Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Bevacizumab

Proprietary Product Name: Avastin

Sponsor: Roche Products Pty Ltd

May 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	adverse event
ALP	alkaline phosphatase
ALAT	alanine aminotransferase
AMG	Arzneimittelgesetz
ASAT	aspartate aminotransferase
aPTT	activated partial thromboplastin time
BBP	bevacizumab beyond first progression
BP	blood pressure
BRiTE	Bevacizumab Reimens: Investigation of Treatment
BUN	blood urea nitrogen
Ca++	calcium
CHF	congestive heart failure
CI	confidence interval
Cl-	chloride
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRO	clinical research organization
CSO	Central Sample Office
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DPD	dihydropyrimidine dehydrogenase
ECG	electrocardiogram
ECHO	echocardiogram

Abbreviation	Meaning
ECOG	Eastern Cooperative Oncology Group
EU-CTD	European Union Clinical Trial Directive
5-FU	5-fluorouracil
5-FU/LV	5-fluorouracil with leucovorin
FDA	Food and Drug Administration
FOLFOX4	oxaliplatin, folinic acid, 5-FU
GCP	Good Clinical Practice
GGT	γ-Glutamyltransferase
GI	gastrointestinal
HR	hazard ratio
ICH	International Conference on Harmonization
IFL	irinotecan, 5-FU, leucovorin
ITT	intent-to-treat
IV	intravenous
K+	potassium
LDH	lactate dehydrogenase
mCRC	metastatic CRC
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
Na+	sodium
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival

Abbreviation	Meaning
PK	pharmacokinetic
PR	partial response
PS	performance status
PTT	partial thromboplastin time
Q2W	every 2 weeks
RBC	red blood cell
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SD	stable disease
ULN	upper limit of normal
USP	U.S. Pharmacopeia
VEGF	vascular endothelial growth factor
VTE	venous thromboembolism
WBC	white blood cell
WBRT	whole-brain radiotherapy

1. Clinical rationale

There was no clinical evidence from randomised clinical trials that bevacizumab containing regimens in the second line setting could improve patient outcomes after progression on a bevacizumab-containing regimen in the first-line setting. Clinical evidence providing insight into the effect of treatment with bevacizumab beyond first progression was from the BRiTE (Biomarkers for Rapid identification of Treatment Effectiveness) study, a large community-based, non-randomised, observational study, in which 1445 patients who were treated with bevacizumab as part of first line therapy, had bevacizumab as part of second-line therapy following disease progression. These patients were associated with improved survival beyond progression compared with patients who did not have bevacizumab. The findings of this study are supported by available data from another observational cohort study (ARIES – Avastin Registry: Investigation of Effectiveness and Safety).

Study ML18147 was designed to examine the effect of adding bevacizumab to cross-over fluoropyrimidine-based chemotherapy in patients with metastatic colorectal cancer (mCRC) who experienced disease progression after first-line standard chemotherapy plus bevacizumab. Study ML 18147 was initiated as Study AIO KRK 0504 in 2006 as a non-registrational study by AIO in Germany and Austria. Sponsorship of the study was transferred to Roche in 2008. Several major amendments were made without knowledge of the aggregate results so as not to compromise the integrity of the study. The amendments included a change in the primary endpoint from progression-free survival (PFS) to Overall Survival (OS).

OS was deemed by the sponsor to be a better measure than PFS because it is easily measured, is unambiguous and objective, and is a variable that is not subject to the potential biases associated with endpoints requiring clinical judgement. The sample size of the study was increased to adequately power the study for OS as the primary endpoint. Details of any subsequent anti-cancer therapy were obtained during follow-up visits until the end of study so that potential confounding of OS by the use of effective subsequent lines of therapy could be prevented.

FDA raised concerns about potential bias having been introduced as a result of the unplanned modifications to the protocol at the time of change in sponsorship. A number of recommendations were made including use of unstratified log rank test as primary analysis, and sensitivity analyses to address the sequential enrolment in the AIO KRK 0504 and ML18147 studies based on data cut-off points. The marketing authorisation holder (MAH) amended the analysis plan accordingly.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained one study, Study ML 18147: pivotal efficacy/safety study.

2.2. Paediatric data

No new data.

2.3. Good clinical practice (GCP)

Study ML18147 was conducted in accordance with US Food and Drug Administration (FDA) regulations, the ICH E6 Guideline for GCP, the Declaration of Helsinki (October 1996), and applicable local, state, and federal laws, as well as other applicable country laws.

3. Pharmacokinetics

No new data.

4. Pharmacodynamics

No new data.

5. Dosage selection for the pivotal studies

No new data.

6. Clinical efficacy

6.1. Pivotal Efficacy Studies

6.1.1. Study ML 18147

6.1.1.1. Study design, objectives, locations and dates

This study was a prospective, randomised, open-label, multinational, controlled, Phase III study to examine the effect of adding bevacizumab to fluoropyrimidine-based chemotherapy in patients with histology confirmed metastatic CRC and disease progression following treatment with a first-line bevacizumab containing regimen.

At the time the Study AIO KRK 0504 was transferred to Roche, the 261 patients had already been randomised under Protocol AIO KRK 0504. Stratification factors used for randomisation in Study ML 18147 were retrospectively collected for all these patients. They were not re-randomised, but continued with the treatment that they were assigned to at the time of enrolment in Study AIO KRK 0504. A stratified and un-stratified analysis will be performed to compare the results and assess the difference.

Study treatment was continued until disease progression, unacceptable toxicity or patient withdrawal. Tumour assessments were made every 8 to 9 weeks until disease progression. An end-of-treatment safety assessment was made 28 days following the last dose and the patients were followed three monthly for survival, tumour assessments, subsequent anti-cancer therapies and study drug related serious adverse events.

6.1.1.1.1. Primary Objective

To assess 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.

6.1.1.1.2. Secondary Objectives

To compare 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

6.1.1.1.3. Inclusion and exclusion criteria

Patients with histological confirmation of unresectable, metastatic colon cancer who progressed within 3 months after discontinuation of first-line therapy with a fluoropyrimidine and bevacizumab containing chemotherapy regimen, were included in the study. Patients with disease progression that was >3 months after the last dose of bevacizumab, patients with disease progression in the first 3 months in first-line treatment and patients who had participated in any other trial within 30 days prior to the start of study treatment in this trial were excluded.

6.1.1.1.4. Study treatments

Eligible patients, under Protocol ML 18147, were randomised 1:1 to receive fluoropyrimidine/irinotecan-based chemotherapy or fluoropyrimidine/oxaliplatin-based chemotherapy with or without bevacizumab until progressive disease, unacceptable toxicity or patient refusal. The bevacizumab dose chosen was 2.5 mg/kg/week equivalent. This decision was based on the demonstrated efficacy in first-line studies, and the desire to demonstrate continued treatment benefit after progression by keeping the same dose in the second-line setting.

Those randomised to Arm A received only fluoropyrimidine/irinotecan-based chemotherapy or fluoropyrimidine/oxaliplatin-based chemotherapy. Those randomised to Arm B, also received bevacizumab therapy. All established second-line fluoropyrimidine/irinotecan and fluoropyrimidine/oxaliplatin based regimens were permitted.

6.1.1.1.5. Efficacy variables and outcomes

The main efficacy variable was: Duration of survival (time from randomisation to death from any cause) in Arm A and Arm B.

The primary efficacy outcome was the demonstration of a statistically significant improvement in OS when bevacizumab is used in combination with fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone.

Other efficacy outcomes included:

- PFS General: time from date of randomisation to day of documented disease progression or death from any cause. The differences between the two arms were tested using an unstratified log-rank test.
- Overall Response: the best response recorded from the start of the treatment until disease progression or recurrence. Response rates (CR or PR) determined at two consecutive investigator assessments conducted ≥ 4 weeks apart were compared using the chi squared test.
- PFS On treatment: time from date of randomisation to day of documented disease progression or death from any cause, provided it occurred within 28 days of last confirmed study treatment. The differences between the two arms were tested using an unstratified log-rank test. Data from patients who neither progressed nor died in this interval and those lost to follow-up were censored at the date of last tumour assessment within this time window.
- Overall survival from time of starting first-line therapy: The time interval from the earliest recorded start date to the date of death from any cause. The difference in OS between the two treatment arms was tested using an unstratified log rank test.

Exploratory efficacy variables

- Time to response: Measured from randomisation to day of documented complete reposene (CR) or partial response (PR).
- Duration of response: Measured from time that measurement criteria were met for CR/PR until disease progression or death.

