ASSESSMENT REPORT
FOR
AVASTIN

International non-proprietary name/Common name:
bevacizumab

Procedure No.EMEA/H/C/000582/II/0014

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

1. Introduction

Avastin (bevacizumab) is a recombinant humanized monoclonal antibody. It recognizes and neutralizes all major isoforms of human VEGF. Bevacizumab potently neutralizes VEGF and blocks its signal transduction through both the VEGFR-1 and VEGFR-2 receptors. It inhibits angiogenesis by neutralizing all isoforms of human vascular endothelial growth factor-A (VEGF), and blocking their binding to VEGF receptors.

Avastin was approved in EU in January 2005 for the first-line treatment of metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan. Subsequently Avastin was also approved for use in combination with paclitaxel for first-line treatment of patients with metastatic breast cancer and in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology and in combination with interferon alfa-2a for first line treatment of patients with advanced and/or metastatic renal cell cancer.

The applicant has now submitted two randomised phase III studies:

- Study NO16966, in patients not previously treated for their metastatic disease, was a randomised double-blind phase III study with Progression free survival as primary endpoint with the two objectives to show non-inferiority of XELOX to FOLFOX-4 and to show superiority of bevacizumab + chemotherapy over chemotherapy alone. The mature overall survival data for this study was submitted in the responses to request for supplementary information.
- Study E3200 evaluating the efficacy and safety of bevacizumab given either in combination with FOLFOX-4 or as monotherapy in patients with advanced carcinoma of the colon or rectum who had received previous treatment with irinotecan and 5-FU. Overall survival was the primary endpoint.

As supportive data the applicant has submitted the following:

- Addenda to the clinical studies AVF2107g and AVF2192g reported in the original marketing authorisation application in order to provide more safety data.
- PK data from two drug-drug interaction studies AVF3135g (Already assessed as FUM 016 and finalised at the January 2007 meeting) and NP18587 concerning the potential interactions between bevacizumab and irinotecan, capecitabine or oxaliplatin.
- Publications and reports of several other trials, conducted by Roche and other sponsors.

These studies form the basis for the following extension of the indication concerning mCRC:
«Avastin (bevacizumab) in combination with fluoropyrimidine-based chemotherapy ~~with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan~~ is indicated for ~~first-line~~ treatment of patients with metastatic carcinoma of the colon or rectum».

The proposed posology to follow this indication is:
The recommended dose of Avastin, administered as an intravenous infusion, is either 5 mg/kg or 10 mg/kg of body weight given once <u>every 2 weeks</u> or 7.5 mg/kg or 15 mg/kg of body weight given once <u>every 3 weeks.</u>

2 Clinical aspects

Study NO16966 was conducted according to the guidelines of Good Clinical Practice (GCP). Clinical audits were conducted at selected sites by the Clinical Quality Assurance Department of Roche to evaluate study compliance with Good Clinical Practice guidelines and relevant local regulations. There were no critical findings affecting the overall validity of study at any of the sites audited.
Study E3200 was conducted according to the Eastern Cooperative Oncology Group (ECOG) standard operating procedures, and in accordance with all Department of Health and Human Services, Office of Human Research Protections, and U.S. Food and Drug Administration (FDA) regulations regarding the conduct of human research that gave their origins in the Declaration of Helsinki.

The two drug interaction studies (AVF3135g and NP1857) were also conducted in accordance to GCP.

2. 1. Clinical Pharmacology

The results of the clinical pharmacology program for bevacizumab have been extensively discussed in the original Marketing Authorization Application for first-line treatment of colorectal cancer and the type II variation for metastatic breast carcinoma (EMEA/H/C/582/II/08) and non-small cell lung cancer (EMEA/H/C/582/II/09).
In this submission two drug-drug interaction studies has been included for which the one already has been assessed as a follow up measure:

- **AVF3135g**: investigated the potential effect of bevacizumab on irinotecan disposition and demonstrated that bevacizumab had no effect on the disposition of irinotecan and SN38. This study was already assessed as Follow-up measure (FUM) and included in this submission as some SPC changes relating to the outcome of this FUM have been introduced into the proposed SPC.
- **NP18587** concerning the potential interactions between bevacizumab, capecitabine or oxaliplatin. The conclusion for this study was that Bevacizumab did not alter the pharmacokinetics of capecitabine and oxaliplatin. A previous study had shown not effect on the pharmacokinetics of irinotecan. Hence, there are no concerns regarding any of the drug combinations in the two pivotal trials for the present application.

2.2. Clinical Efficacy

This application is supported by two large, randomized Phase III studies, one in patients not previously treated for their metastatic disease (first-line treatment, Study NO16966) and the other in previously treated patients (second-line treatment, Study E3200). Supportive efficacy and safety information is provided from a number of additional published studies. A description of study designs and objectives of the two key studies is provided in the table below.

Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Diagnosis Incl. criteria
Study ID NO16966					
Phase III, randomized, multicenter, multinational 2x2 factorial, double-blind, placebo-controlled (Part 2)	**XELOX regimen:** 3-week cycle CAP: 1000 mg/m^2 p.o. bid (days 1-15; day 1 PM dose only, day 15 AM dose only) OX: 130 mg/m^2 IV (day 1) BV: 7.5 mg/kg q3w IV Placebo for BV: equivalent volume to BV IV **FOLFOX-4 regimen:** 2-week cycle LV: 200 mg/m^2 2 h infusion (days 1 and 2) 5-FU: 400 mg/m^2 bolus injection, 600 mg/m^2 22 h infusion, (days 1 and 2) OX: 85 mg/m^2 IV (day 1) BV: 5 mg/kg q2w IV Placebo for BV:	Primary: To demonstrate that the combination of CAP and OX (XELOX) with or without BV is at least equivalent to the combination of fluorouracil (5-FU), leucovorin (LV) and OX (FOLFOX-4) with or without BV in terms of time to tumor progression or death due to any cause. To demonstrate that BV in combination with chemotherapy (XELOX+BV / FOLFOX-4+BV) is superior to chemotherapy alone (XELOX+P/ FOLFOX-4+P) in terms of time to tumor progression or death due to any cause.	Randomized: Part 1 XELOX: 317 FOLFOX-4: 317 Part 2: XELOX+BV: 350 XELOX+P: 350 FOLFOX-4+BV: 350* FOLFOX-4+P: 351	Primary treatment phase: Up to 16 cycles (XELOX arms) or 24 cycles (FOLFOX-4 arms) Post-study treatment phase: Until disease progression or unacceptable toxicity	Metastatic colorectal cancer. Histologically confirmed adeno-carcinoma of the colon or rectum with metastatic disease. ≥18 years old. ECOG PS 0 or 1. Previously untreated for metastatic disease.

	equivalent volume to BV IV				

Study ID: E3200

Phase III, randomized, open-label, controlled, multicenter	FOLFOX-4 regimen: 2-week cycle LV: 200 mg/m2 2 h infusion (days 1 and 2) 5-FU: 400 mg/m2 bolus injection, 600 mg/m2 22 h infusion, (days 1 and 2) OX: 85 mg/m2 IV (day 1) BV: 10 mg/kg q2w IV	Primary: To evaluate the efficacy of BV when combined with FOLFOX-4 versus FOLFOX-4 alone in patients with advanced CRC who have failed therapy with irinotecan and 5-FU as measured by duration of survival. To evaluate the safety of BV when combined with FOLFOX-4 versus FOLFOX-4 alone in patients with advanced CRC who have failed therapy with irinotecan and 5-FU.	Randomized: FOLFOX-4: 292 FOLFOX-4+BV: 293 BV alone: 244	Treatment until disease progression	Advanced or metastatic colorectal cancer. Histologically confirmed adeno-carcinoma of the colon or rectum with metastatic disease. ≥18 years old. ECOG PS 0-2. Previous treatment with with fluoro-pyrimidine-based regimen and irinotecan-based regimen

*Note: One patient was randomized twice, initially in the FOLFOX-4+BV arm (no treatment received) and then in the XELOX+P arm. The patient's data was included in the XELOX+P arm for all analyses

Study NO16966

Study NO16966 was a multinational, randomized, double-blind (for bevacizumab) Phase III study. The study was originally designed to demonstrate that the combination of capecitabine plus oxaliplatin (XELOX) is similarly effective to the combination of oxaliplatin plus 5-FU/LV (FOLFOX4). After publication of the results of the bevacizumab pivotal study AVF2107g, demonstrating a superior survival benefit through the addition of bevacizumab to irinotecan + bolus 5FU/FA (IFL), the addition of bevacizumab was requested by the independent steering committee members and accepted by Roche. The study design was changed to a 2x2 factorial randomized phase III trial in order to address an additional primary objective i.e., superiority for PFS of XELOX/FOLFOX-4 + bevacizumab versus XELOX/FOLFOX-4 + placebo.

Figure 1: Overview of Study Design: Study NO16966

Initial 2-arm Part		**2x2 Factorial 4-arm Part**			
Randomized (n=634)		**Randomized (n=1401)**			
↓	↓	↓	↓	↓	↓
XELOX, Arm A' (n=317)	FOLFOX-4, Arm B' (n=317)	XELOX+P, Arm A (n=350)	FOLFOX+P, Arm B (n=351)	XELOX+BV, Arm C (n=350)	FOLFOX+BV Arm D (n=350)*

*Note: One patient was randomized twice, initially in the FOLFOX-4+BV arm (no treatment received) and then in the XELOX+P arm. The patient's data was included in the XELOX+P arm for all analyses.

Co-primary objectives:

- To demonstrate that the combination of capecitabine and oxaliplatin (XELOX) with or without bevacizumab (BV) is at least equivalent to the combination of fluorouracil and leucovorin and oxaliplatin (FOLFOX-4) with or without BV in terms of PFS. .
- To demonstrate that BV in combination with chemotherapy (XELOX+BV/FOLFOX-4+BV) is superior to chemotherapy alone (XELOX+P/FOLFOX-4+P) in terms of PFS.

Secondary endpoints:

- PFS based on tumour assessments reviewed by an Independent Review Committee (IRC)
- PFS on-treatment (based on investigator tumour assessments during and up to 28 days after last drug intake in the primary study treatment phase [i.e., the first 48 weeks of treatment])
- Overall survival
- PFS based on investigator tumour assessments, patients with surgery with curative intent not censored
- Best overall response (BOR) based on investigator tumour assessments
- Best overall response (BOR) based on tumour assessments reviewed by an Independent Review Committee (IRC)
- Time to response
- Duration of response
- Time to treatment failure
- Safety

No data on QoL has been collected. Patients were asked to complete a Chemotherapy convenience and Satisfaction Questionnaire at baseline and then every second cycle. However the Convenience domain of the Questionnaire failed validation and therefore results were not included in the study report.

Study Participants & Inclusion/Exclusion criterias

The target population for the NO16966 study was patients with inoperable mCRC, who had not previously received systemic treatment for metastatic disease. Treatment groups were well-balanced with respect to demographic and baseline disease characteristics and generally representative of the overall population of patients with mCRC: in the 2x2 factorial part of the study, the median age was approximately 60 years (range 18 to 86 years), the majority were male (58%), Caucasian (88%), had a high ECOG performance status of 0 (59%), and had liver metastases (76%) at baseline. In total, 24% of patients had received prior adjuvant chemotherapy.

Main inclusion criteria were: ECOG performance status of ≤1, histologically confirmed adenocarcinoma of the colon or rectum with metastatic disease, at least one unidimensionally measurable lesion with a diameter >20 mm using conventional CT or MRI scans or >10 mm using spiral CT scans, a life expectancy of at least 3 months.
Main exclusion criteria were: Prior treatment with oxaliplatin, bevacizumab or other systemic therapy for advanced or metastatic disease; History of another malignancy within the last five years ; history or evidence upon physical examination of CNS disease; Clinically significant (ie., active) cardiovascular disease.

A total of 2035 patients from 32 countries were randomized (634 patients in the 2-arm part and 1401 in the 2x2 factorial part of the study). While overall survival data for the first part of the study are mature at the time of intial submission, 64-70% of patients having a death event, this was not yet the case for the 2x2 factorial part of the study with only 32-37% of the patients having a death event. In the mature overall survival (OS) data from part II of NO16966, 62.5% patients have died, after an analysis performed with an additional 12 months of follow-up (34% of patients had died at the cut-off for the primary analysis).

Baseline data

Demographic and prognostic data (e.g. ECOG performance status, time from diagnosis of colorectal cancer to randomization) were generally well balanced within the initial 2-arm part I of the study between the FOLFOX-4 and XELOX treatment arms, as well as within the 2x2 factorial part II of the study across the FOLFOX-4 and XELOX-containing arms.
Demographic and prognostic data were also well balanced between the initial 2-arm part and the 2x2 factorial part of the study, with the following exceptions: The proportion of Caucasian patients that enrolled in the 2x2 factorial part was higher than the initial 2-arm part because centers in China did not participate in the 2x2 factorial part of the study. An increase of approximately 10% was observed in the percentages of patients with an ECOG performance status of 0 in the 2x2 factorial part compared with patients in the initial 2-arm part of the study.

Overall, demographic data, patient prognostic factors and baseline tumour characteristics as well as adjuvant chemotherapy were sufficiently balanced between the treatment arms.

Treatments

The combination of capecitabine 1000 mg/m2 twice daily given on an intermittent schedule (2 weeks of treatment followed by 1 week without treatment) with oxaliplatin 130 mg/m2 given once on day 1 every 3 weeks was shown to be tolerable and feasible. The choice of dosages of the standard chemotherapy (oxaliplatin plus 5-FU/LV) was based on the safety and efficacy profile of the FOLFOX-4 regimen which is an approved standard regimen in the US and Europe, and using a similar planned dose intensity of oxaliplatin in the two selected regimens.

In Study NO16966, Bevacizumab was given at a dose intensity of 2.5 mg/kg/week, consistent with the current prescribing information, where a dose of 5 mg/kg every 2 weeks (2.5 mg/kg/week equivalent) is recommended for the treatment of mCRC. The dose of 5 mg/kg every 2 weeks was selected for the original Phase III pivotal trial in first-line metastatic CRC (Study AVF2107g) and study AVF2192g based on the results of the dose-finding Study AVF0780g. The pivotal study AVF2107g and Study AVF2192g generated data confirming the appropriateness of the 5 mg/kg every 2 weeks dosing interval (in terms of the PFS and OS benefit) and are the basis for the current dosing recommendation in mCRC.

Efficacy Results in First-line Study NO16966

- **Patient flow**

In the primary treatment phase (first 48 weeks of treatment), more patients stopped treatment due to disease progression in the chemotherapy alone arms (44% and 50%) than in the chemotherapy+BV arms (29%). A higher proportion of patients had adverse events in the BV treatment arms that led to discontinuation (31% and 33% vs. 22% and 21%).

