%)	2 (0.5%)
Wound healing complications, Grade ≥ 3	1 (0.2%)	1 (0.2%)
PRES, all grade	0	0

AE = adverse event; AESI = adverse event of special interest; Bev = bevacizumab; Chemo = chemotherapy; GI = gastrointestinal; N/A = not applicable; PRES = posterior reversible encephalopathy syndrome.

[a] Includes 4 patients in the Chemo arm and 3 patients in the Chemo + Bev arm for whom PD leading to death was captured as a Grade 5 AE on the eCRF.

[b] Refers to discontinuation of chemotherapy only (5 patients) or chemotherapy and bevacizumab (48 patients).

[c] Refers to discontinuation of bevacizumab only (10 patients) or bevacizumab and chemotherapy (48 patients).

[d] Patients may report multiple AESIs.

Key safety findings are summarized below:

- The overall incidences of AEs of any grade (Chemo: 98.5% vs. Chemo + Bev: 98.3%), Grade 3–5 AEs (57.7% vs. 63.8%), and SAEs (33.5% vs. 32.4%) were comparable between treatment arms.
- The most frequently reported (≥ 5% in either treatment arm) Grade 3–5 AEs were neutropenia, diarrhea, and asthenia. Grade 3–5 AEs in which the incidence was ≥ 2% higher in the Chemo + Bev arm compared with the Chemo arm were neutropenia (13.2% vs. 17.0%) and mucosal inflammation (1.0% vs. 3.2%).

- There was a higher incidence of Grade 3–5 AESIs in the Chemo + Bev arm (11.5%) compared with the Chemo arm (5.9%) driven mainly by patients with Grade 3–5 VTEs, bleeding/hemorrhage and GI perforations. For each AESI category, however, the difference in incidence between treatment arms for Grade 3–5 events was < 2%.
- There was a similar proportion of deaths due to causes other than progressive disease in each treatment arm (5.4% vs. 6.2%) and of fatal (Grade 5) AEs (3.7% vs. 3.5%).
- The most frequently reported SAEs (> 1% in either treatment arm) were diarrhea, pyrexia, abdominal pain, neutropenia, vomiting, pulmonary embolism, subileus, and drug hypersensitivity. The SAEs with ≥ 1% increased incidence in the Chemo + Bev arm compared with the Chemo arm were subileus (0.5% vs. 1.7%) and drug hypersensitivity (0.2% vs. 1.5%).
- The most frequent AE leading to bevacizumab discontinuation, with or without chemotherapy discontinuation, was thrombocytopenia (1.2%), followed by diarrhea (1.0%), intestinal perforation, subileus, asthenia and pulmonary embolism (0.7% each), and vomiting, neutropenia, disease progression, dyspnea and deep vein thrombosis (0.5% each).
- With the exception of thrombocytopenia (Chemo: 0.2% vs. Chemo + Bev: 1.2%), there was no notable (≥ 1%) difference between the treatment arms with respect to the specific type or frequency of AEs leading to withdrawal of trial treatment.
- No new or unexpected toxicities were reported.

CONCLUSIONS

Overall, the safety profile of adding bevacizumab to fluoropyrimidine-based chemotherapy in patients with mCRC who experienced disease progression after a first-line bevacizumab-containing regimen, based on an additional 24 months of follow-up from the ML18147 study (clinical data cut-off of 31 May 2013), was very similar to that described in the primary ML18147 CSR (clinical data cut-off of 31 May 2011). The incidence and severity of AEs was consistent with those reported in the primary CSR. No new safety concerns were identified.