Both univariate and multivariate Cox regression analyses were performed to estimate the effect of bevacizumab after adjusting for pre-specified prognostic factors for OS. The following baseline and demographic factors were used for subgroup analyses:

- Patient population (AIO KRK 0504 versus ML18147)
- First-line PFS: ≤ 9 months versus > 9 months
- First-line irinotecan-based therapy versus oxaliplatin-based therapy
- Time from last dose of bevacizumab: ≤ 42 days versus > 42 days
- The Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0/1 versus ≥ 1
- Race (White, Black, Other)
- Age (<65 versus ≥ 65)
- Sex (male versus female)
- Liver metastases (yes versus no)
- Number of organs with metastases (≤1 versus >1)

6.1.1.1.6. Randomisation and blinding methods

The second-order minimisation algorithm was used to randomise the patients, to ensure an equal distribution of prognostic factors in the two arms of the study. The prognostic factors were:

- First-line PFS: ≤ 9 months versus > 9 months
- First-line irinotecan-based versus oxaliplatin-based therapy
- Time from last dose of bevacizumab: ≤ 42 days versus > 42 days
- ECOG PS 0/1 versus 2

Eligible patients were randomised 1:1 to Arm A or Arm B, as described above.

This was an open-label study.

6.1.1.1.7. Statistical methods

The sample size was calculated to test for superiority in relation to OS. A total of 613 OS events were required based on:

- Two-sided log rank test,
- Overall 5% type 1 error and 90% power,
- OS that is exponentially distributed,
- Median OS of 10 months in Arm A and 13 months in Arm B (corresponding to Hazard Ratio 0.77, one interim analysis after 65% of the events had occurred (approximately 400 events)).

A total of 810 eligible patients will be enrolled until May 2010 to obtain the 613 OS events across both arms

The primary efficacy analysis population was the Intention-to-Treat (ITT) population (all randomised patients irrespective of whether study treatment was received). The safety population included all randomised patients who received at least one dose of study treatment. The per-protocol population included all of the ITT population who did not have any major protocol violation.

6.1.1.1.8. Participant flow

Study ML18147enrolled 820 patients in 220 sites located in 15 countries in Europe and Saudi Arabia. The first patient was enrolled in February 2006 (Protocol AIO KRK0504) and the last patient was enrolled in May 2010. Of the 820 patients, 261 were from Study AIO KRK0504 and 559 patients were subsequently enrolled in Study ML18147.

Of the randomised patients, 411 were assigned to Arm A and 409 to Arm B. In all 10 patients (Arm A: 4 and Arm B: 6) did not receive any study treatment. At data cut-off date for this analysis, 339 (82.5%) in Arm A and 317 (77.5%) in Arm B had died. Of the 164 patients who were alive at the cut-off date, 14 patients (Arm A: 6 patients, Arm B: 8 patients) remained on treatment, and 9 patients (Arm A: 2 patients, Arm B: 7 patients) were lost to follow-up.

The ITT population consisted of 819 patients (Arm A: 410, Arm B: 409). The per-protocol population consisted of 780 patients (Arm A: 397, Arm B: 383). The safety population consisted of 810 patients (Arm A: 407, Arm B: 403).

Comment: The safety population was Arm A: 409, Arm B: 401. The sponsor is to clarify this discrepancy.

6.1.1.1.9. Baseline data

The demographic data and baseline disease characteristics were well balanced between the treatment arms. The majority had received surgical treatment for their primary tumour (Arm A: 74.2%, Arm B: 75.1%). Pre- and postoperative radiotherapy had been administered to between 5 and 8% of patients in either treatment arm. The majority of patients had metastatic lesions affecting more than one organ. The incidences of previous and concomitant diseases were generally well balanced between the two arms. Deep vein thrombosis (DVT), peptic ulcer, pulmonary embolism, hypertension, diabetes, and depression were the commonest previous and concurrent diseases.

6.1.1.2. Results for the primary efficacy outcome

The study met its endpoint of a significant increase in OS (HR=0.81; 95%CI: 0.69, 0.94). The relative risk of death was reduced by 19% in patients in Arm B (bevacizumab + chemotherapy) compared with those in Arm A (chemotherapy alone). The median survival in Arm B was 1.4 months longer than in Arm A (Arm A: 9.8 months; Arm B: 11.2 months). The Kaplan-Meier plot showed the benefit in favour of Arm B appearing at approximately the second month of treatment and continuing until about the 38th month. See Table 1 and Figure 1 below. OS analysis stratified by the prognostic factors described above was consistent with the unstratified analysis. See Table 2.

Table 1. Summary of Overall Survival from randomisation (ITT population)

	Chemo (N=410)		Chemo + Bev (N=409)
Patients with event	338 (82.4 %)		317 (77.5 %)
Patients without events*	72 (17.6 %)		92 (22.5 %)
Time to event (months)			
Median#	9.8		11.2
95% CI for Median#	[9;11]		[10;12]
25% and 75%-ile#	6;16		7;20
Range##	0 to 46		0 to 44
p-Value (Log-Rank Test)		0.0062	
Hazard Ratio		0.81	
95% CI		[0.69;0.94]	

Chemo= Fluropyrimidine based chemotherapy (oxaliplatin or irinotican). Bev= bevacizumab
*Censored
Kaplan-Meier Estimate
Including Censored Observations

Figure 1. Kaplan-Meier Plots of Overall Survival from Randomisation (ITT Population)

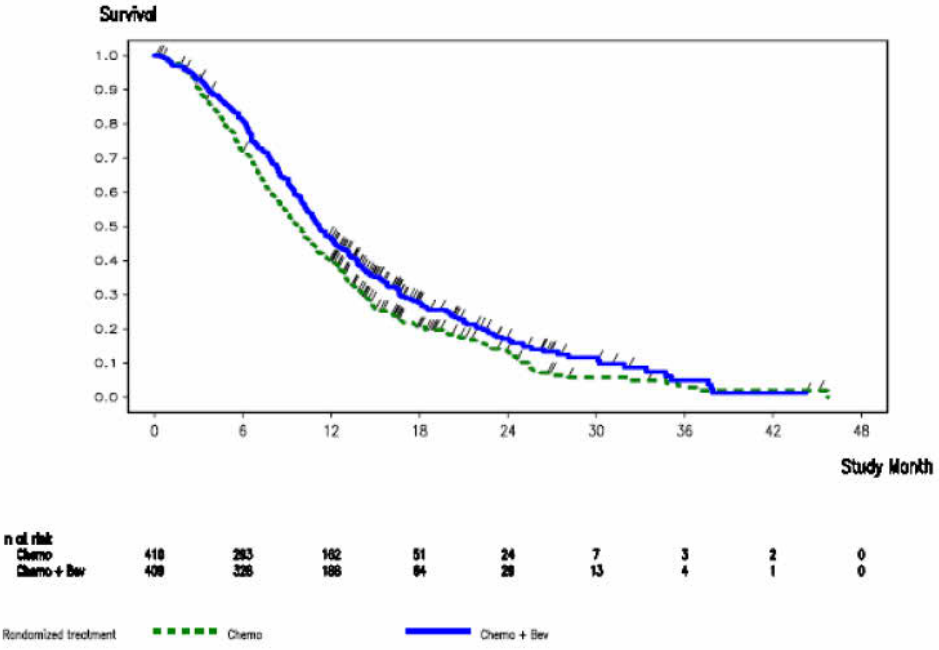

Table 2. Summary of stratified versus non-stratified log-rank test and Cox regression for Overall Survival from randomisation (ITT population)

		Cox Regression		
Chemo + Bev vs. Chemo	Log-rank test (p-value)	Hazard Ratio	95% CI	p-value
No Stratification	0.0062	0.81	[0.69;0.94]	0.0065
With Stratification*	0.0211	0.83	[0.71;0.97]	0.0213

* stratified by Oxaliplatin vs. Irinotecan-based and FL PFS (<=9M vs. >9M) and Time from Last Dose (<=42 vs. >42days) and ECOG (0 vs >=1)
Chemo= Fluropyrimidine based chemotherapy (oxaliplatin or irinotican). Bev= bevacizumab

Subgroup analysis included patient population, sex, age and first line PFS. The analysis showed a trend in support of adding bevacizumab to the fluoropyrimidine-based chemotherapy regimen. See Figure 2 and Table 3. 'Race' was excluded from the analysis because most of the reporting of 'Race' was flawed.