These data show that after the primary treatment phase, few patients continued bevacizumab treatment until disease progression, although allowed in the protocol. For the initial 2-arm part of the study, the first patient was randomised on 15 July 2003 and the last patient was randomised on 7 May 2004. In the 2x2 factorial part of the study, the first patient was randomised on 4 February 2004 and the last patient was randomised on 10 February 2005. The protocol of January 2003, NO16966, was amended five times. The amendment that allowed adding the 2x2 factorial part of the study, investigating the addition of bevacizumab to either FOLFOX-4 or XELOX was applied early in the study. None of the amendments are considered to negatively affect the validity of the study.
Of the 1400 patients in the ITT population of the 2x2 factorial part of the study, 250 patients had one or more protocol deviations, approximately 60 in each treatment arm.

- **Results 2x2 Factorial 4-arm part of the study**

Primary efficacy endpoint: Progression-free survival – General approach

The two co-primary objectives of the study were met:

- Non-inferiority of the XELOX containing arms versus FOLFOX-4 containing arms was demonstrated for the primary analysis of PFS in the EPP (HR = 1.05; 97.5%CI, 0.94-1.18). This result was supported by the analysis of OS (HR = 0.97; 97.5% CI, 0.84-1.14), BOR and TTF, and by a prognostic factor-adjusted multivariate Cox regression analysis.

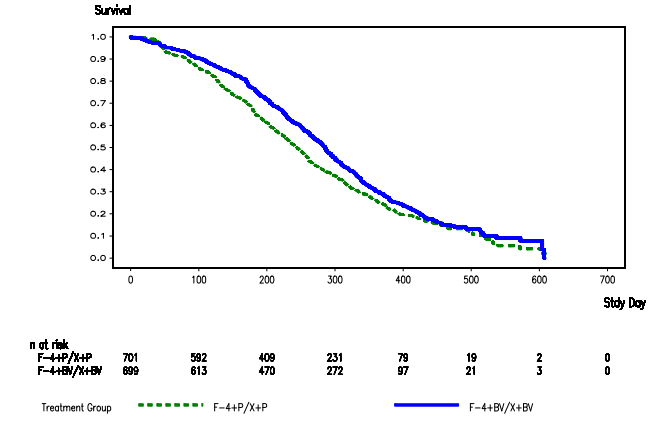
- Superiority of FOLFOX-4/XELOX+BV over FOLFOX-4/XELOX+P was demonstrated in the primary PFS analysis in the ITT population (HR = 0.83; 97.5% CI, 0.72-0.95; p=0.0023), which was supported by consistent results derived from the pre-defined PFS on treatment analysis and the PFS analysis resulting from the pre-defined independent review process. The robustness of the analysis was further confirmed by a prognostic factor-adjusted multivariate Cox regression analysis. Superiority of chemotherapy + BV over chemotherapy + placebo was demonstrated. The Kaplan-Meier curve for PFS shows an early separation suggesting an early effect of the combined biologic therapy.

Main efficacy results for superiority of chemotherapy plus bevacizumab over chemotherapy alone for progression-free survival (investigator's assessment)

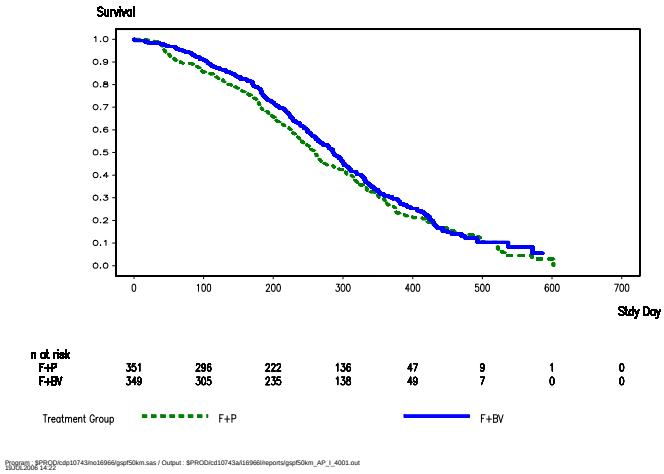
Pop.	Treatment Regimens				Hazard Ratio	97.5% CI	p-Value (Log-Rank)
	OVERALL COMPARISON:						
	FOLFOX-4+P/XELOX+P		FOLFOX-4+BV/XELOX+BV				
	Number of Patients with Event	Median Time to Event [Days]	Number of Patients with Event	Median Time to Event [Days]			
ITT	547	244.0	513	285.0	0.83	[0.72;0.95]	0.0023
EPP	512	242.0	488	282.0	0.83	[0.72;0.95]	0.0029
PP	450	256.0	415	297.0	0.80	[0.69;0.93]	0.0010
	TREATMENT SUBGROUP COMPARISONS:						
	FOLFOX-4+P		FOLFOX-4+BV				
	Number of Patients with Event	Median Time to Event [Days]	Number of Patients with Event	Median Time to Event [Days]			
ITT	277	261.0	255	286.0	0.89	[0.73;1.08]	0.1871
EPP	256	260.0	238	285.0	0.88	[0.72;1.08]	0.1619
PP	224	267.0	211	298.0	0.89	[0.72;1.10]	0.2130
	XELOX+P		XELOX+BV				
	Number of Patients with Event	Median Time to Event [Days]	Number of Patients with Event	Median Time to Event [Days]			
ITT	270	225.0	258	282.0	0.77	[0.63;0.94]	0.0026
EPP	256	226.0	250	281.0	0.78	[0.64;0.95]	0.0049
PP	226	239.0	204	294.0	0.72	[0.58;0.89]	0.0006

Figure 2: Kaplan-Meier curves for superiority in progression-free survival (ITT, investigator's assessment)

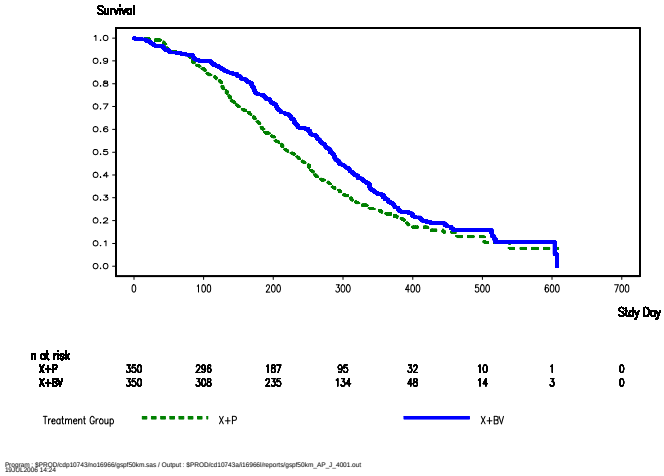
a) Comparison FOLFOX-4+P/XELOX+P versus FOLFOX-4+BV/XELOX+BV



b) Comparison FOLFOX-4+P versus FOLFOX-4+BV



c) Comparison XELOX+P versus XELOX+BV



Secondary Efficacy Endpoints

- **PFS based on tumour assessment reviewed by an independent review committee (IRC)**

For calculation of PFS in the analysis of IRC tumour assessments:

- Tumour scans taken up to and including disease progression or until study week 60, whichever came first, were to be sent to the IRC for independent review and assessment of response, including PD.
- Only PD as assessed by the IRC were considered as PD events
- Deaths (without prior PD) that occurred within 28 days from the last tumour assessment reviewed by the IRC were considered as death events
- Surgery with curative intent was taken into account for censoring only if it occurred within 28 days from the last tumour assessment made by the IRC.

Superiority of the BV containing arms compared with the placebo-containing arms was demonstrated for PFS in the ITT for the overall comparison and the treatment subgroup comparisons when tumor assessments were independently reviewed by the IRC.

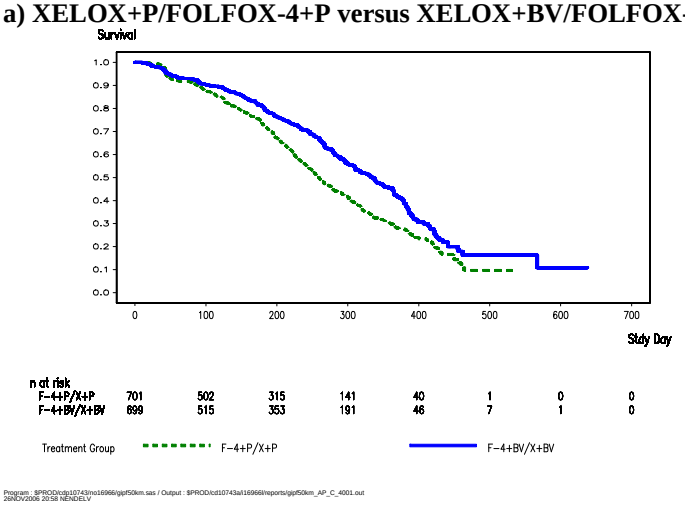
PFS as assessed by the IRC was prolonged by a median of 76 days in the chemotherapy+bevacizumab arm compared to the chemotherapy alone arm (HR=0.70, 97.5% CI [0.58; 0.83], p<0.0001). In the XELOX and FOLFOX-4 treatment subgroups the PFS was prolonged by a median of 61 (HR=0.73, 97.5% CI [0.57; 0.95], p=0.0071) and 72 days (HR=0.66, 97.5% CI [0.52; 0.85], p=0.0002), respectively. Thus, addition of bevacizumab significantly prolonged PFS in both chemotherapy subgroup arms. Contrary to the PFS analysis by the investigator, defined as the primary endpoint,

there was a benefit of adding bevacizumab also to the FOLFOX-4 arm in the IRC analysis. In the IRC analysis, the differences in PFS between the bevacizumab and placebo arms were greater than in the primary analysis. This is not surprising since patients who withdraw and subsequently die >28 days after last date of tumour assessment are censored and do not contribute with an event. Discrepancy in the number of events between the IRC and the investigator analyses is due to the definition of event and lower number of available tumour scans as well as discrepancy between the IRC and investigators assessment of PFS.

The Kaplan-Meier plots of PFS based on IRC assessments in the ITT population show an early separation of the curves, with the BV curve above the placebo curve for the overall comparison and the two treatment subgroup comparisons. These analyses support the analyses of the primary endpoint. Superiority of BV versus placebo was demonstrated in the overall comparison (figure 4a) and in both XELOX and FOLFOX-4 treatment subgroups (figure 4c and figure 4b, respectively), thus supporting the main superiority analysis of the study. Unlike the results in the investigator dataset, the result of the comparison of FOLFOX-4+BV versus FOLFOX-4+P was significant in the IRC dataset.

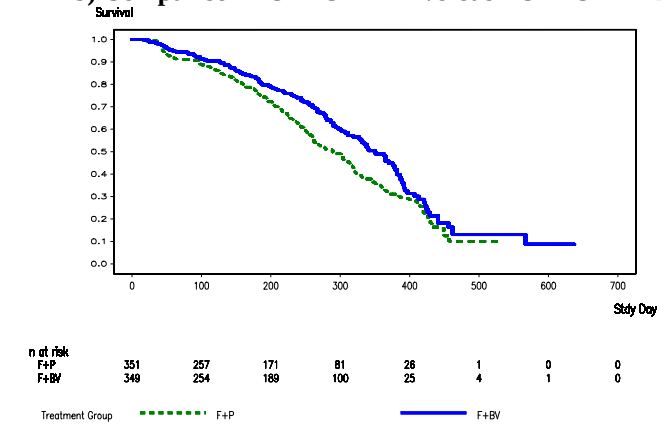
Figure 3 Kaplan-Meier Curves for Superiority in Progression-free Survival (ITT, IRC Assessment)

a) XELOX+P/FOLFOX-4+P versus XELOX+BV/FOLFOX-4+BV



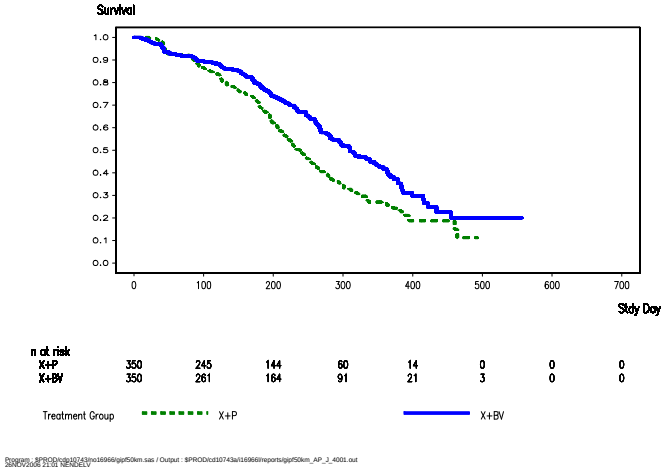
Program : $PROD/cdp10743/no16966/gip/50km.sas / Output : $PROD/cd10743al16966l/reports/gip/50km_AP_C_4001.out
26NOV2006 20:58 NENDELV

b) Comparison FOLFOX-4+P versus FOLFOX-4+BV



Program : $PROD/cdp10743/no16966/gip/50km.sas / Output : $PROD/cd10743al16966l/reports/gip/50km_AP_I_4001.out
26NOV2006 21:00 NENDELV

c) Comparison XELOX+P versus XELOX+BV



PFS On-treatment Approach

A greater magnitude of PFS benefit with BV was seen in the on-treatment analysis compared with the primary PFS analysis (general approach) and was statistically significant in the pooled comparison and the XELOX and FOLFOX-4 treatment subgroup comparisons: chemotherapy + BV was significantly superior to chemotherapy alone (HR = 0.63; 97.5% CI, 0.52-0.75; p <0.0001) and statistical superiority was achieved in both treatment subgroups (HR=0.61; 97.5% CI, 0.48-0.78; p<0.0001 for the XELOX treatment subgroup comparison and HR=0.65; 97.5% CI, 0.50-0.84; p=0.0002 for the FOLFOX-4 treatment subgroup comparison). These results support the conclusions of the primary analysis.

PFS Patients with Curative Surgery not Censored

The number of patients censored in the PFS analysis due to curative surgery was 50 (7.2%) in the bevacizumab arms and 32 (4.6%) in the placebo arms. When patients with curative surgery were not censored the results were similar to those of the primary PFS analysis. In the overall comparison, chemotherapy+BV was significantly superior to chemotherapy alone (ITT: HR=0.83, 97.5% CI = [0.72; 0.95], p=0.0015). Similarly, XELOX+BV was significantly superior to XELOX+P (HR=0.76, 97.5% CI = [0.63; 0.93], p=0.0015), whereas statistical superiority of treatment with FOLFOX-4+BV over treatment with FOLFOX-4+P was not reached (HR=0.89, 97.5% CI = [0.74; 1.08], p=0.1851).

Overall survival

In the overall comparison in the ITT population according to the Kaplan-Meier estimate, the overall median OS was approximately 18 months (574 days for patients in the chemotherapy + placebo arm versus 551 days for patients in the chemotherapy + BV arm). At 18 months, 40 patients and 53 patients in the placebo-containing arm and in the BV-containing arm, respectively, were still at risk (width of the 97.5% CI = 0.111 and 0.128, respectively). Thus, the Kaplan-Meier estimates at the median OS were considered as not reliable enough.