Figure 2. Forest Plot of Hazard Ratios for OS by Subgroup (ITT Population)

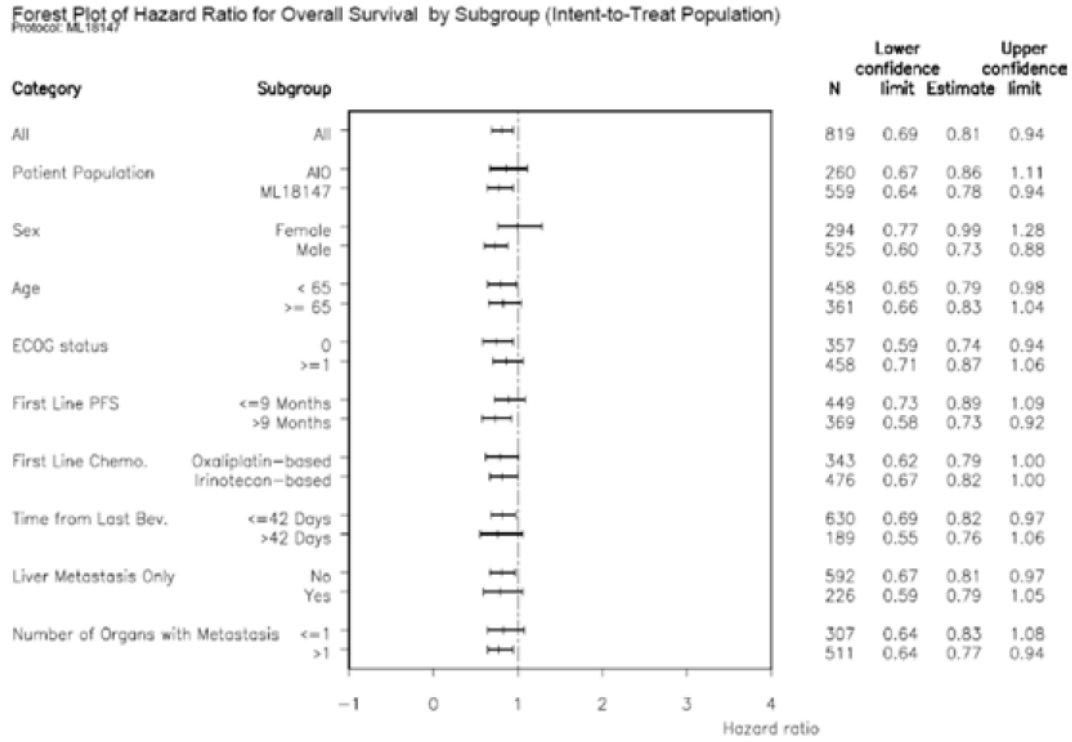

Table 3. Summary of Univariate Cox Regression Analysis for Overall Survival (ITT population)

		Covariate Effect*			Treatment Effect Adjusted for Covariate**		
Effect/Covariate	No. of Patients	Hazard Ratio	95% CI for Hazard Ratio	p-Value	Hazard Ratio	95% CI for Hazard Ratio	p-Value
Randomized treatment	819				0.81	[0.69;0.94]	0.0065
ML18147 vs AIO	819	1.01	[0.86;1.19]	0.9021	0.81	[0.69;0.94]	0.0066
Sex (Male vs. Female)	819	1.12	[0.95;1.31]	0.1637	0.81	[0.70;0.95]	0.0091
Age (<65 vs >=65)	819	1.11	[0.95;1.30]	0.1791	0.81	[0.69;0.94]	0.0069
ECOG (0 vs >=1)	815	1.41	[1.20;1.65]	<.0001	0.82	[0.70;0.95]	0.0107
FL PFS (<=9M vs. >9M)	818	0.68	[0.58;0.79]	<.0001	0.82	[0.71;0.96]	0.0137
Oxaliplatin vs. Irinotecan-based	819	1.03	[0.88;1.20]	0.7348	0.81	[0.69;0.94]	0.0064
Time from Last Dose (<=42 vs. >42days)	819	0.77	[0.64;0.93]	0.0054	0.81	[0.69;0.94]	0.0059
Liver Metastasis Only (Yes vs No)	818	0.94	[0.80;1.12]	0.5024	0.81	[0.69;0.94]	0.0059
Number of Organs with Metastasis (<=1 vs >1)	818	1.24	[1.06;1.46]	0.0077	0.80	[0.68;0.93]	0.0037

Time to Death [months] (TTMDIED) - Censoring: Censor for Overall survival (CSDIED)
* Model that includes only the covariate
** Model that includes the covariate and treatment (no interaction term)

6.1.1.3. Results for other efficacy outcomes

Progression-Free Survival (PFS): There was a statistically significant reduction by 32% in the risk of disease progression or death of patients in Arm B compared with Arm A (HR = 0.68, 95% CI: 0.59, 0.78; unstratified log-rank p-value < 0.0001) The median time to disease progression or death was longer in Arm B (5.7 months) than in Arm A (4.1 months). See Table 4 and Figure 3 below**.** The stratified PFS analysis was consistent with the un-stratified analysis. See Table 5.

Table 4. Summary of PFS

	Chemo (N=410)		Chemo + Bev (N=409)
Patients with event	394 (96.1 %)		386 (94.4 %)
Patients without events*	16 (3.9 %)		23 (5.6 %)
Time to event (months)			
Median#	4.1		5.7
95% CI for Median#	[4;4]		[5;6]
25% and 75%-ile#	2;7		3;9
Range##	0 to 27		0 to 38
p-Value (Log-Rank Test)		<.0001	
Hazard Ratio		0.68	
95% CI		[0.59;0.78]	

Time to CSPFS [months] (TTMPFS) - Censoring: Censor - First Inv PD or Death (CSPFS)
Chemo= Fluropyrimidine based chemotherapy (oxaliplatin or irinotican). Bev= bevacizumab
*Censored
Kaplan-Meier Estimate
Including Censored Observations

Figure 3. Kaplan-Meier Plot of Progression-Free Survival (General) (ITT Population)

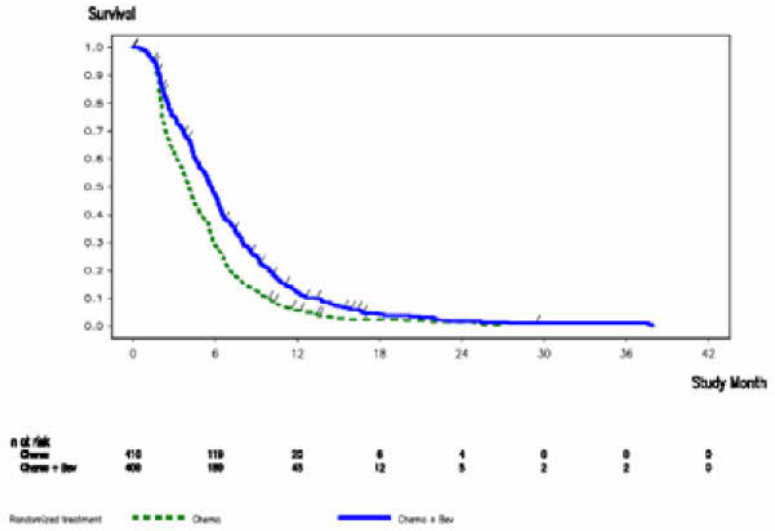

Table 5. Summary of Stratified versus non-stratified Log-Rank Test for PFS (ITT)

		Cox Regression		
Chemo + Bev vs. Chemo	Log-rank test (p-value)	Hazard Ratio	95% CI	p-value
No Stratification	<.0001	0.68	[0.59;0.78]	<.0001
With Stratification*	<.0001	0.67	[0.58;0.78]	<.0001

* stratified by Oxaliplatin vs. Irinotecan-based and FL PFS (<=9M vs. >9M) and Time from Last Dose (<=42 vs. >42days) and ECOG (0 vs >=1)
Chemo= Fluropyrimidine based chemotherapy (oxaliplatin or irinotican). Bev= bevacizumab

Progression-Free Survival on Treatment: Results of PFS-On Treatment were consistent with the results obtained for PFS (HR=0.63; 95% CI: 0.53, 0.74). See Figure 4.

Overall Response: The response rate (confirmed CR or confirmed PR) was 5.4% in Arm B and 3.9% in Arm A. The difference between the two arms was not significant (p=0.3113). See Table 6.

Figure 4. KM Plots of PFS (On treatment) (ITT Population)

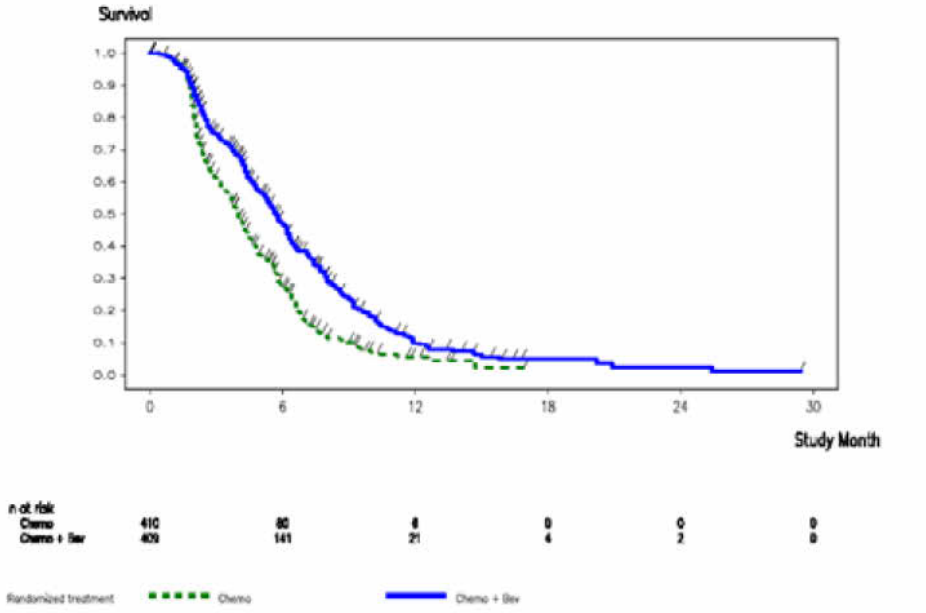

Table 6. Summary of best Overall Response

	Chemo (N=406)		Chemo + Bev (N=404)
Responders$	16 (3.9 %)		22 (5.4 %)
Non-Responders	390 (96.1 %)		382 (94.6 %)
95% CI for Response Rates*	[2.3; 6.3]		[3.4; 8.1]
Difference in Response Rates		1.50	
95% CI for Difference in Response Rates#		[-1.5; 4.5]	
p-Value (Chi-squared Test)		0.3113	
p-Value (CMH Test)		0.4315	
Complete Response (CR)	2 (0.5 %)		1 (0.2 %)
95% CI for CR Rates*	[0.1; 1.8]		[0.0; 1.4]
Partial Response (PR)	14 (3.4 %)		21 (5.2 %)
95% CI for PR Rates*	[1.9; 5.7]		[3.2; 7.8]
Stable Disease (SD)	204 (50.2 %)		253 (62.6 %)
95% CI for SD Rates*	[45.3; 55.2]		[57.7; 67.4]
Progressive Disease (PD)	142 (35.0 %)		87 (21.5 %)
95% CI for PD Rates*	[30.3; 39.8]		[17.6; 25.9]
Missing (No Response Assessment)	44 (10.8 %)		42 (10.4 %)

BORESP (BORESP)
* 95% CI for one sample binomial using Pearson-Clopper method
# Approximate 95% CI for difference of two rates using Hauck-Anderson method
Chemo= Fluropyrimidine based chemotherapy (oxaliplatin or irinotican). Bev= bevacizumab
$ Patients with best overall response of confirmed CR or PR
CMH= Cochran-Mantel-Haenszel stratified by : first line CTx (irinotecan-based vs. oxaliplatin-based therapy), first-line PFS (<= 9 months, > 9 months), time from last bevacizumab treatment at baseline (<= 42 days, > 42 days), and ECOG PS at baseline (0, >= 1)

Other analyses: The study was not planned for analyses such as the 'Overall response from start of first-line therapy'. The results therefore cannot be considered. A valid estimation of 'Time to response' and 'Duration of response' was not possible because the number of patients with a response (CR or PR) was small.

KRAS status: Subgroup analysis by KRAS mutational status was an exploratory exercise that was not powered to detect a statistically significant difference between the two arms of treatment.

Of the 616 patients who had conclusive KRAS genotype data, 300 (49%) demonstrated a mutation. Arm A had 45.2% and Arm B, 52.1% of the 300 patients with mutant KRAS. Patients with mutant KRAS had a poorer outcome. See Table 12, page 17, part B.

6.2. Evaluator's Conclusions on Clinical Efficacy

This was a prospective, randomised, open-label, multinational, controlled, Phase III study. Concerns were raised about potential bias possibly being introduced as a result of the unplanned modifications to the protocol when sponsorship was changed from AIO to Roche in 2008. The concerns were addressed and included the use of unstratified log rank test as the primary analysis. The impact of sequential enrolment in the AIO KRK 0504 and ML18147 studies was also addressed in the analysis plan. The sponsor used the second-order minimisation algorithm to randomise the patients 1:1, to ensure an equal distribution of prognostic factors in the two arms of the study. Randomisation was stratified by the four factors that were described. The majority of patients in the two arms were ECOG PS ≥ 1 at baseline, had received irinotecan-based chemotherapy as first-line treatment, had progressed on first-line treatment within nine months and had received their last dose of bevacizumab as first-line treatment within 42 days of randomisation. The primary efficacy endpoint was changed from PFS to OS, which required larger patient populations. The sample size was accordingly increased to power this change. While the traditional endpoint for assessing efficacy in first-line chemotherapies for advanced cancer is OS, it is open to confounding by the effects of second-line therapies. The study protocol therefore required that monitoring was continued to check on subsequent anti-cancer therapy.

The study met its primary efficacy endpoint of a significant increase in OS in patients treated with bevacizumab in combination with chemotherapy (fluoropyrimidine/irinotecan- or fluoropyrimidine/oxaliplatin-based chemotherapy regimens) over patients treated with chemotherapy alone. The median duration of survival increase was 1.4 months. The results however were short of the expected 30% improvement in median time to death in the bevacizumab-containing arm. OS analysis stratified by the prognostic factors was consistent with the unstratified analysis. The results were supported by the results of subgroup analyses.

The secondary end-point was met, by a statistically significant reduction in disease progression in the bevacizumab plus chemotherapy arm compared with the chemotherapy alone arm. The Objective Response Rate was higher in the bevacizumab plus chemotherapy arm but the small difference between the two arms was not statistically significant.

Subgroup analysis by KRAS mutational status did not provide evidence to suggest a valid treatment difference between patients with wild-type versus mutant KRAS mCRC tumours.

7. Clinical safety

7.1. Pivotal Study That Assessed Safety as a Primary Outcome

7.1.1. Study ML18147

7.1.1.1. Patient Exposure

The median duration of exposure in Arm B (bevacizumab+chemotherapy) was longer by a month than in Arm A (chemotherapy alone). There were no significant differences in dose intensity between the two arms. See Table 7 below.

Table 7 Extent of Exposure to Study Drug (Safety Population)

	Chemo n = 409		Chemo + Bev n = 401	
	Treatment duration (months)[a] median (range)	Dose Intensity[b] mean ± SEM	Treatment duration (months)[a] median (range)	Dose Intensity[b] mean ± SEM
Overall	3.22 (0.03-20.07)	–	4.18 (0.03-29.54)	–
Chemotherapy	3.22 (0.03-20.07)	–	4.15 (0.03-29.54)	–
oxaliplatin	2.80 (0.03-12.96)	79.5 ± 1.4	3.49 (0.03-29.08)	74.0 ± 1.6
irinotecan	3.26 (0.03-20.07)	67.5 ± 1.8	4.18 (0.03-25.89)	62.8 ± 2.0
capecitabine	2.63 (0.13-13.36)	78.6 ± 2.1	3.95 (0.23-26.32)	76.6 ± 2.4
5-FU bolus	3.03 (0.03-20.07)	70.9 ± 1.9	3.82 (0.03-29.54)	69.8 ± 1.9
5-FU continuous	3.03 (0.03-20.07)	76.3 ± 1.9	4.18 (0.03-29.54)	71.5 ± 1.7
Bevacizumab	–	–	3.95 (0.03-29.54)	86.3 ± 0.97

SEM = standard error of the mean.

[a] Duration in months from the first dose of study treatment (bevacizumab or chemotherapy) until discontinuation of all study drugs.

[b] Defined as total cumulative dose/planned dose x 100%.

7.1.1.2. Adverse Events (AEs)

Almost all the patients in the two arms of the study equally experienced at least one adverse event of any grade. The majority of adverse events were Grade 1 or 2 (≥ 83% of total adverse events), while the incidence of Grades 3-5 adverse events was higher in Arm B (57.5% in Arm A versus 63.6% in Arm B). See Table 8 below.