Mature overall survival (OS) data from part II of NO16966 (62.5% patients have died) are now available after an analysis performed with an additional 12 months of follow-up (34% of patients had died at the cut-off for the primary analysis).

The result shows a trend for longer OS with BV compared with placebo (median 92.3 weeks vs. 86.6 weeks, HR=0.89) however statistical significance was not reached (p=0.0769). Two key factors may have reduced the magnitude of OS benefit observed:

- Early discontinuation of BV therapy
- The impact of a cohort with an outlying efficacy result: patients with previous adjuvant treatment in the FOLFOX+P arm had a more favourable baseline characteristic (longer time from start of adjuvant therapy to randomisation) than the cohorts of adjuvant-treated patients in the other treatment arms. This may explain the unexpectedly good outcome in the FOLFOX-4+P arm. A Cox regression model confirmed that time from start of adjuvant chemotherapy to randomization (recurrence) has an influence on OS.

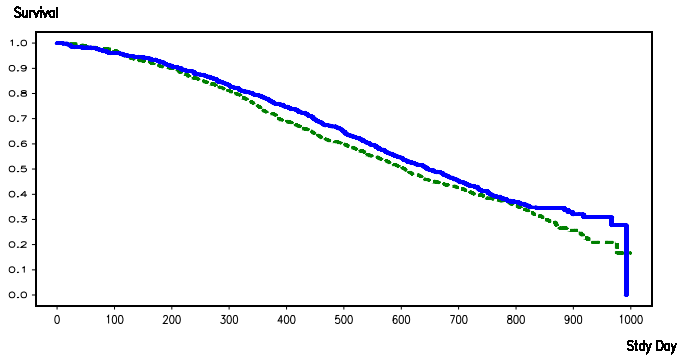
Three exploratory analyses, aimed at reducing the impact of this cohort on OS, show a significant OS benefit of BV vs. Placebo in the 2x2 factorial part II of NO16966. Moreover, an exploratory analysis of OS including all patients in NO16966 (from part I and II) shows a similar result.
An overall survival benefit has therefore also been shown in this study.

Study NO16966: Overall Survival - HR after Step-wise Exclusion of Subgroups of Patients with Previous Adjuvant Chemotherapy (4MSU)

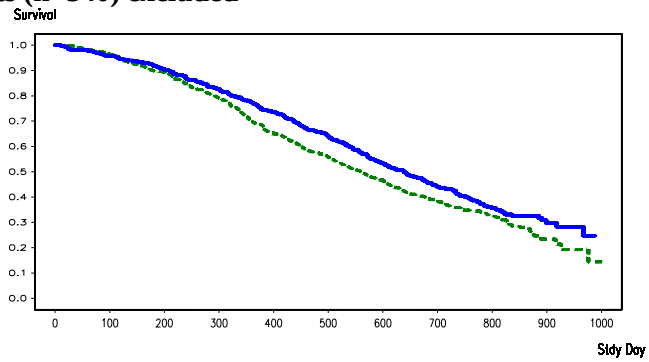
Population	No. of pts excluded from analysis	No. of pts included in analysis	HR (97.5%CI)	P-Value
All patients included (ITT)	0	1400	0.89 (0.76, 1.03)	0.0769
Exclusion of patients with adjuvant chemotherapy from all four treatment arms	85+91+88+76	1060 (1400-340)	0.83 (0.70, 0.99)	0.0183
Exclusion of patients with adjuvant chemotherapy from FOLFOX-4 arms only	85+88	1227 (1400-173)	0.85 (0.72, 1.00)	0.0242
Exclusion of patients with adjuvant chemotherapy from FOLFOX-4+P arm only	85	1315 (1400-85)	0.84 (0.72;0.98)	0.0116

Kaplan-Meier Curves for Superiority in Overall Survival (ITT, Overall Comparison)

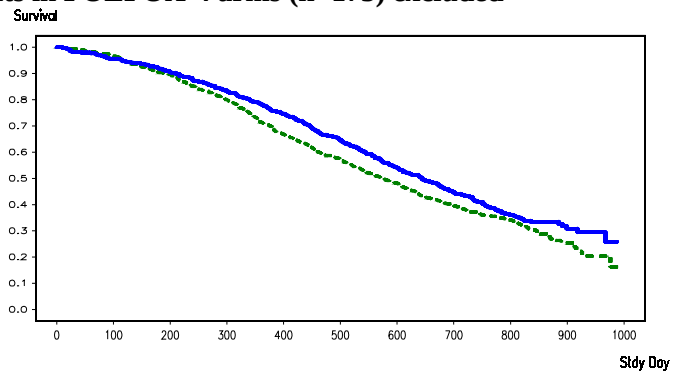
a) All Patients



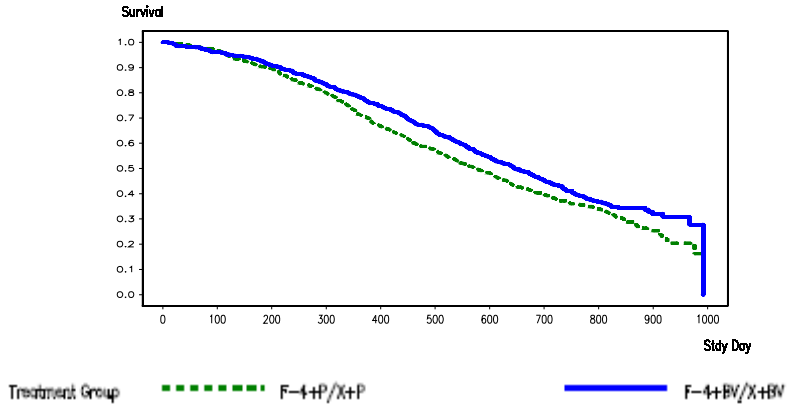
Adjuvant-treated patients (n=340) excluded



Adjuvant treated patients in FOLFOX-4 arms (n=173) excluded



Adjuvant-treated patients in FOLFOX-P arm (n=85) excluded



Additional anti-cancer treatments after discontinuing study treatment and after disease progression were administered to 46% to 54% of the patients across all treatments arms. More patients in the placebo-containing arms received second-line chemotherapy compared with bevacizumab-containing arms. The most common therapy given as second-line treatment was irinotecan, the second most frequent agent was 5-FU. Second-line treatment was generally equally distributed across the treatment arms and will probably not confound the OS data.

Time to Response

The majority of responses (approximately 70%) occurred between week 6 and week 18 in both the placebo-containing and the BV-containing groups

There was no significant difference in the time to response between treatment arms. This, lends support to the concept that bevacizumab does not produce tumour shrinkage by itself, but rather delays progression. Hence, these data are of no concern regarding the efficacy of bevacizumab.

Duration of Response

Overall, duration of response was longer for patients who received bevacizumab in combination with chemotherapy compared with patients who received chemotherapy. However, for the FOLFOX-4 and XELOX subgroups the prolongation in duration of response was not statistically significant (median difference 21 days, p=0.24 and 49 days, p=0.057, respectively).

Time to Treatment Failure

The results of the time to treatment failure (TTF) analyses for superiority (performed on the safety population (N=1369, excluding 32 patients who did not receive study medication) are in support of those achieved for the primary endpoint PFS.

Statistical superiority was observed using the general approach for chemotherapy + BV over chemotherapy alone in the overall comparison (HR=0.84; 97.5% CI, 0.74-0.96) and in the XELOX treatment subgroup (HR=0.80; 97.5% CI, 0.67-0.97). A trend for a longer time to treatment failure

was observed for FOLFOX-4+BV over FOLFOX-4 alone (HR=0.88; 97.5% CI, 0.73-1.06; p=0.1274). Similar results were observed using the on-treatment approach.
These analyses support the conclusions of the analyses of the primary endpoint.

Supportive analyses
Subgroup Analyses
A number of Subgroup analyses were performed to investigate the internal consistency of the study and the robustness of the findings for the efficacy endpoints. Data are only presented for PFS and BOR as OS data are not yet mature for the analyses of superiority of chemotherapy+bevacizumab vs. chemotherapy+placebo.

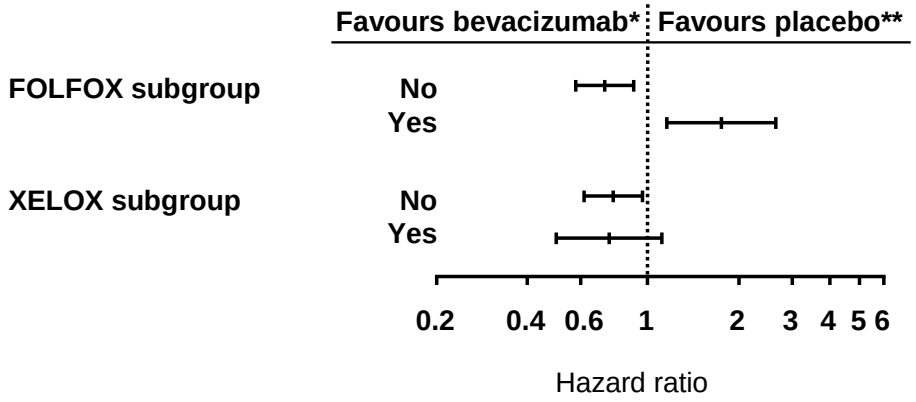
Among other analyses three categories of subgroups were used for the superiority comparisons. The three categories of subgroups and their components are listed below:
• Demographic and baseline characteristics: Gender (male, female), Age (<65 years, ≥65 years), Use of adjuvant therapy (yes, no). Race (White, Black, Asian or Pacific Islander, American Indian, Other)
• Stratification variables used for randomisation: ECOG performance status (0, 1), Number of metastatic sites (organs) at baseline (1, >1), Alkaline phosphatase level at baseline (within normal range, above normal range)
Liver as a site of metastasis (yes, no)
• Geographic region

In the overall comparison with respect to PFS based on the ITT, 14 of 16 subgroups defined by demographic and baseline characteristics and stratification variables used for randomisation had point estimates for HR below 1. The two exceptions were: receiving adjuvant chemotherapy before randomisation (HR=1.12, 97.5% CI = 0.84; 1.50) and not having liver as a metastatic site (HR=1.03, 97.5% CI = 0.77; 1.38). Three geographic regions: USA (HR=1.06, 97.5% CI = [0.64; 1.74]), British Isles (HR=1.26, 97.5% CI = [0.83; 1.91]), and Oceania (HR=1.19, 97.5% CI = [0.70; 2.02]), had point estimates for HR above 1, but not statistically different.
Although variability was observed, the results from the subgroup analyses support the primary finding of superiority of XELOX+BV/FOLFOX-4+BV over XELOX+P/FOLFOX-4+P.

In the FOLFOX-4 treatment subgroup comparison with respect to PFS based on the ITT, 12 of 16 subgroups examined in demographic and baseline characteristics and stratification variables used for randomisation had point estimates for HR below 1. The exceptions were: age ≥65 years (HR=1.08, 97.5% CI = [0.77; 1.51]), receiving adjuvant chemotherapy before randomisation (HR=1.75, 97.5% CI = [1.15; 2.65]), more than 1 metastatic site at baseline (HR=1.03, 97.5% CI = [0.81; 1.33]), and not having liver as a metastatic site (HR=1.47, 97.5% CI = [0.98; 2.21]). For these subgroups, the results in the FOLFOX-4 and XELOX treatment groups went in opposite directions. There was a high variability across geographic regions.

As mentioned above, in patients with prior adjuvant chemotherapy addition of bevacizumab reduced the PFS compared to patients without (HR=1.75, 97.5% CI [1.15; 2.65]). This was true only for the comparison between the FOLFOX-4 arms. In contrast, in the XELOX groups the HR of 0.75 indicates a benefit of BV in patients with prior adjuvant chemotherapy, see Figure below.

Study NO16966: Hazard Ratios for PFS for BV versus Placebo by Previous Adjuvant Treatment



The HR of 0.75 in favour of BV in the XELOX subgroup of patients with prior adjuvant treatment is similar to that in patients without prior adjuvant treatment in both the XELOX and FOLFOX-4 groups. This further emphasizes that the result in adjuvant-treated patients in the FOLFOX-4 groups is an outlier, see Table below.

Study NO16966: Comparison of HR for PFS in FOLFOX and XELOX Treatment arms in Patients with and without Prior Adjuvant Therapy (ITT)

N=88 FOLFOX-4 + Bev adjuvant	VS	N=85 FOLFOX-4 + placebo adjuvant	**HR=1.75** [97.5% CI 1.15–2.65]
N=261 FOLFOX-4 + Bev NO adjuvant	VS	N=266 FOLFOX-4 + placebo NO adjuvant	HR=0.72 [97.5% CI 0.58–0.90]
N=76 XELOX + Bev adjuvant	VS	N=91 XELOX + placebo adjuvant	HR=0.75 [97.5% CI 0.50–1.12]
N=274 XELOX + Bev NO adjuvant	VS	N=259 XELOX + placebo NO adjuvant	HR=0.77 [97.5% CI 0.61–0.96]

Additional exploratory analyses showed that the time from start of adjuvant treatment to randomization was associated with outcome in the NO16966 study. A longer time from start adjuvant therapy to randomization in NO16966 could partially explain the better outcome in adjuvant-treated patients in the FOLFOX-4+P arm. This patient cohort had the highest proportion of patients with a long time (>4 years) and the lowest proportion with a short time (<1 year) from start of adjuvant therapy to randomization compared with the cohorts of adjuvant-treated patients in the other arms. This baseline imbalance in a significant prognostic factor likely explains the outlying HR of 1.75 in the subgroup of patients with prior adjuvant therapy in the FOLFOX-4 treatment arms.

In addition, patients without liver metastases did not benefit from bevacizumab compared to patients with liver metastasis (HR=1.47, 97.5% CI [0.98; 2.21). However, the favourable prognostic characteristic (i.e., longer time from start of adjuvant therapy to randomisation) of the adjuvant-treated subgroup of patients in the FOLFOX-4+P arm is also driving the result in the subgroup of patients with no liver metastases at baseline, based on the following observations

- In the overall comparison including all patients, the HR is 1.03 for patients with no liver metastases at baseline. In the subgroups, the HR in patients with no liver metastases is 1.47 in the FOLFOX-4 treatment groups but 0.72 in XELOX group. Thus, the FOLFOX-4 subgroup is confounding the overall result while there is a clear benefit for patients treated with BV in the XELOX group, see Table below.

Study NO16966: Treatment Subgroup Comparisons of HR for PFS in Patients with no Liver Metastases at Baseline (ITT)

Comparison	N	HR [95% CI]
Overall comparison	332	1.03 [0.77,1.38]
F-4 +BV/F-4+P	165	1.47 [0.98,2.21]
XEL+BV/XEL+P	167	0.72 [0.48,1.08]

Source: espf13st_AP_C_4001, espf13st_AP_I_4001, espf13st_AP_J_4001

- The subgroup of patients with no liver metastases is partially overlapping with the subgroup of adjuvant patients (i.e., the subgroup in which there is an imbalance in a significant prognostic factor favouring the placebo arm): 54% (178/332) of the group with no liver metastases were treated in the adjuvant setting (compares with 24% [340/1400] of the ITT population) – therefore the influence of the prior adjuvant patients is greater in this subgroup than in the overall population.
- A comparison of the HR for PFS in the subgroup with no liver metastases at baseline in patients with and without previous adjuvant treatment indicates that the outlying result is driven by the former patient group, see Table below.
- Exclusion of a) all adjuvant-treated patients b) adjuvant-treated patients only in the FOLFOX-P arm resulted in a similar HR of 0.89 and 0.88 in favour of treatment with BV in patients with no liver metastases, see Table below.