The most common adverse events of any grade (incidence ≥ 20%) were diarrhoea, nausea, vomiting, asthenia, neutropaenia, fatigue, abdominal pain and constipation. See Table 9. Adverse events that were commoner (≥ 5%) in Arm B were neutropaenia, mucosal inflammation, pyrexia and hypertension. Diarrhoea and epistaxis were also commoner (incidence ≥ 10%) in Arm B See Table 10 below.

Table 8. Summary of Overall Safety (Safety Population)

Parameter	Chemo n = 409	Chemo + Bev n = 401
Patients with:		
Any AE	403 (98.5%)	394 (98.3%)
Serious AE	137 (33.5%)	129 (32.2%)
Grade ≥ 3	235 (57.5%)	255 (63.6%)
AE leading to death (Grade 5)	15 (3.7%) [a]	14 (3.5%) [a]
AE leading to discontinuation of any treatment	36 (8.8%)	63 (15.7%)
AE leading to discontinuation of chemotherapy	36 (8.8%)	53 (13.2%) [b]
AE leading to discontinuation of bevacizumab	N/A	58 (14.5%) [c]
Adverse events of special interest:		
Any AESI	85 (20.8%)	163 (40.6%) [e]
Any AESI, [d] Grade ≥ 3	24 (5.9%)	47 (11.7%)
Hypertension, Grade ≥ 3	5 (1.2%)	7 (1.7%)
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	3 (0.7%)
GI perforation, Grade ≥ 3	3 (0.7%)	7 (1.7%)
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-chemotherpy; 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 eCRF; [b] Refers to discontinuation of chemotherapy only (5 patients) or Chemo+Bev (48 patients); [c]refers to discontinuation of Bev only (10 patients) or Bev+ Chemo (48 patients); [d] patients may report multiple adverse events of special interest; [e]includes 4 patients where a single reported event was considered as two distinct AESI

Table 9. Summary of Adverse Events with an Incidence Rate of ≥ 5% (Safety Population)

Adverse Event	CHEMO N = 409 No. (%)	CHEMO + BEV N = 401 No. (%)	TOTAL N = 810 No. (%)
DIARRHOEA	183 (44.7)	238 (59.4)	421 (52.0)
NAUSEA	170 (41.6)	178 (44.4)	348 (43.0)
VOMITING	107 (26.2)	121 (30.2)	228 (28.1)
ASTHENIA	106 (25.9)	106 (26.4)	212 (26.2)
NEUTROPENIA	87 (21.3)	116 (28.9)	203 (25.1)
FATIGUE	81 (19.8)	94 (23.4)	175 (21.6)
ABDOMINAL PAIN	83 (20.3)	91 (22.7)	174 (21.5)
CONSTIPATION	74 (18.1)	82 (20.4)	156 (19.3)
DECREASED APPETITE	77 (18.8)	79 (19.7)	156 (19.3)
PARAESTHESIA	67 (16.4)	78 (19.5)	145 (17.9)
ALOPECIA	68 (16.6)	71 (17.7)	139 (17.2)
MUCOSAL INFLAMMATION	44 (10.8)	77 (19.2)	121 (14.9)
THROMBOCYTOPENIA	51 (12.5)	70 (17.5)	121 (14.9)
PYREXIA	49 (12.0)	70 (17.5)	119 (14.7)
ANAEMIA	60 (14.7)	42 (10.5)	102 (12.6)
NEUROPATHY PERIPHERAL	52 (12.7)	45 (11.2)	97 (12.0)
POLYNEUROPATHY	43 (10.5)	51 (12.7)	94 (11.6)
EPISTAXIS	19 (4.6)	70 (17.5)	89 (11.0)
LEUKOPENIA	35 (8.6)	54 (13.5)	89 (11.0)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	36 (8.8)	49 (12.2)	85 (10.5)
DYSPNOEA	38 (9.3)	37 (9.2)	75 (9.3)
STOMATITIS	32 (7.8)	40 (10.0)	72 (8.9)
HYPERTENSION	25 (6.1)	45 (11.2)	70 (8.6)
COUGH	31 (7.6)	35 (8.7)	66 (8.1)
ABDOMINAL PAIN UPPER	23 (5.6)	38 (9.5)	61 (7.5)
WEIGHT DECREASED	24 (5.9)	35 (8.7)	59 (7.3)
PERIPHERAL SENSORY NEUROPATHY	21 (5.1)	32 (8.0)	53 (6.5)
BACK PAIN	20 (4.9)	30 (7.5)	50 (6.2)
NASOPHARYNGITIS	18 (4.4)	28 (7.0)	46 (5.7)
OEDEMA PERIPHERAL	25 (6.1)	20 (5.0)	45 (5.6)
HEADACHE	15 (3.7)	29 (7.2)	44 (5.4)
HYPOKALAEMIA	19 (4.6)	25 (6.2)	44 (5.4)
URINARY TRACT INFECTION	22 (5.4)	20 (5.0)	42 (5.2)
NEUROTOXICITY	13 (3.2)	26 (6.5)	39 (4.8)

Investigator text for Adverse Events encoded using MedDRA version 14.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Adverse events reporting period includes all events with onset date reported following first study drug treatment and within 28 days
of the last study treatment.
Chemo= Fluropyrimidine based chemotherapy (oxaliplatin or irinotican). Bev= bevacizumab

Table 10. Summary of Adverse Events with Difference in Incidence ≥ 5% between Treatment Arms (Safety Population)

Superclass Term/ Preferred Term	Chemo N= 409	Chemo + Bev N= 401
GASTROINTESTINAL DISORDERS		
DIARRHOEA	183 (44.7%)	238 (59.4%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
MUCOSAL INFLAMMATION	44 (10.8%)	77 (19.2%)
PYREXIA	49 (12.0%)	70 (17.5%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
NEUTROPENIA	87 (21.3%)	116 (28.9%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
EPISTAXIS	19 (4.6%)	70 (17.5%)
VASCULAR DISORDERS		
HYPERTENSION	25 (6.1%)	45 (11.2%)

V

Adverse events reporting period includes all events with onset date reported following first study drug treatment and within 28 days of the last study treatment.
Chemo= Fluropyrimidine based chemotherapy (oxaliplatin or irinotican). Bev= bevacizumab

The most frequently reported Grade 3-5 adverse events were neutropaenia, diarrhoea, and asthenia. The Grade 3-5 adverse events that were commoner (≥ 2% higher) in Arm B than in Arm A included neutropaenia and mucosal inflammation. See Table 11.

Table 11. Summary of Most Frequent Grade 3-5 Adverse Events (Incidence ≥ 2%) (safety Population)

Adverse Event	CHEMO N = 409 No. (%)	CHEMO + BEV N = 401 No. (%)	TOTAL N = 810 No. (%)
NEUTROPENIA	52 (12.7)	65 (16.2)	117 (14.4)
DIARRHOEA	34 (8.3)	40 (10.0)	74 (9.1)
ASTHENIA	17 (4.2)	23 (5.7)	40 (4.9)
LEUKOPENIA	12 (2.9)	16 (4.0)	28 (3.5)
ABDOMINAL PAIN	12 (2.9)	15 (3.7)	27 (3.3)
VOMITING	13 (3.2)	14 (3.5)	27 (3.3)
FATIGUE	10 (2.4)	14 (3.5)	24 (3.0)
NAUSEA	11 (2.7)	13 (3.2)	24 (3.0)
DYSPNOEA	12 (2.9)	6 (1.5)	18 (2.2)
POLYNEUROPATHY	6 (1.5)	12 (3.0)	18 (2.2)
PULMONARY EMBOLISM	8 (2.0)	10 (2.5)	18 (2.2)
HYPOKALAEMIA	8 (2.0)	9 (2.2)	17 (2.1)
MUCOSAL INFLAMMATION	4 (1.0)	13 (3.2)	17 (2.1)
NEUROPATHY PERIPHERAL	10 (2.4)	5 (1.2)	15 (1.9)
DECREASED APPETITE	9 (2.2)	5 (1.2)	14 (1.7)
SUBILEUS	2 (0.5)	8 (2.0)	10 (1.2)

Investigator text for Adverse Events encoded using MedDRA version 14.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Adverse events reporting period includes all events with onset date reported following first study drug treatment and within 28 days
of the last study treatment.