Study NO16966: Patients with no liver metastases at baseline – Influence of adjuvant-treated Subgroups on PFS

Population	N	Xelox/Folfox Bev-Xelox/Folfox-P
ITT	332	HR 1.03 [0.77,1.38]
ITT only adjuvant treated patients	178	HR 1.17 [0.79,1.73]
ITT all adjuvant –treated patients excluded	154	HR 0.89 [0.58,1.38]
ITT adjuvant in FOLFOX-4+ P arm excluded	287	HR 0.88 [0.65,1.21]

Source: gspf51st_AP_C_4001, gspf51st_AP_C_4006, gspf51st_AP_C_4007, gspf51st_AP_C_4017

In conclusion, patients without liver metastases at baseline generally benefit from treatment with BV. The subgroup of adjuvant treated patients in the FOLFOX-4+P group, who had a more favourable prognostic characteristic (longer time to recurrence after adjuvant therapy) compared with the FOLFOX-4+BV arm, confound the result observed for the overall comparison.

Exploratory analyses (not pre-specified): Prognostic factor analyses of the influence of prior adjuvant chemotherapy:

In the subgroup analysis result there was a clear distinction between patients who received prior adjuvant chemotherapy and those who did not. Additional exploratory analyses were performed in an effort to better understand the PFS outcome in the FOLFOX-4+P treatment arm .

Approximately 25% of the patients in each of the six treatment groups received adjuvant chemotherapy prior to randomisation, including 85 (24%) patients in the FOLFOX-4+P arm. These results indicate that patients in the FOLFOX-4+P arm had the longest time from start and end of adjuvant treatment to randomisation and also the longest time from first diagnosis of colorectal cancer to randomisation. These differences suggest that patients with previous adjuvant treatment who were randomised into the FOLFOX-4+P group may have had slower tumour progression compared with patients with previous adjuvant treatment randomised into FOLFOX+BV, XELOX+P and XELOX+BV arms.

An exploratory efficacy analysis was performed excluding patients who received prior adjuvant chemotherapy from all treatment arms, XELOX, XELOX+P, XELOX+BV, FOLFOX-4, FOLFOX-4+P, FOLFOX-4+BV.
Another exploratory analysis was performed where patients with prior adjuvant treatment were excluded from the FOLFOX+P treatment group only.
These analyses show that removing the subgroup of patients that may have slower tumour progression, improves the results, and even the subgroup analysis of FOLFOX-4 becomes significant in favour of addition of bevacizumab. This is a post-hoc analysis which must be viewed with caution.

Study E3200

Study E3200 was an open-label, randomized, multicenter, active-controlled Phase III trial to evaluate the safety and efficacy of FOLFOX-4 + 10 mg/kg/q2w bevacizumab versus FOLFOX-4 versus 10 mg/kg/q2w bevacizumab alone in previously treated patients with advanced CRC.

The study was conducted in the USA by the Eastern Cooperative Oncology Group (ECOG) in collaboration with a number of other cooperative groups. Initially, patients were randomized in a 1:1:1 ratio to one of three treatment arms: FOLFOX-4 + bevacizumab, FOLFOX-4, or bevacizumab alone (referred to as Arms A, B, and C, respectively, in the E3200 protocol).

Objectives
The primary objectives was to evaluate the efficacy and safety of bevacizumab when combined with FOLFOX-4 versus FOLFOX-4 alone in patients with advanced CRC who have failed therapy with irinotecan and 5-fluorouracil, as measured by duration of survival.
The secondary objective was to evaluate the efficacy of bevacizumab when combined with FOLFOX-4 versus FOLFOX-4 alone in patients with advanced CRC who have failed therapy with irinotecan and 5-fluorouracil, as measured by progression-free survival, objective response, and duration of objective responses.
Exploratory objectives included comparisons of all efficacy and safety endpoints between each of the remaining pairs of treatment arms (FOLFOX-4 + bevacizumab vs. bevacizumab monotherapy, and FOLFOX-4 vs. bevacizumab monotherapy).

Outcomes/endpoints
The primary efficacy endpoint was: Duration of survival (DS), defined as the time from randomisation to death from any cause. All reported deaths were included in the analysis.
The Secondary efficacy endpoints were: Progression free survival (PFS), Objective response (ORR), defined as a complete or partial best confirmed response (CR or PR) and Duration of objective response (DR) was determined for the subset of patients who achieved an objective response.
Treatment assignment was open-label. Tumour response and disease progression were assessed by the ECOG Coordinating Centre based on a review of tumour assessments provided by the investigator. Tumour evaluations were performed according to the Response Evaluation Criteria in Solid Tumours (RECIST). Pre-study scans and X-rays were performed within 6 weeks prior to Randomisation. Pre-study complete blood count (CBC) and chemistries were performed within 4 weeks prior to Randomisation. While on protocol therapy, tumour assessments were performed every 8 weeks. Patients who discontinued protocol therapy prior to progression continued to be evaluated for tumour response until disease progression. Patients who discontinued protocol therapy were followed for survival status until death. The schedule for follow-up was every 3 months (if the patient was < 2 years from study entry), every 6 months (if the patient was 2–5 years from study entry), or every 12 months (if the patient was > 5 years from study entry).

Study Participants & Inclusion/Exclusion Criterias
Study E3200 was a multicenter study conducted at 220 investigative sites in the United States. The protocol called for the enrolment of approximately 880 patients across the three treatment arms (approximately 293 per treatment arm). Total of 829 patients were randomised to the study; 292 patients to FOLFOX-4, 293 patients to FOLFOX-4+BV, and 244 patients to BV monotherapy.

The target population for Study E3200 was patients with mCRC who had previously received treatment with a fluoropyrimidine-based and an irinotecan-based regimen, either alone or in combination, for advanced disease. The demographic and baseline disease characteristics were well-balanced across groups. The patient characteristics were broadly similar to those of patients recruited into Study NO16966, excepting that patients were more heavily pretreated (in both adjuvant [~80%] and metastatic settings [~97% of the 664 patients with ECOG eligibility checklist available]). A total of 829 patients were randomized (292 patients to FOLFOX-4, 293 patients to FOLFOX-4 + bevacizumab, and 244 patients to bevacizumab monotherapy prior to this arm being discontinued). At the time of the final analysis, among the 585 patients randomized to the two principal arms, 525 (90%) deaths had occurred.

In the E3200 study there were fewer withdrawals in the bevacizumab arm than there were in NO16966. This may be due to the fact that E3200 was an open-label study, which may well have made the patients more motivated to carry on treatment including the new drug despite some side effects. In this respect the two pivotal studies are not quite comparable. However, it would seem possible that a longer duration of treatment in the bevacizumab arms of the NO16966 trial might have improved results in that trial further.

Baseline data
The mean age of the patients was 60.4 years (range: 21 to 85 years). Sixty percent of all patients were male, and the majority of patients were white (87%). Overall, 49% of patients had a baseline ECOG performance status of 0. The median baseline carcinoembryonic antigen (CEA) value was 62 ng/mL. Approximately 80% of patients received adjuvant chemotherapy and 26% received radiotherapy prior to study entry. Out of the patients who received prior cancer therapy for advanced disease, only few (approximately 3%) had irinotecan based therapy in the adjuvant or first-line setting.
The median number of involved metastatic sites was 2 and the sites of organ involvement were similar across treatment arms. However, the proportion of patients with more than one organ site with metastatic disease was higher in the BV monotherapy arm than in the FOLFOX-4 and FOLFOX-4 + BV arms. Overall, metastatic sites most frequently involved were liver (73.5%), lung (55.4%), and other abdominal (23.2%).

Treatments
In study E3200 the bevacizumab dose in the second-line study was 10 mg/kg every 2 weeks, i.e., 5 mg/kg/week equivalent. Although Phase II data (Study AVF0780g) had suggested that both the 5 mg/kg and 10 mg/kg doses every 2 weeks were tolerable and active, a clear dose-response relationship was not established. At the time ECOG initiated the E3200 study, results from AVF2107g demonstrating a clear positive benefit risk ratio for the 2.5 mg/kg/week equivalent dose were not yet available. In the absence of a clear dose response relationship from Phase II, or demonstration of a dose providing positive risk benefit ratio from Phase III, ECOG selected the dose of 5 mg/kg/week equivalent for the E3200 trial. This decision was based on the desire to increase the likelihood of selecting a beneficial dose in this more advanced and refractory population and was consistent with the general principle in oncology of using the highest tolerable dose to reach maximum efficacy. Therefore, the data from the dose of 10 mg/kg every 2 weeks (5 mg/kg/week equivalent) have established a positive risk benefit ratio, based on an acceptable safety profile and an overall survival benefit for bevacizumab, in second-line treatment. The efficacy of the lower dose in the second-line setting has not been tested.

As previously mentioned no dose finding study has been performed which is not ideal, but considered acceptable to have two different dose levels.

Dosing interval
The dose of 2.5 mg/kg/week equivalent was used in the NO16966 study. As in previous phase II and III studies the dosing frequency of BV administration was synchronized to concomitant chemotherapies. This dosing is supported by the fact that BV has a slow clearance and a long terminal half-life of approximately 20 days as with other IgG antibodies. In addition, data generated in a PK simulation of BV administration showed that BV exposure is similar when using the same weekly

dose intensity in a 2-weekly and a 3-weekly dosing regimen. Accordingly, a dose of 7.5 mg/kg every 3 weeks was used with XELOX and a dose of 5 mg/kg every 2 weeks was used with FOLFOX-4.

- **RESULTS – study E3200**

Participant flow

Overall, 806 patients (97.2%) received protocol therapy. Protocol therapy was not considered ended until the last component of any study treatment was stopped. A total of 805 patients (97.1%) have ended protocol therapy: 285 (97.6%) in the FOLFOX-4 arm, 287 (98.0%) in the FOLFOX-4+ bevacizumab arm, and 233 (95.5%) in the bevacizumab monotherapy arm. One patient indicated on the case report form (CRF) as continuing protocol therapy had died. Therefore, no patients remained on protocol therapy.

The most common reason that protocol therapy ended (withdrawal from study treatment) was disease progression or relapse during active treatment: 147 patients (50.3%) in the FOLFOX-4 arm, 141 (48.1%) in the FOLFOX-4+bevacizumab arm, and 159 (65.2%) in the bevacizumab monotherapy arm. Approximately a fifth of all randomised patients withdrew due to safety reasons (69 patients (23.6%) in the FOLFOX-4 arm, 66 patients (22.5%) in the FOLFOX-4+BV arm, and 28 patients (11.5%) in the BV monotherapy arm).

Recruitment

Between 13 November 2001 and 28 April 2003, 829 patients with advanced CRC were randomised to one of the three treatment arms; 292 patients to FOLFOX-4, 293 patients to FOLFOX-4+BV, and 244 patients to BV monotherapy. Enrolment into the BV monotherapy arm was closed 11 Match 2003.

Conduct of the study

The protocol was amended eight times after November 2001 when the first patients began treatment. The amendments to the study protocol are not considered to influence the result of the analysis of OS.

Protocol deviations

A total of 9 patients (1.1%) were assessed as ineligible for the study by ECOG. The most common explanation provided for ineligibility based on available comments was lack of measurable disease. The protocol deviations were mostly similarly distributed across the two principal arms (FOLFOX-4+bevacizumab arm and FOLFOX-4 arm). There were no major protocol deviations.

Primary Endpoint

Overall survival

The analysis population for the primary efficacy endpoint consisted of all patients randomised to the principal treatment arms (FOLFOX-4+BV and FOLFOX-4). The final analysis was performed using the most current and complete efficacy data available (received from Genentech Inc. by ECOG on 1 August 2005). Among the 585 patients randomised to the two principal arms, 525 deaths had occurred at the time of the final analysis: 265 in the FOLFOX-4 arm and 260 in the FOLFOX-4 + BV arm.

Overview of efficacy endpoints in study E3200 (randomised patients in the principal arms)

	FOLFOX-4 (n = 292)	**FOLFOX-4 + BV (n = 293)**
Patients who died	265	260
Censored observations	27 (9.2%)	33 (11.3%)
Duration of survival [a] (mo)		
Median	10.8	13.0
95% CI	10.12-11.86	12.09-14.03
25%–75% percentile	6.9–17.4	8.4–22.3
Range	0.0–40.0 +	0.3–39.1 +
Stratified analysis		
Hazard ratio [b]	0.751	
95% CI	0.63-0.89	
p-value (log-rank)	0.0012	

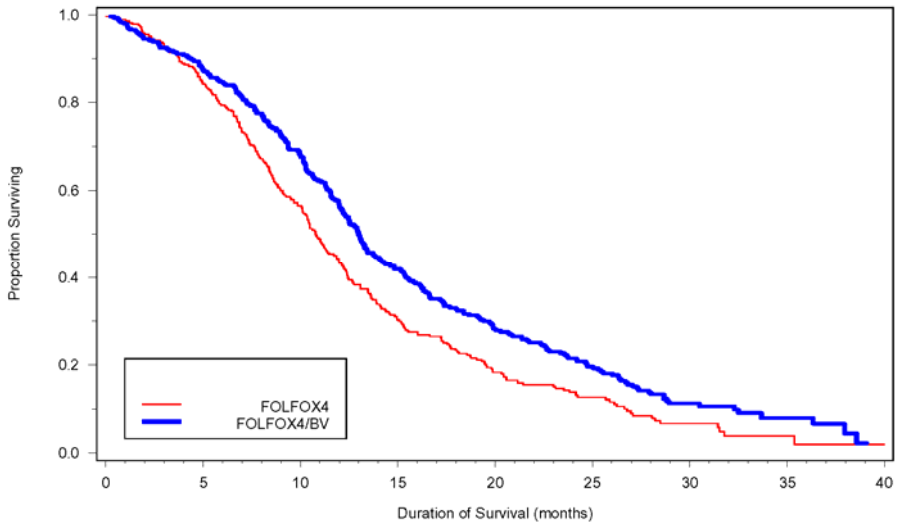
CI = confidence interval; FOLFOX-4 = oxaliplatin/5-fluorouracil/leucovorin; NA = not applicable; + indicates a censored value.

[a] Summary statistics are from Kaplan-Meier analysis; 95% CI was computed using the method of Brookmeyer and Crowley.

[b] Relative to FOLFOX-4. Estimated by Cox regression. The strata are ECOG performance status (0, ≥ 1) and prior radiotherapy (yes, no)

Overall survival was statistically significantly longer for patients in the FOLFOX-4+BV arm (13.0 months) compared with patients in the FOLFOX-4 arm (10.8 months). The stratified hazard ratio for death for FOLFOX-4+BV relative to FOLFOX-4 was 0.751 (95% CI: 0.63, 0.89). There were 13.1 % more patients alive after 12 months in the FOLFOX-4+BV treated group compared to the group receiving FOLFOX-4 treatment.

Study E3200 – Kaplan-Meier estimate of duration of survival (randomised patients in the principal arms)



A total of 56.3% of FOLFOX-4+BV patients and 43.2% of FOLFOX-4 patients were alive 12 months after randomisation (Table 6). Median follow-up for surviving patients was 25.0 months (FOLFOX-4) and 28.9 months (FOLFOX-4+BV).

Table 6: Proportion of patients alive by time point in study E3200 (randomised patients in the principal arms)

Time from Randomisation	**FOLFOX-4 (n = 292)**	**FOLFOX-4+BV (n = 293)**
3 months	92.8%	92.5%
6 months	79.3%	84.6%
9 months	59.9%	72.4%
12 months	43.2%	56.3%

FOLFOX-4 = oxaliplatin/5-fluorouracil/leucovorin. Note Summary statistics are from Kaplan-Meier analysis
(Source: Module 5(15))

Secondary endpoint

Progression-free survival

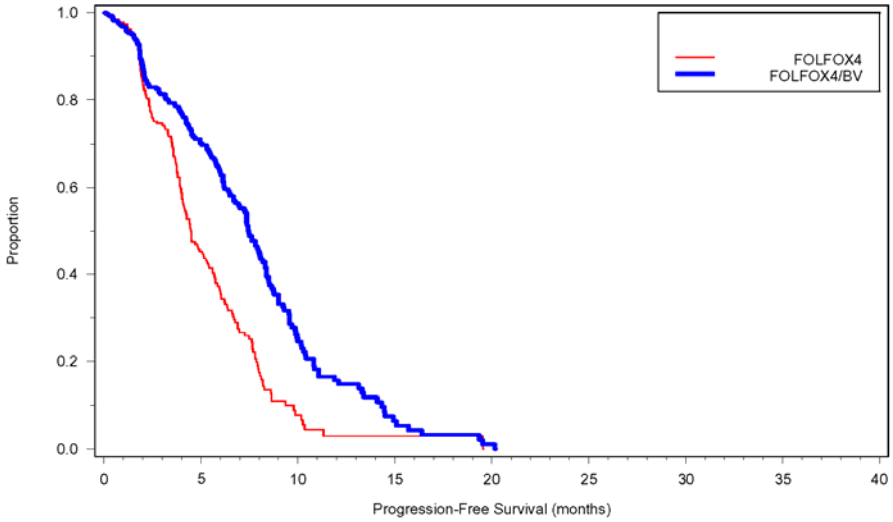
A total of 356 patients in the principal arms had died or experienced disease progression during protocol therapy at the time of the final analysis, 179 patients in the FOLFOX-4 arm and 177 patients in the FOLFOX-4+BV arm (Table 7 and Figure 3). The difference in median PFS was 3 months in favour of the FOLFOX-4+BV group, which was statistically significant ($p < 0.0001$).

Table 7: Overview of secondary endpoints in study E3200 (randomised patients in the principal arms)

Efficacy Parameter	FOLFOX-4 (n = 292)	FOLFOX-4+BV (n = 293)
Patients with an event (progression or death)	179	177
Median PFS[a] (95% CI)	4.5 months (4.07-5.26)	7.5 months (6.77-8.18)
Hazard ratio[b] (95% CI)	0.52 (0.42-0.65)	
p-value (stratified log-rank)	< 0.0001	
Objective response rate[c] (95% CI)	8.6% (5.7%-12.5%)	22.2% (17.6%-27.5%)
p-value (stratified analysis[d])	< 0.0001	
Complete response	0.7%	1.7%
Partial response	7.9%	20.5%
Median duration of response[e)] (95% CI)	6.0 (4.63-6.21)	6.2 (5.85-7.66)

CI = confidence interval; FOLFOX-4 = oxaliplatin/5-fluorouracil/leucovorin; NA = not applicable
[a] Summary statistics are from Kaplan-Meier analysis; 95% CI was computed using the method of Brookmeyer and Crowley.
[b] Relative to FOLFOX-4. Estimated by Cox regression. The strata are ECOG performance status (0, ≥ 1) and prior radiotherapy (yes, no). [c] Complete or partial response (RECIST).
[d] The p-value is based on the Cochran-Mantel-Haenszel test. The strata are ECOG performance status (0, ≥ 1) and prior radiotherapy (yes, no). [e)] For patients who had an objective response, n=25 in FOLFOX-4 and n=65 in FOLFOX-4+BV

Figure 4: Kaplan-Meier estimate of progression-free survival in study E3200 (randomised patients in the principal arms)



(Source: Module 5(15))

Objective response rate

Among all randomised patients in the principal arm, the objective response rate was significantly higher ($p < 0.0001$) in the FOLFOX-4+BV arm (22.2%) than in the FOLFOX-4 arm (8.6%). The majority of responses were partial responses (FOLFOX-4+BV (20.5%) and FOLFOX-4 (7.9%)).

Duration of response

For patients with an objective response, the median duration of objective response in the FOLFOX-4 arm was 6.0 months and ranged from 1.8 to 8.3 months. Median duration of objective response in the FOLFOX-4+bevacizumab arm was 6.2 months and ranged from 0 to 13.7 months. Because the determination of duration of objective response was based on a non-randomised subset of patients, formal hypothesis testing was not performed. However, treatment arms were compared for descriptive purposes (HR = 0.650; log-rank p = 0.2014, unstratified analysis).

Supportive analyses

Subgroup Analyses

Subgroup analyses of the primary efficacy endpoint duration of survival were performed according to the following parameters:

- ECOG performance status at study entry (0, ≥ 1)
- Prior radiotherapy (yes, no)
- Age (< 40, 40–64, ≥ 65 years)
- Gender, race (white, non-white)
- Number of involved sites (1, > 1)
- Baseline CEA value (≤ ULN, > ULN)
- Baseline sum of longest diameters of all target lesions (< median, ≥ median).

The results of these subgroup analyses were consistent with those for the randomised population as a whole. Overall, there was a trend for prolonged duration of survival for patients in the FOLFOX-4+BV arm compared with those in the FOLFOX-4 arm regardless of the baseline risk factor examined. For patients with baseline CEA values below ULN, the hazard ratio was 1.11. Most likely, this is due to the relatively small number of patients in this subgroup which is also reflected in the wide confidence interval.

Treatment effect with adjustment for risk factors

Hazards regression was applied to estimate the effect of bevacizumab after adjusting for important prognostic factors for overall survival. The adjusted hazard ratio indicate an approximately 31% reduction in the hazard of death among patients who received FOLFOX-4+BV treatment compared to those who received FOLFOX-4, and thus support the primary analysis.

Exploratory analyses

Sensitivity analysis of duration of survival

At the FDA's request, a sensitivity analysis was performed for duration of survival for the principal treatment arms, in which patients who were lost to follow-up for survival were analyzed as events as of the date of last contact, rather than as censored observations. The sensitivity analyses support the result of the primary analysis.

Bevacizumab monotherapy arm

Exploratory analyses of duration of survival, PFS, and objective response were performed for the bevacizumab monotherapy arm. The objective response rate in the bevacizumab monotherapy arm was 3.3%. All objective responses were partial responses.

In the BV monotherapy arm OS was not significantly different from the FOLFOX-4 arm (p=0.7631), while PFS was 2 months shorter (p<0.0001) in the BV arm. Additionally, the ORR was significantly lower (p=0.0121) in the BV monotherapy treatment arm.

As patients stopped therapy in the BV monotherapy arm, it is likely that they received standard oxaliplatin and/ or irinotecan-based regimens. This may have led to a similar overall survival in the BV monotherapy arm to that in the FOLFOX-4 alone arm. However, since information on the therapies received after progression was not collected in this study, it is not possible to confirm this.

Symptomatic deterioration

Symptomatic deterioration was assessed by the investigator for treated patients on the ECOG Follow-Up Disease Evaluation Form. Overall, the symptomatic deterioration was equally distributed across the treatment arms. However, there were significantly more patients who experienced symptomatic deterioration without disease progression in the FOLFOX-4+BV arm compared to the other treatment arms, with the lowest incidence in the BV monotherapy arm. This may be due to FOLFOX-4 related toxicity.

Duration of survival: Comparison of the FOLFOX-4+BV arm with the FOLFOX-4 and bevacizumab monotherapy arms

At the request of the FDA, an exploratory analysis was performed to evaluate whether the FOLFOX-4+ BV arm was superior to both the FOLFOX-4 and bevacizumab monotherapy arms as measured by duration of survival. Not surprisingly, the results of the Bayesian analysis were in line with the results of the primary analysis and indicated that it is highly likely that FOLFOX-4+bevacizumab is superior both to FOLFOX-4 and to bevacizumab monotherapy as measured by duration of survival.

2. 4. Clinical Safety

Introduction:

The two clinical trials (NO16966 and E3200), together with a number of published studies (Table 2) yield a total of approximately 5800 patients exposed to bevacizumab in combination with various fluoropyrimidine-based therapies in different lines of treatment. Of these patients approximately 5000 have been treated with an oxaliplatin-based regimen.

Table 2: Safety Information from Studies in mCRC of Bevacizumab in Combination with First-Line Chemotherapy

Study	Design and Status	Treatment	Available Safety Information	No. of Patients[1]
AVF2107g CSR addendum	Phase III, R, DB, C, PC, PG 163 centers: USA and AUS. Completed	IFL + P IFL + 5 mg/kg/q2w BV 5-FU/LV + 5 mg/kg/q2w BV	AEs, SAEs	397 392 109
AVF2192g CSR addendum	Phase II, R, DB, C, PC, PG 60 centers: USA, AUS, NZ. Completed	Roswell Park regimen (5-FU/LV) + P Roswell Park regimen (5-FU/LV) + 5 mg/kg/q2w BV	AEs, SAEs	104 100
ARD 5099 (TREE) Hochster et al. 2006	Phase II, R, OL, C, PG Multicenter in USA Completed	mFOLFOX6 ± 5 mg/kg/q2w BV bFOL ± 5 mg/kg/q2w BV XELOX ± 7.5 mg/kg/q2w BV	Grade 3/4 AEs in first 12 weeks of treatment	147 TREE-1 213 TREE-2
MO18024 (First BEAT) Berry et al. 2006	Phase IV, single arm, observational study Multicenter in 40 countries Ongoing	5-FU based CT + 5 mg/kg/q2w BV Capecitabine based CT + 7.5 mg/kg/q3w BV	SAEs	1603
AVF2941n (BRiTE) Hedrick et al. 2006	Registry study in USA, single arm, observational study Ongoing	First-line CT + BV	SAEs, BV targeted AEs	1968
MO18458 (AVIRI) Sobrero et al. 2006	Phase IV, OL, NC 31 centers: Australia, Canada, China, Italy, Spain. Ongoing	FOLFIRI + 5 mg/kg/q2w BV	Full safety (AEs, labs)	209

AE: adverse events; b FOL: bolus 5-FU/LV and oxaliplatin; BV: bevacizumab; C: comparative; CO: cross over; CT: chemotherapy; DB: double blind; FOLFIRI: 5-FU/LV/irinotecan; FOLFOX: 5-FU/LV and oxaliplatin; 5-FU: 5-fluorouracil; IFL: irinotecan/5-FU/LV; LV: leucovorin; OL: open label; mCRC: metastatic colorectal cancer; NC: non-controlled; P: placebo; PC: placebo controlled; PG: parallel group; q2w: every 2 weeks; q3w: every 3 weeks; R: randomized; SAE: serious adverse event. [1] treated patients only

The differences between the two key studies in this submission (NO16966 and E3200) in overall design and, in particular, the safety reporting requirements, do not support meaningful pooling or quantitative comparisons of the safety profile across studies. Rather a qualitative comparison of the safety profiles can be made. However, the number of patients treated and included in safety evaluation is large, yielding robust data on safety of bevacizumab in combination with fluoropyrimidine-based chemotherapy regimens in mCRC. The data from the E3200 trial conform to the usual principles of registration of side effects in ECOG, and although this differs from the usual European standards, it is of no concern for the present evaluation, because no bias is introduced and because the data material is so large.

2. 4. 1. Exposure

Study NO16966

A total of 353 patients in the XELOX + BV arm and 341 in the FOLFOX-4 + BV arm were exposed to BV. In the primary treatment phase, the median duration of treatment with BV vs placebo was similar in the XELOX and FOLFOX-4 arms (182 vs 168 days and 184 days vs 192 days, respectively). The median duration of treatment with chemotherapy was also similar in the BV arms and their placebo counterparts. 10 patients in the FOLFOX-4 + P arm and 6 patients in the XELOX + P arm received BV at some time during the study and were, therefore, analyzed for safety in the respective BV arms.

Overall, patients received triple therapy for their entire treatment duration in the primary treatment phase: a median of 8 cycles (24 weeks) in the XELOX + BV arm, 7 cycles (21 weeks) in the XELOX + P arm, and 11 cycles (22 weeks) in each of the FOLFOX-4 arms. There were a higher number of patients in the BV arms that received chemotherapy alone for some cycles compared with the placebo arms (69 vs 35 patients, respectively). These numbers include patients who interrupted BV for one or more cycles and re-started again, or who discontinued BV permanently.

Median cumulative doses of BV were similar in the XELOX + BV and FOLFOX-4 + BV arms (4231.0 and 4320.0 mg, respectively) and similar to placebo (3862.5 and 4118.0 mg, respectively). The median cumulative doses of the FOLFOX-4 treatment components (5-FU bolus, 5-FU infusion, leucovorin, and oxaliplatin) and the XELOX treatment components (capecitabine and oxaliplatin) were slightly higher in the BV arms compared with their corresponding placebo arms.

Overall, in study NO16966 the median duration of chemotherapy treatment was similar between the BV arms and their corresponding placebo arms (approx. 6 months), despite the fact that the protocol allowed continuation of the study therapy until PD or unacceptable toxicity.

Study E3200

A total of 285 patients in the FOLFOX-4 arm and 287 patients in the FOLFOX-4 + BV arm received treatment, defined as at least one component of protocol therapy. As per NCI-CTC AE reporting standards, data were not collected for exposure to individual components of protocol therapy. The number of cycles of protocol therapy received was higher for patients in the FOLFOX-4 + BV arm (median of 10 cycles) than in the FOLFOX-4 arm (median of 7 cycles). The duration of exposure, defined as time from initiation of protocol therapy until termination of protocol therapy, was longer in the FOLFOX-4 + BV arm (median 160 days) than in the FOLFOX-4 arm (median of 105 days)

It is noted that the exposure to treatment was as long as or longer in the bevacizumab arms of the protocols compared to the control arms. There is, therefore, no problem with the exposure to bevacizumab containing regimens in the analyses of toxicity.