7.1.1.2.1. Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) were those associated with bevacizumab treatment. They were, as expected, more frequently reported in Arm B (40.6%) than in Arm A (20.8%). Hypertension, proteinuria, bleeding, abscesses and fistulae, gastrointestinal (GI) perforation, congestive heart failure, thrombo-embolic events (venous and arterial), and wound healing complications are known adverse events associated with bevacizumab therapy. Most of these were Grades 1-2. There was a higher proportion of patients with Grade 3-5 AESIs in Arm B compared with Arm A. The difference in incidence between the arms for each individual AESI was < 2%. See Table 8.

7.1.1.2.2. Hypertension

The incidence of hypertension was higher in Arm B than in Arm A (11.5% versus 6.6%). The majority of hypertension events were of Grades 1/2 severity. One patient in Arm A and 2 patients in Arm B had hypertension that was reported as a serious AE (SAE). In all, hypertension of any grade led to discontinuation of bevacizumab in 2 patients and interruption of bevacizumab dosing in 5 patients. See Table 12.

Table 12. Summary of Hypertension (Safety Population)

	Chemo n = 409	Chemo + Bev n = 401
Patients with at least one adverse event of:		
Hypertension (included preferred terms)	27 (6.6%)	46 (11.5%)
Grade 3-5 hypertension [a]	5 (1.2%)	7 (1.7%)
Hypertension leading to death (Grade 5)	0	0
Serious hypertension	1 (0.2%)	2 (0.5%) [b]
Hypertension resulting in discontinuation of bevacizumab	N/A	2 (0.5%) [c]
Hypertension leading to dose modification of bevacizumab	N/A	5 (1.2%) [d]
Hypertension occurring > 28 days after last study treatment	1 (0.2%) [e]	1 (0.2%) [e]

[a] Includes the preferred terms hypertension, hypertensive crisis and hypertensive emergency; [b] One patient with Grade 2 hypertension and one patient with Grade 4 hypertensive emergency; [c]One patient with Grade 4 hypertensive emergency and one patient with Grade 3 hypertension; [d] One patient Grade 3 and four patients with Grade 2.; [e] One patient Grade 1 in the Chemo arm and one patient in the Chemo+Bev arm.

7.1.1.2.3. Proteinuria

Proteinuria was commoner in Arm B than in Arm A (5% versus 1%). The majority of the proteinuria events were of Grades 1/2 severity. None of the events were reported as SAEs. See Table 13.

Table 13. Summary of Proteinuria (Safety Population)

	Chemo n = 409	Chemo + Bev n = 401
Patients with at least one adverse event of:		
Proteinuria [a]	4 (1.0%)	20 (5.0%)
Grade 3-5 proteinuria	0	3 (0.7%) [b]
Proteinuria leading to death (Grade 5)	0	0
Serious proteinuria	0	0
Proteinuria that resulted in discontinuation of bevacizumab	0	1 (0.2%) [c]
Proteinuria leading to dose modification of bevacizumab	0	8 (2.0%)
Proteinuria occurring > 28 days after last study treatment	0	0

[a] includes the preferred terms Proteinuria and Protein urine present; [b]Grade 3 Proteinuria in three patients; [c]One patient

7.1.1.2.4. Arterial Thrombo-Embolic (ATE) Events

ATE was reported in 4 patients in Arm A and in 3 patients in Arm B. All 4 ATE events in Arm A and 2 events in Arm B were reported as SAEs. The only case of ATE leading to death (cerebrovascular accident) was in Arm B. Bevacizumab was discontinued in a patient in Arm B who suffered Grade 3 myocardial infarction. See Table 14.

Table 14. Summary of Arterial Thromboembolic Events (Safety Population)

	Chemo n = 409	Chemo + Bev n = 401
Patients with at least one adverse event of:		
ATE	4 (1.0%)	3 (0.7%)
Grade 3-5 ATE	2 (0.5%)	2 (0.5%)
ATE leading to death (Grade 5)	0	1 (0.2%) [a]
Serious ATE	4 (1.0%)	2 (0.5%)
ATE that resulted in discontinuation of bevacizumab	N/A	1 (0.2%) [b]
ATE leading to dose modification of bevacizumab	N/A	0
ATE occurring > 28 days after last study treatment	0	1 (0.2%) [c]

ATE=arterial thromboembolic event; N/A=not applicable; [a]Grade 5 cerebrovascular accident in one patient; [b] one patient discontinued Chemo+Bev because of Grade 3 Myocardial Infarction; [c] One patient had Grade 3 cerebrovascular accident with onset > 28 days after last study treatment.

7.1.1.2.5. Venous Thrombo-Embolism (VTE) Events

The incidence of VTEs was greater in Arm B than in Arm A (5.7% versus 3.9%). The majority were Grade ≥ 3 VTEs, and were reported in 12 patients (2.9%) in Arm A and in 19 patients (4.7%) in Arm B. The VTEs included pulmonary embolism, deep vein thromboses, jugular vein thrombosis and venous thrombosis. The VTEs were reported as SAEs in 6 patients (1.5%) in Arm A and 10 patients (2.5%) in Arm B. See Table 15.

Table 15. Summary of Venous Thromboembolic Events (Safety Population)

	Chemo n = 409	Chemo + Bev n = 401
Patients with at least one adverse event of:		
VTE (any)	16 (3.9%)	23 (5.7%)
Grade 3-5 VTE	12 (2.9%) [a]	19 (4.7%)
VTE leading to death (Grade 5)	2 (0.5%)	0
Serious VTE	6 (1.5%)	10 (2.5%)
VTE that resulted in discontinuation of bevacizumab	N/A	6 (1.5%)
VTE leading to dose modification of bevacizumab	N/A	2 (0.5%)
VTE occurring > 28 days after last study treatment	0	1 (0.2%) [b]

N/A=not applicable; VTE=venous thromboembolic event; a One patient had 2 VTEs of Grade 4 pulmonary embolism and Grade 3 venous thrombosis limb; b One patient Grade 3 venous thrombosis.

7.1.1.2.6. Bleeding/Haemorrhage

Bleeding events were commoner in Arm B (25.7% of patients) than in Arm A (8.6% of patients). The great disparity in the incidence of bleeding events was attributed to a high incidence of epistaxis in Arm B. The incidence of serious bleeding events was small (Arm A: 3 patients; Arm B: 8 patients). There were two deaths reported in Arm B. See Table 16.

Table 16 Summary of Bleeding/Haemorrhage Events (Safety Population)

	Chemo n = 409	Chemo + Bev n = 401
Patients with at least one adverse event of:		
Bleeding/hemorrhage	35 (8.6%)	103 (25.7%)
Grade 3–5 bleeding/hemorrhage	1 (0.2%)	8 (2.0%)
Bleeding/hemorrhage leading to death (Grade 5)	0	2 ((0.5%) [a]
Serious bleeding/hemorrhage	3 (0.7%)	8 (2.0%)
Bleeding/hemorrhage resulting in discontinuation of bevacizumab	N/A	2 (0.5%) [b]
Bleeding/hemorrhage leading to dose modification of bevacizumab	N/A	8 (2.0%)
Bleeding/hemorrhage occurring > 28 days after last study treatment	1 (0.2%) [c]	3 (0.7%) [c]

N/A=not applicable; [a]One patient upper GI haemorrhage and one patient cerebrovascular accident; [b] One patient Grade 3 GI haemorrhage abd one patient Grade 3 post procedural haemorrhage; [c] Chemo arm: One patient Grade 1 epistaxis and Chemo+ Bev arm: one patient Grade 1 epistaxis, one patient Grade 3 cerebrovascular accident and one patient Grade 2 metrorrhagia.

7.1.1.2.7. Gastrointestinal Perforation (including absesses and fistulae)

Gastrointestinal perforations were reported in 3 patients (0.7%) in Arm A and in 11 patients (2.7%) in Arm B. All but one were Grade ≥3 perforations (Arm A: 3; Arm B: 7). One intestinal perforation in each arm led to death. See Table 17.

Table 17 Summary of Gastrointestinal Perforation - Including Abscess and Fistulae (Safety Population)

	Chemo n = 409	Chemo + Bev n = 401
Patients with at least one adverse event of:		
Any grade GI perforation	3 (0.7%)	11 (2.7%)
Grade 3–5 GI perforation	3 (0.7%)	7 (1.7%)
GI perforation leading to death (Grade 5)	1 (0.2%) [a]	1 (0.2%) [a]
Serious GI perforation	3 (0.7%)	8 (2.0%)
GI perforation that resulted in discontinuation of bevacizumab	N/A	4 (1.0%)
GI perforation leading to dose modification of bevacizumab	N/A	6 (1.5%)
GI perforation occurring > 28 days after last study treatment	0	1 (0.2%) [b]

N/A=not applicable; [a] One patient had intestinal perforation in the Chemo arm and one patient had intestinal perforation in the Chemo+Bev arm; [b] One patient had Grade 5 intestinal perforation.