2. 4. 2. Adverse Events

Study NO16966

Analysis of AEs is based primarily on the comparison of the pooled chemotherapy + BV arms (XELOX + BV and FOLFOX-4 + BV) vs the chemotherapy + P arms (XELOX + P and FOLFOX-4 + P) The following key results were observed with the addition of BV to chemotherapy:

- The overall incidence of grade 3/4 AEs was higher in the chemotherapy + BV arms than in the chemotherapy + P arms (80.0% vs 74.8%, respectively).

AEs of special interest for chemotherapy, as predefined in the protocol, were seen in a similar proportion of patients in the chemotherapy + BV and chemotherapy + P arms, with the following exceptions:

1. The incidence of PPE was increased in the chemotherapy + BV arms (grade 3: 7.1% vs 3.4%), predominantly in the XELOX arms only.
2. The incidence of gastrointestinal disorders was increased in the chemotherapy + BV arms (grade 3/4: 32.4% vs 27.1%), due to higher incidences in a number of different events (eg, diarrhea, nausea/vomiting, and stomatitis) in the BV groups.
3. The incidence of all grade and grade 3/4 cardiac AEs (including cardiac arterial thromboembolic AEs) was increased in the chemotherapy + BV arms compared with the

chemotherapy + P arms (all grades: 7.8% vs 5.2%; grade 3/4: 3.5% vs 0.4%, respectively). The increase was seen in both treatment subgroups (FOLFOX-4: 2.9% vs 0.3%; XELOX: 4.0% vs 0.6%, respectively).

4. The incidences of AEs of special interest defined for BV were the following:
   a. Bleeding (all grades) events were increased in the chemotherapy + BV arms vs chemotherapy + P (30.5% vs 25.9%); the majority of events were grade 1/2.
   b. Thromboembolic events were increased in the chemotherapy + BV arms vs chemotherapy + P, respectively:
      1. Grade 3/4 arterial thromboembolic events: 12 patients (1.7%) vs 7 (1.0%).
      2. Grade 3/4 venous thromboembolic events: 54 patients (7.8%) vs 33 (4.9%).
   c. Hypertension was increased in the chemotherapy + BV arms vs chemotherapy + P (all grade: 18.9% vs 6.4%, grade 3/4: 3.7% vs 1.2%, respectively).
   d. Grade 3/4 gastrointestinal perforations, proteinuria, and wound healing complications were all uncommon.
5. A higher proportion of patients discontinued all study treatment due to AEs in the BV treatment arms (approximately 31% vs 21%) mainly due to chemotherapy-related toxicity; however, 21% of the patients in the BV treatment arms versus 15% in the placebo arms discontinued all therapy due to grade 3/4 AEs, showing that discontinuations due to AEs that were not severe or life-threatening were not uncommon. Only 5% of the patients in the BV treatment arms and 2% in the placebo arms discontinued all study treatment due to AEs of special interest for BV.
6. Thirty (4.3%) patients in the chemotherapy + BV arms and 15 (2.2%) patients in the chemotherapy + P arm died due to causes other than progressive disease (PD) (deaths up to 28 days after last drug administration. The incidence of treatment-related deaths (up to 28 days after last drug administration) was 2.0% (14 patients) in the chemotherapy + BV arms and 1.5% (10 patients) in the chemotherapy + P arms; the 60-day mortality rate was 2.0% (14 patients) in the chemotherapy + BV arms and 1.6% (11 patients) in the chemotherapy + P arms.

Common Adverse Events

- All Grade Adverse Events

Nearly all patients in each treatment group (99% to 100%) experienced at least one AE. The overall incidence of the most commonly occurring AEs was similar between the BV arms and the corresponding placebo arms. Increases in the incidence (≥ 5% in absolute difference) of common AEs with the addition of BV to each treatment regimen included the following:

Increases in the chemotherapy + BV arms vs chemotherapy + P, respectively:

- Anorexia: 30% vs 25% (the increase was more marked in XELOX + BV arm)
- Epistaxis: 21% vs 13% (with an overall higher incidence in FOLFOX-4 arms)
- Hypertension: 16% vs 6%

Increases in the XELOX + BV arm vs the XELOX + P arm, respectively:

- Vomiting: 47% vs 41%
- PPE: 39% vs 30%
- Stomatitis: 29% vs 22%

Increases in the FOLFOX-4 + BV arm vs the FOLFOX-4 + P arm, respectively:

- Chest pain: 9% vs 4%,
- Dysphonia: 8% vs 1%

The following AEs had a lower incidence in the chemotherapy + BV arms vs chemotherapy + P, respectively:

- Neutropenia: 37% vs 43%
- Thrombocytopenia: 13% vs 21%

Grade 3/4 Adverse Events

Grade 3/4 AEs were reported in a higher percentage of patients in the chemotherapy + BV arms compared with the chemotherapy + P arms (80% vs 75%). Similar results were seen in the 4-arm comparison (76% vs 70% in the XELOX + BV and XELOX + P arms, respectively, and 84% vs 80% in the FOLFOX-4 + BV and FOLFOX-4 + P arms, respectively. The incidence of the following grade 3/4 AEs was higher in the BV arms compared with their corresponding placebo arms:

In the chemotherapy + BV arms vs chemotherapy + P arms, respectively

- Gastrointestinal disorders: 32% vs 27%, including diarrhea (17% vs 15%) and vomiting (6% vs 4%)
- Vascular disorders: 10% vs 5%, including hypertension (3% [23 patients] vs < 1% [6 patients]) and deep vein thrombosis (DVT, 3% [19 patients] vs 1% [10 patients])
- Cardiac disorders: 3% (24 patients) vs < 1% (3 patients), the events in the BV arms including a mixture etiologies, ie, ischemic events, arrhythmias and heart failure.
- Pulmonary embolism: 3% (18 patients) vs < 1% (6 patients)

In the XELOX + BV arm vs the XELOX + P arm, respectively:

- PPE: 12% vs 6%

Neutropenia was the most frequently reported grade 3/4 AE and had a lower incidence in the chemotherapy + BV arms compared with the chemotherapy + P arms (23% vs 26%, respectively). Most of these adverse events were expected to be somewhat more common in the bevacizumab arms, based on the known toxicity profile of bevacizumab.

Deaths

All Deaths

The overall proportion of patients who died during the whole study was lower in the chemotherapy + BV arms (32%) than in the chemotherapy + P arms (36%). The majority of deaths were directly attributed to PD. With respect to the non-PD related deaths, causes were generally of similar nature between arms. However, more deaths in the chemotherapy + BV arms compared with the chemotherapy + P arms were reported in the cardiac system organ class (1.4%, 10/694 patients vs 0.3%, 2/675 patients, respectively), and due to gastrointestinal obstruction (0.6%, 4/694 patients vs none, respectively). AEs of special interest for BV with fatal outcome were rare and occurred with a similar incidence in each group: gastrointestinal perforation, hemorrhage, (single patients in each group) and thromboembolic events (4 patients in each group). Other causes of death such as infection and gastrointestinal toxicity occurred with similar incidence in both treatment groups.

The pattern in overall causes of death was similar between the BV arms and their corresponding placebo arms in the 4-arm comparison, with the exception of: gastrointestinal obstruction and cardiac deaths. Four cases of gastrointestinal obstruction leading to death occurred in the XELOX + BV arm. All 4 cases were considered by the investigators to be unrelated to treatment, and PD was considered the likely cause in 3 of 4 cases. The fourth case was not clearly associated with PD. More deaths in the BV arms were reported in the cardiac system organ class compared with their corresponding placebo arms (7/353 in XELOX + BV vs 1/339 in XELOX + P; 3/341 in FOLFOX-4 + BV vs 1/336 in FOLFOX-4 + P).

Deaths within 60 Days of Treatment Start

The overall incidence of death cases occurring within 60 days of start of study treatment was the same in the chemotherapy + BV arms (2%, 14/694 patients) and in the chemotherapy + P arms (2%, 11/675 patients). The most frequent causes of these early deaths were infections (4 vs 3 patients in the chemotherapy + BV and chemotherapy + P arms, respectively) and cardiac deaths (4 vs 1 patient, respectively). Pulmonary embolism accounted for 3 deaths within 60 days of study treatment initiation in the chemotherapy + P arms only.

Of all deaths that occurred in the study due to infection, 7/14 occurred in the first 60 days of treatment start, and were evenly distributed across the 4 treatment arms (2 in XELOX + BV, 2 in FOLFOX-4 + BV, 3 in FOLFOX-4 + P, and none in XELOX + P). Of the cardiac deaths in the study, 5/12 occurred in the first 60 days of treatment (3 in XELOX + BV, 1 in FOLFOX-4 + BV, and 1 in FOLFOX-4 + P)

Deaths within 28 Days of Last Dose of Study Medication

In the chemotherapy + BV arms, 33 patients (5%) died within 28 days of their last dose of study medication (ie, at any time between start of treatment and 28 days after last dose) compared with 16

patients (2%) in the chemotherapy + P arms. Four of these deaths (3 in the chemotherapy + BV and 1 in the chemotherapy + P arms) were attributed to PD. Cardiac-related deaths (9 patients) and infections (7 patients) were the most frequent causes of non-PD related deaths in the chemotherapy + BV arms while infections (5 patients) were the most frequent cause in the chemotherapy + P arms.

In the 4-arm comparison, deaths within 28 days of the last dose of study medication occurred in 19 patients (5%, XELOX + BV) and 14 patients (4%, FOLFOX + BV) in the BV arms compared with 9 patients (3%, XELOX + P) and 7 patients (2%, FOLFOX + P) in the placebo arms. Of the 4 deaths attributed to PD, 2 were in the XELOX + BV arm, 1 was in the FOLFOX-4 + BV arm and 1 was in the XELOX + P arm. Most non-PD related causes of death were seen in only 1 or 2 patients per treatment group, with the following exceptions:

Infections were the cause of death in 4 patients (1%) in both FOLFOX-4 arms and 3 patients (< 1%) in the XELOX + BV arm.

Cardiac deaths occurred in 6 patients (2%) in the XELOX + BV arm and in 3 patients (< 1%) in the FOLFOX-4 + BV arm compared with none and 1 in the corresponding placebo arms.

Respiratory organ system-related deaths occurred in 3 patients (< 1%) in the XELOX + BV arm.

- **Other Serious Adverse Events**

The overall incidence of SAEs was similar in the chemotherapy + BV and chemotherapy + P arms (40% and 37%, respectively). Small increases in incidence were seen in the chemotherapy + BV arms vs chemotherapy + P, respectively, in the following system organ classes:

Gastrointestinal disorders: 17% vs 15%

Respiratory, thoracic, and mediastinal disorders: 6% vs 4%

Cardiac disorders: 3% vs < 1%

There were no major differences between treatment arms for the most commonly occurring individual SAEs, Table 26, with the exception of pulmonary embolism (17 patients [2%] in the chemotherapy + BV arms vs 7 patients [1%] in the chemotherapy + P arms).

The overall incidence of SAEs was similar between the XELOX + BV and XELOX + P arms (37% and 36%, respectively), but higher in the FOLFOX-4 + BV compared with the FOLFOX-4 + P arms (43% vs 38%, respectively).

Increases in incidence of SAEs were seen in the BV arms vs their corresponding placebo arms, respectively, in the following system organ classes:

- Cardiac disorders: 3% vs < 1%, mainly due to the occurrence of more cardiac events in the BV arms
- Respiratory, thoracic, and mediastinal disorders: 6% in XELOX + BV vs 4% in XELOX + P; 5% in FOLFOX-4 + BV vs 3% in FOLFOX-4 + P; the difference in incidence partly due to an increased incidence of pulmonary embolism in the BV arms compared with their corresponding placebo arms

In the XELOX + BV arm vs the XELOX + P arm, respectively:

- Vascular disorders: 5% vs < 1%, mainly due to DVT (2% vs < 1%), as well as, the occurrence of more single events

In the FOLFOX-4 + BV arm vs the FOLFOX-4 + P arm, respectively:

- Gastrointestinal disorders: 14% vs 10%, mainly due to vomiting and obstruction of the small intestine (2% vs < 1% for both events), and the occurrence of more single events in the FOLFOX-4 + BV arm

- **Other Significant Adverse Events**

Adverse Events Leading to Discontinuation of Trial Treatment

The overall incidence of AEs leading to discontinuation of all trial treatment, as recorded on the AE page of the CRF, was higher in the chemotherapy + BV arms (30%, 207/694 patients) than in the chemotherapy + P arms (21%, 141/675 patients)

The types of AEs leading to discontinuation of all study treatment were generally chemotherapy-related AEs. Nervous system disorders were the most frequent causes of withdrawal from all study treatment, occurring with a similar incidence across treatment arms (7% in XELOX + BV, 6% in XELOX + P, 7% in FOLFOX-4 + BV, and 8% in FOLFOX-4 + P).

Increases in the incidence of AEs leading to treatment discontinuation with the addition of BV to each treatment regimen included the following:
In the chemotherapy + BV arms vs the chemotherapy + P arms, respectively:
Gastrointestinal disorders: 8% (54/694 patients) vs 5% (31/675 patients), the difference attributable mainly to the incidence of diarrhea, which was more common in both XELOX arms
Cardiac disorders: 2% (17/694 patients) vs < 1% (2/675 patients), the difference mainly due to ischemic events and arrhythmias

In the XELOX + BV arm vs the XELOX + P arm, respectively:
PPE: 2% (7/353 patients) vs < 1% (2/339 patients)
Vascular disorders: 2% (6/353 patients) vs 0 – the AEs being thrombosis (3 patients) hypertension, hypertensive crisis, and thrombophlebitis (1 patient each)
Fatigue: 1% (5/353 patients) vs < 1% (1/339 patient)

In the FOLFOX-4 + BV arm vs the FOLFOX-4 + P arm, respectively
- Infections and infestations: 4% (12/341 patients) vs < 1% (3/336 patients)
- Skin reactions: 2% (6/341 patients – including allergic reactions in 3 patients and PPE in 2 patients]) vs 0.3% (1/336 patient)

The incidence of grade 3/4 AEs leading to discontinuation of all trial treatment was higher in the chemotherapy + BV arms than in the chemotherapy + P arms (21%, 145/694 patients vs 15%, 101/675 patients), although the increase was not as pronounced as for all AEs leading to discontinuation. Increases in the incidence of grade 3/4 AEs leading to treatment discontinuation in the chemotherapy + BV arms vs chemotherapy + P arms, respectively, were seen in the following system organ classes:
- Gastrointestinal disorders: 6% (43/694 patients) vs 4% (24/675 patients)
- Cardiac disorders: 2% (14/694 patients) vs < 1% (1/675 patients)
- Infections and infestations: 2% (12/694 patients) vs < 1% (5/675 patients)

Nervous system disorders (grade 3/4) frequently led to trial treatment discontinuation in a similar proportion of patients in both treatment groups (4% [26/694 patients] in the chemotherapy + BV arms and 5% [33/675 patients] in the chemotherapy + P arms).