7.1.1.2.8. Fistulae (non-gastrointestinal)

Five fistulae (3 enterovesicular fistulae, 1biliary fistula, 2 urogenital fistulae) were reported in Arm B and none in Arm A. Bevcizumab was either discontinued or interrupted. See Table 18.

Table 18 Summary of Abscesses and Fistulae (Safety Population)

	Chemo n = 409	Chemo + Bev n = 401
Patients with at least one adverse event of:		
Any grade abscesses/fistulae	0	5 (1.2%)
Grade 3-5 abscesses/fistulae	0	3 (0.7%)
Abscesses/fistulae leading to death (Grade 5)	0	0
Serious abscesses/fistulae	0	3 (0.7%)
Abscesses/fistulae resulting in discontinuation of bevacizumab	N/A	2 (0.5%)
Abscesses/fistulae leading to dose modification of bevacizumab	N/A	3 (0.7%)
Abscesses/fistulae occurring > 28 days after last study treatment	0	0

N/A = not applicable.
[a] Excludes GI abscesses and fistulae.

7.1.1.2.9. Wound healing complications

One patient in Arm A and 4 patients in Arm B reported wound healing complications. Chemotherapy and not bevacizumab was considered to be the cause of the problem in each case and was resolved by discontinuing chemotherapy. See Table 19.

Table 19 Summary of Wound Healing Complications (Safety Population)

	Chemo n = 409	Chemo + Bev n = 401
Patients with at least one adverse event of:		
Any grade WHC	1 (0.2%)	4 (1.0%)
Grade 3-5 WHC	1 (0.2%)	1 (0.2%)
WHC leading to death (Grade 5)	0	0
Serious WHC	1 (0.2%)	0
WHC that resulted in discontinuation of bevacizumab	N/A	0
WHC leading to dose modification of bevacizumab	N/A	0
WHC occurring > 28 days after last study treatment	0	0

N/A = not applicable; WHC = wound healing complications.

7.1.1.2.10. Congestive Cardiac Failure

Two patients in Arm A and 1 patient in Arm B developed CCF. There were no deaths due to CCF. See Table 20.

Table 20 Summary in Congestive Heart Failure (Safety Population)

	Chemo n = 409	Chemo + Bev n = 401
Patients with at least one adverse event of:		
Any grade CHF	2 (0.5%)	1 (0.2%)
Grade 3–5 CHF	2 (0.5%)	0
CHF leading to death (Grade 5)	0	0
Serious CHF	1 (0.2%)	0
CHF that resulted in discontinuation of bevacizumab	N/A	0
CHF leading to dose modification of bevacizumab	N/A	0
CHF occurring > 28 days after last study treatment	0	0

CHF = congestive heart failure; N/A = not applicable.

7.1.1.3. Deaths

At the time of data cut-off, 340 patients (83%) in Arm A and 310 patients (77%) in Arm B had died. The major cause of death was disease progression. The proportion of patients who died from causes other than disease progression was comparable between the two arms of the study (Arm A: 5.4%; Arm B: 5.7%). The adverse events related to study treatment, leading to death included intestinal perforation, general physical health deterioration and acute pre-renal failure in Arm A, and upper GI haemorrhage, sudden death, cerebrovascular accident and neutropaenia in Arm B. See Table 21.

Table 21 Summary of Adverse Events Leading to Death (Safety Population)

Patients with Grade 5 Adverse Events of:	Date of Onset	Durat. in Days	Last Txt Day	Day of Death	Relat. to Trial Txt
Chemo arm					
Intestinal obstruction	38	15	14	52	no
Ileus	36	12	44	57	no
Intestinal perforation	42	≤ 1	35	42	yes
General physical health deterioration	77	3	72	79	yes
Sudden cardiac death	13	≤ 1	1	13	no
Pneumonia primary atypical	196	10	190	205	no
Septic shock	64	≤ 1	58	64	no
Pulmonary embolism	56	≤ 1	53	56	no
	1	≤ 1	1	1	no
Lung disorder	77	15	79	91	no
Acute prerenal failure	13	2	4	14	yes
Chemo + Bev arm					
Subileus	280	48	275	327	no
	6	28	22	33	no
Intestinal perforation	106	2	106	107	no
Enteritis	49	7	44	55	no
Upper gastrointestinal hemorrhage	21	2	14	22	yes
Multi organ failure	8	16	16	23	no
Sudden death	28	≤ 1	17	28	yes
Cerebrovascular accident	276	6	261	281	yes
Neutropenia	614	3	610	616	yes
Dyspnea	77	≤ 1	76	77	no
	91	18	72	108	no

[information redacted]

7.1.1.4. Serious Adverse Events

The incidences of serious adverse events were 33.5% in Arm A and 32.2% in Arm B. The commonly reported SAEs were diarrhoea, pyrexia, abdominal pain, neutropaenia, vomiting, pulmonary embolism, sub-ileus and drug hypersensitivity. The distribution between the two arms was similar. See Table 22.

Table 22 Summary of Serious Adverse Events Affecting ≥ two patients (> 0.5%) in Either Treatment Arm (Safety Population)

	Chemo n = 409	Chemo + Bev n = 401
Patients with any serious adverse event	137 (33.5%)	129 (32.2%)
Patients with at least one serious adverse event of:		
Diarrhea	16 (3.9%)	13 (3.2%)
Pyrexia	11 (2.7%)	7 (1.7%)
Abdominal pain	9 (2.2%)	6 (1.5%)
Neutropenia	7 (1.7%)	8 (2.0%)
Vomiting	4 (1.0%)	7 (1.7%)
Pulmonary embolism	4 (1.0%)	7 (1.7%)
Subileus	2 (0.5%)	7 (1.7%)
Infection	4 (1.0%)	3 (0.7%)
Disease progression	4 (1.0%)	3 (0.7%)
Febrile neutropenia	4 (1.0%)	3 (0.7%)
Drug hypersensitivity	1 (0.2%)	5 (1.2%)
Sepsis	4 (1.0%)	2 (0.5%)
Cholestasis	4 (1.0%)	2 (0.5%)
Intestinal obstruction	4 (1.0%)	2 (0.5%)
Ileus	4 (1.0%)	1 (0.2%)
Intestinal perforation	1 (0.2%)	4 (1.0%)
Pneumonia	2 (0.5%)	3 (0.7%)
Abdominal hernia	3 (0.7%)	3 (0.7%)
Dehydration	3 (0.7%)	1 (0.2%)
Device related infection	1 (0.2%)	3 (0.7%)
General physical health	1 (0.2%)	3 (0.7%)
Enteritis	0	3 (0.7%)
Nausea	0	3 (0.7%)
Deep vein thrombosis	0	3 (0.7%)

7.1.1.5. Discontinuation Due To Adverse Events

A greater proportion of patients in Arm B discontinued any component of trial treatment (15.7%) than in Arm A (8.8%). In Arm B, 58 patients discontinued bevacizumab treatment. Of these, 10 continued with chemotherapy and the rest discontinued both bevacizumab and chemotherapy at the same time. See Table 8. The commonest reasons for discontinuing bevacizumab were thrombocytopaenia (5 patients), diarrhoea (4 patients), intestinal perforation, sub-ileus, asthenia and pulmonary embolism (3 patients each), neutropaenia, deep vein thrombosis and dyspnoea (2 patients each). Hypertension was the cause of discontinuation of bevacizumab in one patient.

7.1.2. Laboratory Tests

There were no significant differences between the treatment arms in shifts from a lower grade to a higher grade (Grades 3 or 4) in haematological or biochemical parameters during treatment. The commonest post baseline shifts were in relation to neutrophil count, alkaline

phosphatase, white blood cell counts (WBC), bilirubin and lactose dehydrogenase (LDH). See Tables 23 and 24.