AEs of special interest for BV (all grades) led to discontinuation of all trial treatment in 5% (36/694) of patients in the chemotherapy + BV arms compared with 2% (16/675) in the chemotherapy + P arms. The most frequent causes of these treatment discontinuations in the BV arms were thromboembolic AEs (venous and arterial), accounting for 19/36 patients. With respect to the 4-arm comparison, arterial thromboembolic events leading to discontinuation occurred with a similar frequency in the XELOX + BV and FOLFOX-4 + BV arms (6 patients each), whereas venous thromboembolic events occurred in the XELOX + BV arm only (7 patients).
In the chemotherapy + P arms, venous thromboembolic events were the most frequent cause of discontinuation of all trial treatment (8/675 patients), occurring with a similar frequency in both XELOX + P and FOLFOX-4 + P arms.
The incidence of grade 3/4 AEs of special interest for BV leading to discontinuation of all trial treatment was 4% (28/694 patients) in the chemotherapy + BV arms compared with 2% (12/675) in the chemotherapy + P arms, indicating that most of the AEs of special interest for BV leading to treatment discontinuation (28/36 in the chemotherapy + BV arms) were of grade 3/4 intensity. Similar to all AEs of interest for BV, grade 3/4 venous and arterial thromboembolic AEs were the most frequent cause of treatment discontinuation in the BV arms, accounting for 15/28 patients. With respect to the 4-arm comparison, grade 3/4 arterial thromboembolic events leading to discontinuation occurred with a similar frequency in the XELOX + BV and FOLFOX-4 + BV arms (5 and 3 patients,

respectively), whereas grade 3/4 venous thromboembolic events leading to discontinuation occurred in the XELOX + BV arm only (7 patients).
In the chemotherapy + P arms, grade 3/4 venous thromboembolic events were the most frequent cause of discontinuation of all trial treatment (5/12 patients), occurring with a similar frequency in both XELOX + P and FOLFOX-4 + P arms.

Adverse Events Leading to Dose Modifications
A similar proportion of patients receiving chemotherapy + BV (81% [559/694 patients]) to those receiving chemotherapy + P (83% [561/675 patients]) required dose modifications for AEs. In general, the incidence of these AEs was similar across treatment arms in each system organ class.
Increases in the incidence of AEs leading to dose modifications with the addition of BV to each treatment regimen included the following:
In the chemotherapy + BV arms vs the chemotherapy + P arms, respectively:

- Vascular disorders: 7% (46/694 patients) vs 4% (25/675 patients), attributable to both hypertension and DVT
- Pulmonary embolism: 2% (12/694 patients) vs 0.1% (1/675 patients)

In the XELOX + BV arm vs the XELOX + P arm, respectively:

- PPE: 19% (67/353 patients) vs 9% (29/339 patients)
- Fatigue: 7% (23/353 patients) vs 2% (7/339 patients)
- Proteinuria: 3% (11/353 patients) vs < 1% (3/339 patients)

There were no other single AEs with an increased incidence in the FOLFOX-4 + BV arm compared with the FOLFOX-4 + P arm

Adverse Events Requiring Treatment
Overall, 96% (666/694) of patients in the chemotherapy + BV arms and 92% (619/675) in the chemotherapy + P arms had at least one AE requiring treatment. Common gastrointestinal toxicities (eg, diarrhea, nausea, vomiting) required treatment in a similar proportion of patients in both the chemotherapy + BV and chemotherapy + P arms (77% [536/694 patients] and 75% [505/675 patients], respectively). Events in other system organ classes requiring treatment were also balanced across arms. As was seen for AEs leading to dose modifications, vascular events (hypertension and DVT) more often required treatment in the chemotherapy + BV arms compared with the chemotherapy + P arms
Increases in the incidence of other AEs requiring treatment in the XELOX + BV arm vs the XELOX + P arm, respectively:

- Stomatitis: 12% (43/353 patients) vs 7% (23/339 patients)
- Headache: 9% (31/353 patients) vs 4% (13/339 patients)

There were no appreciable increases (≥ 5%) in the incidence of other AEs requiring treatment in the FOLFOX-4 + BV arm compared with the FOLFOX-4 + P arm.

Events of Special Interest to Bevacizumab Study No. 16966

The overall incidence of grade 3/4 events pre-defined to be of special interest to BV was 16% (chemotherapy+BV) vs 8% (Chemotherapy+placebo). The most common of these events were venous thromboembolic events, hypertension, bleeding, and arterial thromboembolic events.

Hypertension: All-grade hypertension occurred in 19% (4% grade 3/4) of BV-treated patients (vs 6% [1% grade 3/4] in the chemotherapy arms). The majority of hypertension events were managed with standard anti-hypertensive therapy and resolved without sequelae. Median time to onset of hypertension AEs (all-grade) was not markedly different between the arms (9-10 weeks), while the duration of hypertension (defined as time of onset to time of resolution of the AE) was longer in the BV arms (median 15 vs 8 days). Three patients experienced grade 4 hypertension in the chemotherapy+BV arms, two instances of which occurred on the day of the infusions of oxaliplatin and BV, (the other occurring three days later). All three patients had a history of hypertension, all discontinued BV therapy, and all events resolved with treatment. As noted in the prescribing information, BV treatment should be stopped in the case of uncontrolled hypertension or hypertensive crisis.

Proteinuria: The incidence of grade 3 proteinuria was very low (three grade 3 events in the BV arms) and resolved or improved despite ongoing BV treatment. In the single case of grade 4 proteinuria, the event improved to grade 1 after stopping BV therapy.

Bleeding: The increase in bleeding events (all-grade) in the BV arms relative to the chemotherapy alone arms was mainly attributable to grade 1 or 2 epistaxis. The incidence of clinically significant bleeding (grade 3/4) was slightly higher in the BV arms (13 patients [1.9%] vs 8 patients [1.2%]) and comprised mainly GI bleeds. Few bleeding events required withdrawal from all treatment (five vs three in the Chemo+BV vs Chemo+P arms). Neither anti-coagulant therapy nor major blood vessel involvement with the tumors appeared to increase the risk of bleeding in the BV arms (24% of patients experienced bleeds while on anti-coagulant therapy vs 28% of patients who never received anti-coagulant therapy). However, due to relatively low patient numbers and the potential influence of other confounding factors and co-morbidities in these patients, the analyses should be interpreted with caution.

GI Perforation: The incidence of gastrointestinal perforation events was low in both treatment groups: 0.6% (4/694 patients) in the chemotherapy + BV arms and 0.3% (2/675 patients) in the chemotherapy arms. Of the four GI perforation events in the BV arms, one was fatal, while the other three events resolved without sequelae after stopping study treatment. One of the two GI perforations in the placebo arms was fatal.

The investigation of another event of special interest for BV was introduced into the NO16966 study in order to assess the incidence of fistulae and intra-abdominal abscesses. The finding is that such events (all grades) were observed at an incidence of 2.0% in the chemotherapy + BV arms compared with only 0.3% the chemotherapy + P arms, while grade 3/4 events were reported in the chemotherapy + BV arms only (six patients [0.9%]). These events may have a similar underlying pathophysiological mechanism to events of GI perforation, yet the actual mode of action needs still to be further characterized for both types.

Thromboembolic events (TEs): Arterial and venous TEs were leading causes of BV-related discontinuation. Most events resolved without sequelae. Fatal events were rare and equally distributed across treatment arms. Of the twelve grade 3/4 arterial TEs in the chemotherapy+BV arms, 10 events occurred within the first five weeks of treatment and six of the ten occurred in patients with no relevant medical history. The remaining two events with later onset were fatal and occurred in patients with a relevant history (NIDDM, coronary artery arteriosclerosis). The incidence of venous TEs was also higher in the chemotherapy + BV arms relative to the chemotherapy arms: grade 3/4 events: 7.8% vs 4.9%.

The BV-associated increase in both arterial and venous TEs was observed only in the older (≥ 65 years) age group. An increase in incidence of arterial TEs, particularly in older patients, was observed in previous studies, whereas an increased incidence in venous TEs was not seen previously e.g., in studies AVF2107g and AVF2192g. The current prescribing information recommends permanent discontinuation of BV treatment in the case of an arterial TE and contains general precautionary wording with respect to venous TEs such as pulmonary embolism.

Wound healing events: Per protocol, and in line with the current label, patients were not to initiate BV therapy until at least 28 days after previous surgery. Only one patient had clinically significant (grade 3/4) wound healing complications in the NO16966 study.

- **Influence of Bevacizumab on Adverse Events of Special Interest for Chemotherapy**

The overall incidence of grade 3/4 AEs of special interest for chemotherapy was similar in the chemotherapy + BV and chemotherapy + P arms (57% and 55%, respectively).

Grade 3 PPE showed the biggest difference in incidence between the chemotherapy + BV and the chemotherapy + P arms (7% vs 3%, respectively). This increased incidence in the BV arms is driven by the higher percentage of patients with PPE in both XELOX arms, in particular in the XELOX + BV

arm (12% in XELOX + BV and 6% in XELOX + P arm vs 2% in FOLFOX-4 + BV and 1% in FOLFOX-4 + P).

Although diarrhea and vomiting show only a 2% increase in incidence in the chemotherapy + BV arms compared with the chemotherapy + P arms (17% vs 15%, and 6% vs 4%, respectively), this drives the overall increase in incidence of these grade 3/4 gastrointestinal AEs of special interest for chemotherapy in the chemotherapy + BV arms (25% vs 20%, respectively).

The incidence of grade 3/4 AEs in the system organ class 'cardiac disorders' was higher in the chemotherapy + BV arms compared with the chemotherapy + P arms (3% [24/694] vs 0.4% [3/675], respectively). Two patients in the XELOX + BV arm had more than one cardiac AE: patient 35969/9855 experienced atrial fibrillation and cardiogenic shock, and patient 42141/8760 first reported sinus bradycardia and later was diagnosed with sick sinus syndrome. Cardiac disorders can be grouped by etiology as follows

- Arrhythmic events occurred in 10 patients in the chemotherapy + BV arms (3 in FOLFOX-4 + BV, 7 in XELOX + BV) vs 1 patient in the chemotherapy + P arms (XELOX + P)
- Ischemic type events occurred in 8 patients in the chemotherapy + BV arms (4 each in FOLFOX-4 + BV and XELOX + BV) vs 1 patient in the chemotherapy + P arms (XELOX + P)
- Heart failure events occurred in 2 patients in the chemotherapy + BV arms only (both in FOLFOX-4 + BV)
- Events of unspecified etiology occurred in 4 patients in the chemotherapy + BV arms (1 in FOLFOX-4 + BV, 3 in XELOX + BV) vs 1 patient in the chemotherapy + P arms (FOLFOX-4 + P)

A by-patient review of these grade 3/4 cardiac AEs showed that in the BV arms, 13/24 patients had cardiac risk factors present at baseline (eg, preexisting coronary artery disease, hyperlipidemia, hypertension, diabetes). In addition, for 3/24 patients, the cardiac AEs had an alternative explanation (eg, consequence of severe polytrauma, respiratory failure secondary to PD, or due to sepsis and respiratory failure). For the remaining 8/24 patients, there were no common underlying patterns to explain these AEs. In the chemotherapy + P arms, 1/3 patients had identifiable cardiac risk factors at baseline (ie, hypertension, cholesterolemia, and preexisting coronary artery disease).
Of the above, grade 3/4 cardiac AEs had a fatal outcome in 7 patients in the chemotherapy + BV arms (these include patients that died as a consequence of severe polytrauma, respiratory failure secondary to PD, or due to sepsis and respiratory failure) and in 1 patient in the chemotherapy + P arms. In addition, 4 patients (3 in the chemotherapy + BV arms and 1 in the chemotherapy + P arms) died of a cardiac-related cause. However, for these 4 patients either the AE was not classified under the system organ class 'cardiac disorders' (eg, AE of sudden death which is coded to the system organ class 'general disorders and administration site conditions'), or death occurred more than 28 days after last administration of study medication in which case the cardiac AE was not collected for these patients. In total, cardiac-related deaths occurred in 10 patients in the chemotherapy + BV arms and in 2 patients in the chemotherapy + P arms.
On review of the 10 death cases in the chemotherapy + BV arms 4 had underlying causes other than cardiac disorders (2 had PD, 1 car accident, 1 sepsis). Of the remaining 6 cases, all had identifiable cardiac risk factors at baseline.

Summary of Laboratory Abnormalities
In general, the addition of BV to the XELOX or the FOLFOX-4 treatment regimen did not increase the incidence of laboratory abnormalities for either treatment. The only difference between treatment arms was seen for increases in the incidence of high potassium levels in the FOLFOX-4 + BV arm relative to the FOLFOX-4 + P arm (grade 1-4: 18.5% vs 13.1%, respectively).

Adverse Events in Study E3200

Comparison of the safety profile between the two principal treatment arms in the E3200 study has a number of limitations, which should be borne in mind:

- AEs reported on E3200 Toxicity Form were considered 'related' to protocol therapy and as a consequence reporting is influenced by investigators' attribution of causality in this open-label study.
- Events reported in NCI AdEERS, while not affected by attribution of causality, may have been affected by different expedited reporting requirements across the treatment arms
- Duration of safety observation was greater in the FOLFOX-4 + BV arm than in the FOLFOX-4 arm.
- Discontinuations and dose modifications for AEs were collected retrospectively and only for BV-related events.

The duration of safety observation (defined as the number of weeks from initiation of protocol therapy until the last toxicity assessment) was longer in the FOLFOX-4 + BV arm than in the FOLFOX-4 arm (median 26.5 vs 18.1 weeks). The incidence of treatment-related grade 3-5 AEs was increased in the FOLFOX-4 + BV arm versus the FOLFOX-4 arm. Deaths within 30 days of last dose of protocol therapy were mostly attributed to PD in both treatment arms. AEs leading to withdrawal or dose modification of BV were collected retrospectively: 29% of patients had AEs leading to BV discontinuation and 20% had AEs leading to BV dose reduction.

The data on toxicity in this trial are not optimal, but they are as usually performed in ECOG studies. As far as one can judge from the data, there is no cause for concern.

- **Common Adverse Events**

Overall, 76% and 60% of patients in the FOLFOX-4 + BV and FOLFOX-4 arms, respectively, reported at least one grade 3–5 non-hematological or grade 4 or 5 hematological AE considered related to protocol therapy. The most frequently reported AEs in the FOLFOX-4 + BV arm vs the FOLFOX-4 arm, respectively, were:

- Diarrhea: 18% vs 13%
- Fatigue: 18% vs 13%
- Peripheral sensory neuropathy: 16% vs 9%
- Nausea: 11% vs 4%
- Vomiting: 10% vs 3%

These AEs are commonly known to be associated with chemotherapy treatment.
Of the most frequently reported AEs, an additional 10 treatment-related events were reported in NCI AdEERS in the FOLFOX-4 + BV arm only: 3 AEs of nausea, 2 of vomiting, 3 of infection, 1 of hypertension, and 1 of abdominal pain.