Table 23 Summary of Treatment-Emergent Grade 3 or 4 Laboratory Haematology Test Values (Shift Table)

	Chemo n = 409			Chemo + Bev n = 401		
		Shift to			Shift to	
	n [a]	Grade 3 [b] n (%)	Grade 4 [b] n (%)	n [a]	Grade 3 [b] n (%)	Grade 4 [b] n (%)
Hematology						
↓ Hemoglobin	402	6 (1.5%)	0	397	3 (0.8%)	0
↓ WBC	402	17 (4.2%)	3 (0.7%)	397	20 (5.0%)	2 (0.5%) [c]
↓ Platelets	402	5 (1.2%)	2 (0.5%)	397	5 (1.3%)	1 (0.3%)
↓ Neutrophils	381	30 (7.9%)	18 (4.7%) [d]	383	45 (11.7%)	19 (5.0%)

Only the most severe grade is counted for patients reporting multiple occurrence of the same laboratory abnormality.

[a] Number of patients with at least one post-baseline evaluation.

[b] Rates includes patients with baseline value reported as Grade 0, 1, 2 or missing and a Grade 3 or 4 during treatment (does not include patients with Grade 3 or 4 value at baseline).

The following patients were not included in the table as their hematology laboratory test values were elevated at baseline:

[c] One additional patient had Grade 4 low WBC at baseline.

[d] Two additional patients had Grade 4 neutropenia at baseline.

Table 24 Summary of Treatment-Emergent Grade 3 or 4 Laboratory Biochemistry Test Values

	Chemo n = 409			Chemo + Bev n = 401		
		Shift to			Shift to	
	n [a]	Grade 3 [b] n (%)	Grade 4 [b] n (%)	n [a]	Grade 3 [b] n (%)	Grade 4 [b] n (%)
Coagulation						
↑ PT	153	0 [c]	0	180	1 (0.6%) [c]	0
↑ PTT	236	8 (3.4%) [d]	0	241	7 (2.9%) [d]	0
Heart Function						
↑ LDH	379	25 (6.6%) [e]	0	380	12 (3.2%) [e]	0
Liver Function						
↑ ALP	386	36 (9.3%) [f]	0	387	40 (10.3%) [f]	0
↑ ALAT	389	6 (1.5%)	0	391	6 (1.5%)	0
↑ Bilirubin	387	18 (4.7%)	3 (0.8%)	391	16 (4.1%)	3 (0.8%)
Renal Function						
↑ Creatinine	391	4 (1.0%)	0	392	2 (0.5%)	0

ALAT = alanine aminotransferase; ALP = alkaline phosphatase; PTT = partial thromboplastin time.

Only the most severe grade is counted for patients reporting multiple occurrence of the same laboratory abnormality.

[a] Number of patients with at least one post-baseline evaluation.

[b] Rates includes patients with baseline value reported as Grade 0, 1, 2 or missing and a Grade 3 or 4 during treatment (does not include patients with Grade 3 or 4 value at baseline).

The following patients were not included in the table as their biochemistry laboratory test values were elevated at baseline:

[c] One additional patient in the Chemo arm and 1 patient in the Chemo + Bev arm had had Grade 3 PT (normalized ratio) at baseline.

[d] Four additional patients in the Chemo arm and 3 patients in the Chemo + Bev arm had Grade 3 partial thromboplastin time at baseline.

[e] Eleven additional patients in the Chemo arm and 4 patients in the Chemo + Bev arm had Grade 3 elevated LDH at baseline.

[f] Four additional patient in the Chemo arm and eight patients in the Chemo + Bev arm had Grade 3 elevated ALP at baseline.

7.1.3. Vital Signs

There were no marked changes from baseline readings for mean diastolic and systolic blood pressure (BP).

7.1.4. ECOG Performance Status

The ECOG PS declined over the course of the study. The decline was equal in the two arms of the study.

7.2. Evaluator's Overall Conclusions on Clinical Safety

All the safety evaluations were performed on the safety population. The duration of exposure was slightly longer in Arm B but the dose intensity of chemotherapy between the two arms was similar. The frequency of adverse events, of any severity, was similar in the two arms of the study. Many of the commonly reported adverse events (diarrhoea, vomiting, neutropaenia, fatigue, abdominal pain and constipation) were in keeping with the adverse event profiles of the chemotherapy agents. Adverse events associated with bevacizumab were examined under '*Adverse events special interest*'. As expected, they were reported more frequently in Arm B (40.6% versus 20.8%). The large disparity was attributed to a higher incidence of Grade 1-2

bleeding/haemorrhage events (mainly epistaxis) in Arm B. The difference between Grade 3-5 'adverse events of special interest' in the two arms was ≤ 2%. The sponsor states that the low rate of difference compared to studies in previously bevacizumab naive patients, suggests that previous exposure to bevacizumab identified adverse events that have probably been managed appropriately. This seems a reasonable assumption. A higher proportion of patients in Arm B discontinued treatment, with most discontinuing chemotherapy as well as bevacizumab. The incidence of deaths not due to progressive disease was similar in the two arms of the study.

8. First round benefit-risk assessment

8.1. First Round Assessment of Benefits

- The primary efficacy endpoint of a significant increase in OS was met by a prolongation in median survival of 1.4 months.
- The secondary endpoint of PFS was met by a statistically significant reduction in the bevacizumab-containing chemotherapy arm.
- The secondary endpoint of Best Overall Response was not met because the results were not statistically significant. The difference in response rate between the two arms was small.
- Subgroup analysis of the efficacy endpoints by patient KRAS mutational status did not provide any evidence to suggest a valid treatment difference attributable to the use of additional bevacizumab.

8.2. First Round Assessment of Risks

- The frequencies of adverse event of any severity were similar in the two arms of the study.
- The most frequently reported adverse events were in keeping with the known adverse event profiles of the chemotherapy agents.
- The difference in frequencies of Grade 3-5 adverse events that were known to be associated with bevacizumab were ≤ 2% between the bevacizumab containing chemotherapy arm and the chemotherapy alone arm.
- The incidences of Serious Adverse Events and Deaths not due to progressive disease were comparable between the two arms of the study.
- A higher proportion of patients in the bevacizumab-containing arm discontinued treatment (15.7% versus 8.8%). Most of the discontinuations in this arm were due to adverse effects associated with bevacizumab.

8.3. First Round Assessment of Benefit-Risk Balance

The benefit-risk balance of bevacizumb 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg body weight given once every 3 weeks as the proposed usage in second-line treatment of metastatic colorectal cancer, is favourable.

9. First round recommendation regarding authorisation

The application to amend the Product Information document to include the above dosage regimen for the use of Avastin in second-line treatment of metastatic colorectal cancer is recommended for approval provided the Clinical Question is addressed.

10. Clinical questions

10.1. Safety

The safety population as described in Table 25: '*Summary of Analysis Population in Study ML 18147 (Randomized Patients)*' was 407 patients in the Chemo arm and 403 patients in the Chemo + Bev (bevacizumb) arm. However, the safety population described in Table 8: '*Summary of Overall Safety (Safety Population)*' was 409 patients in the Chemo arm and 401 patients in the Chemo + Bev arm. An explanation for the discrepancy in the two tables is sought.

Table 25 Summary of analysis population

	CHEMO	CHEMO + BEV	TOTAL
No. of Patients Randomized	411	409	820
No. Included in INTENT-TO-TREAT	410	409	819
No. Excluded from INTENT-TO-TREAT	1	-	1
No informed consent date	1	-	1
No. Included in MEASURABLE DISEASE	406	404	810
No. Excluded from MEASURABLE DISEASE	5	5	10
Patients without measurable disease	4	5	9
No informed consent date	1	-	1
No. Included in PER-PROTOCOL	397	383	780
No. Excluded from PER-PROTOCOL	14	26	40
No confirmation of progressive disease after 1st line therapy	7	11	18
No cross-over chemotherapy or failure to receive treatment according to randomization	2	13	15
Failure to receive at least one dose of second-line study medication	4	6	10
No evidence of measurable lesions at baseline	4	5	9
No informed consent date	1	-	1
No. Included in SAFETY	407	403	810
No. Excluded from SAFETY	4	6	10
Did not receive at least one full or partial dose of bevacizumab or CTx	4	6	10

Chemo= Fluropyrimidine based chemotherapy (oxaliplatin or irinotican). Bev= bevacizumab

11. Second round evaluation of clinical data submitted in response to questions

Nil information provided.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Avastin in the proposed usage are unchanged from those identified in the First Round Evaluation.

13. Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of Avastin in the proposed usage are unchanged from those identified in the First Round Evaluation.

13.1. Second round assessment of benefit-risk balance

The benefit-risk balance of Avastin, given the proposed usage, is favourable.

14. Second round recommendation regarding authorisation

The application to amend the Product Information document to include the above dosage regimen for the use of Avastin in second-line treatment of metastatic colorectal cancer is recommended for approval.

15. References

Nil.

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