The greatest differences in incidence of AEs between treatment arms were:

- Peripheral sensory neuropathy: 16.4% vs 9.1%
- Vomiting: 10.1% vs 3.2%
- Nausea: 10.8% vs 4.2%
- Fatigue: 18.5% vs 13.0%

Similar results were seen for the most common AEs reported either in the E3200 Toxicity Form or in NCI AdEERS. Peripheral sensory neuropathy is generally associated with the chemotherapy, but bevacizumab seems to increase the risk of this complication. The increased risk of adverse events is within the range of the expected, considering the known toxicity profile of bevacizumab, and considering the fact that this was an open-label study where both patient and investigator knew that the patients in the bevacizumab arm received this additional experimental therapy. This fact may well have influenced the awareness of side effects in the bevacizumab arm.

- **Deaths**

All Deaths

Among treated patients, 254 (89%) in the FOLFOX-4 + BV arm and 259 (91%) in the FOLFOX-4 arm died during the study or in follow-up. Causes of death were similar across treatment arms; the majority of the deaths were considered by the investigators to be due to CRC. One patient's death was attributed to both disease progression and protocol therapy (sepsis syndrome). Fifteen deaths were categorized as 'due to another causes', although the cause was given as CRC in two of these cases.

Deaths within 30 Days of Last Dose of Study Medication

Consistent with all reported deaths, the majority of deaths within 30 days of the last dose of protocol therapy in both treatment arms were considered by the investigator to be due to CRC.

Adverse Events Leading to Death

In total, 17 patients in the FOLFOX-4 + BV arm and 11 patients in the FOLFOX-4 arm had grade 5 AEs reported either in the E3200 Toxicity Form or in NCI AdEERS). The majority of these AEs were considered unrelated to protocol therapy (reported mainly in AdEERS) and 9 AEs were directly attributed to disease progression (3 patients in FOLFOX-4 + BV and 6 patients in FOLFOX-4).

Five patients in the FOLFOX-4 + BV arm experienced grade 5 AEs considered related to protocol therapy either as reported in the E3200 Toxicity Form, or in in NCI AdEERS, or as cause of death in the E3200 Long-Term Follow-up Form. None of the events were reported in more than one patient.

- **Other Serious Adverse Events**

Expedited reporting of AEs in Study E3200 was conducted via NCI AdEERS. Since the criteria for expedited reporting of AEs were different in each treatment arm, comparisons between treatment arms must be interpreted with caution.

A total of 123/287 patients (42.9%) in the FOLFOX-4 + BV arm experienced at least one event that required expedited reporting in NCI AdEERS. The most frequent AEs requiring expedited reporting in this treatment arm were diarrhea (6.3%, 18/287 patients), vomiting (6.3%, 18/287 patients), infection (6.3%, 18/287 patients), and dehydration (5.2%, 15/287 patients).

A total of 75/285 patients (26.3%) in the FOLFOX-4 arm experienced at least one event that required expedited reporting in NCI AdEERS. The most frequent AEs requiring expedited reporting in this treatment arm were dehydration (3.5%, 10/285 patients), infection (3.5%, 10/285 patients), and pyrexia (3.2%, 9/285 patients).

- **Other Significant Adverse Events**

Adverse Events Leading to Dose Modification of Bevacizumab

Protocol-specified criteria for BV dose reduction were grade 1/2 hypertension, grade 2 hemorrhage, grade 2 coagulopathy, grade 3/4 liver function test abnormalities, or proteinuria ≥ 500 mg/24 h. Lower grades of AEs were collected on these forms compared to the AEs collected in the E3200 Toxicity Forms (ie, grade 4-5 hematological and grade 3-5 non-hematological AEs). Therefore, comparisons between the datasets are not possible.

The E3200 Bevacizumab Dose Modification Form was collected for 241 of 287 treated patients (84.0%). Among the 241 patients with any dose modification data, the BV dose was reported as reduced from 10 mg/kg to 5 mg/kg for toxicity in 47 patients (20%). The most common AEs leading to dose modification were hypertension (10% [23/241]) and proteinuria (9% [21/241]). Hypertension events resolved or improved in 18/23 patients (78.3%), note that treatments received for AEs were not collected, as per standard NCI-CTC AE reporting procedures). Proteinuria events resolved or improved in 15/21 patients (71.4%). Most other events resolved or improved. No patient reported a dose reduction for liver function test abnormalities.

Adverse Events Leading to Discontinuation of Bevacizumab

AEs that led to discontinuation of BV were retrospectively collected in the BV discontinuation section of the E3200 Bevacizumab Dose Modification Form. Protocol-specified criteria for BV

discontinuation included grade ≥ 3 hypertension, grade ≥ 3 hemorrhage, grade ≥ 3 coagulopathy, a new or worsening grade ≥ 2 arterial thromboembolic event, or any protocol-specified AE requiring BV dose reduction for a patient who had already had one reduction.

Among the 241 patients with BV discontinuation data, BV was reported as discontinued for toxicity in 69 patients (29%). The most common AEs leading to BV discontinuation were hypertension (7% [16/241]) and fatigue (4% [10/241]).

Adverse Events of Special Interest - Study E3200
A summary of treatment-related grade 3-5 AEs of special interest for BV reported in the E3200 Toxicity Form only and recoded using MedDRA show as expected, more patients in the FOLFOX-4 + BV arm experienced at least one AE of special interest for BV (15% vs 5% in FOLFOX-4 arm). The most common of these AEs was hypertension (6% vs 2%).

Hypertension: The incidence of treatment-related grade 3/4 hypertension was increased in the FOLFOX-4 + BV arm compared with the FOLFOX-4 arm (6.3% [18/287 patients] vs 1.8% [5/285 patients], respectively). One additional AE of hypertension was reported in NCI AdEERS in the FOLFOX-4 + BV arm, giving an overall incidence of treatment-related grade 3/4 hypertension of 6.6% (19/287 patients) in this arm compared with 1.8% (5/285 patients) in the FOLFOX-4 arm.

Proteinuria: The incidence of treatment-related proteinuria was 0.7% (2/287) in the FOLFOX-4 + BV arm. No events were reported in the FOLFOX-4 arm. No grade 4 or 5 proteinuria events were reported. No additional proteinuria AEs were reported in NCI AdEERS.

Bleeding: The incidence of treatment-related grade 3–5 bleeding events was increased in the FOLFOX-4 + BV arm compared with the FOLFOX-4 arm (3.8% [11/287 patients] vs 0.4% [1/285 patient], respectively). In the FOLFOX-4 + BV arm, 1 patient (2000137/33033) had grade 5 hemorrhage. The incidence of grade 3-5 bleeding events reported either in the Toxicity Form or in AdEERS was 4.9% (14/287 patients) in the FOLFOX-4 + BV arm and 0.7% (2/285 patients) in the FOLFOX-4 arm. Two grade 5 events were reported in the FOLFOX-4 + BV arm (gastrointestinal hemorrhage and cerebral hemorrhage).

Gastrointestinal Perforation, Intra-Abdominal Abscess, and Fistula Adverse Events: There is no unique term or grade for gastrointestinal perforation or abscess events in NCI-CTC version 2.0. For this reason, verbatim AE terms were not collected on the E3200 Toxicity Form, and fistula events not considered related to protocol therapy were also not collected on the E3200 Toxicity Form. Identification of these events was performed by a Genentech review of data from both the E3200 Toxicity Form and NCI AdEERS reports.

No treatment–related grade 3-5 AEs of gastrointestinal perforation were reported in the E3200 Toxicity Form. However, gastrointestinal perforations were reported in NCI AdEERS for 5/287 patients (1.7%) in the FOLFOX-4 + BV arm only. One of these events was associated with death within 30 days of the event.

No treatment–related grade 3-5 AEs of intra-abdominal abscesses were reported in the E3200 Toxicity Form. However, intra-abdominal abscess was reported in NCI AdEERS for 6/287 (2.1%) patients in the FOLFOX-4 + BV arm only. Among these patients, 3 were not considered to have had a gastrointestinal perforation event.

In the FOLFOX-4 + BV arm, treatment-related grade 3/4 fistula was reported in 2/287 patients (0.7%) in the E3200 Toxicity Form. If AEs reported in NCI AdEERS are taken into account, fistula was reported in 5/287 (1.7%) patients in the FOLFOX-4 + BV arm and in 1/287 (0.4%) patient in the FOLFOX-4 arm. Among these patients, 3 in the FOLFOX-4 + BV arm and 1 in the FOLFOX-4 arm were not considered to have had a gastrointestinal perforation event.

Venous Thromboembolic Events: The verbatim term thrombosis/embolism has been translated by MedDRA into embolism. There are no other embolism terms recorded in the glossaries.
The overall incidence of treatment-related grade 3/4 venous thromboembolic events as reported in the E3200 Toxicity Form was similar in both the FOLFOX-4 + BV (3.5%, 10/287 patients) and FOLFOX-4 (2.5%, 7/285 patients) arms. No grade 5 events were reported.

The incidence of grade 3–5 venous thromboembolic events reported either on the E3200 Toxicity Form or in NCI AdEERS was 4.2% (12/287 patients) in the FOLFOX-4 + BV arm and 3.5% (10/285 patients) in the FOLFOX-4 arm. One grade 5 venous thromboembolic event was reported in the FOLFOX-4 arm.

Arterial Thromboembolic Events: The incidence of treatment-related grade 3/4 arterial thromboembolic events was rare in the two treatment arms: 0.3% (1/287 patient) in the FOLFOX-4 + BV arm and 0.4% (1/285 patient) in the FOLFOX-4 arm. In addition, 2 patients in the FOLFOX-4 + BV arm had grade 3/4 treatment-related troponin I elevation, which according to NCI-CTC is consistent with unstable angina (grade 3) and myocardial infarction (grade 4).

The incidence of grade 3-5 arterial thromboembolic events reported either in the E3200 Toxicity Form or in NCI AdEERS was 2.4% (7/287 patients) in the FOLFOX-4 + BV arm and 0.7% (2/285 patients) in the FOLFOX-4 arm (includes patients with troponin I elevation). One grade 5 event (cerebral ischemia) was reported in the FOLFOX-4 + BV arm.

Wound Healing Complications: Wound infection (grade 3) was reported in 1 patient (0.3%) in the FOLFOX-4 + BV arm only. No additional wound healing complications were reported in NCI AdEERS

Overall, as the reporting in the AdEERS was not uniform between the two treatment arms, these information are of somewhat limited value. The character of the events is compatible with the known toxicity of bevacizumab, and therefore do not give cause for concern.

Study E3200 Influence of Bevacizumab on Adverse Events of Special Interest for Chemotherapy
More patients in the FOLFOX-4 + BV arm experienced at least one AE of special interest for chemotherapy compared with those in the FOLFOX-4 arm (37% vs 25%, respectively).
Sensory Neuropathy: The incidence of treatment-related grade 3/4 peripheral sensory neuropathy events was higher in the FOLFOX-4 + BV arm (16.4%, 47/287) compared with the FOLFOX-4 arm (9.1%, 26/285), as reported in the E3200 Toxicity Form. No grade 5 events were reported, and for each treatment arm, only 1 grade 4 event was reported. No additional peripheral sensory neuropathy events were reported in NCI AdEERS.
Diarrhea: The incidence of treatment-related grade 3/4 diarrhea events was higher in the FOLFOX-4 + BV arm (17.8%, 51/287) compared with the FOLFOX-4 arm (12.6%, 36/285), as reported in the E3200 Toxicity Form. No grade 5 events were reported. No additional diarrhea events were reported in NCI AdEERS.

Nausea and Vomiting: The incidence of treatment-related grade 3/4 nausea and vomiting events was higher in the FOLFOX-4 + BV arm (13.6%, 39/287) compared with the FOLFOX-4 arm (6.0%, 17/285), as reported in the E3200 Toxicity Form. No grade 5 events were reported and no grade 4 nausea events were reported.
The incidence of grade 3/4 nausea and vomiting events reported either in the E3200 Toxicity Form or in NCI AdEERS was 15.3% (44/287 patients) in the FOLFOX-4 + BV arm vs 6.3% (18/285 patients) in the FOLFOX-4 arm.
Stomatitis: No treatment-related grade 4 or 5 stomatitis events were reported in the E3200 Toxicity Form. The incidence of treatment-related grade 3 events was low and similar in the two treatment arms: 1.7% (5/287 patients) in the FOLFOX-4 + BV arm and 1.1% (3/285) in the FOLFOX-4 arm. No additional stomatitis events were reported in NCI AdEERS.

Safety in Special Groups and Situations across studies

Intrinsic Factors - Gender
A consistent effect of BV on the key events of interest was seen across male and female subgroups. Possible exceptions are grade 3/4 hypertension that occurred with a higher frequency in female patients compared with male patients in the BV arms, and grade 3/4 proteinuria that was only seen in female patients in the BV arms, although the number was small (4 patients).

Intrinsic Factors - Age
A consistent effect of BV on the key AEs of interest was seen across age subgroups with the exception that an increase in arterial and venous thromboembolic events was seen with BV in patients ≥ 65 years compared with those < 65 years

Extrinsic factors : Comparison of Safety Profile of Bevacizumab in Combination with Different Chemotherapy Regimens

Oxaliplatin-Based Regimens
A comparison of the safety profile of BV in combination with various oxaliplatin-based regimens from the TREE-2 (ARD 5099) and NO16966 studies show that overall tolerability was similar in the two studies and across the various regimens, with approximately 70% to 85% of patients reporting grade 3/4 AEs. In general, the incidences of grade 3/4 AEs of special interest for BV were lower in the NO16966 study compared with TREE-2, in particular, hypertension (range across BV treatment arms of 3.2% to 4.2% vs 7% to 15%, respectively), gastrointestinal perforation (range 0.3% to 0.8% vs 2.8% to 4.2%, respectively), and wound healing complications (range 0 to 0.3% vs 1.4% to 5.6%, respectively). Incidences of grade 3/4 chemotherapy-related AEs, however, were similar in both studies. The difference in patient numbers between the two studies warrants caution when comparing incidences of AEs between these studies. In addition, as Roche was not the sponsor of the TREE study and does not have access to the safety database, this complicates the comparison across studies further, especially with respect to lack of information regarding exposure to BV.
Although the patient population and safety reporting requirements were different for study E3200, the incidences of grade 3/4 AEs of special interest for BV and for chemotherapy are generally comparable to those for NO16966 and TREE-2.
Incidences of grade 3/4 AEs of special interest for BV are also generally comparable to those reported in the ongoing, observational studies MO18024 (First BEAT) and AVF2941n (BRiTE), although safety data collection in these latter studies is limited.

Other Fluoropyrimidine-Based Regimens
The updated safety profile of BV in combination with other fluoropyrimidine-based regimens from the pivotal phase III study AVF2107g and the phase II study AVF2192g is compared to that of NO16966 (pooled chemotherapy + BV arms vs chemotherapy + P arms). The overall tolerability of the different combination therapies across the three studies was similar, with approximately 75% of patients reporting grade 3/4 AEs. Of the grade 3/4 AEs of special interest for BV, the following were consistently increased in the BV arms over control in the three studies: hypertension (3.7% - 15% vs 1.2% – 2.5%), arterial thromboembolic events (1.7% – 9.0% vs 1.0% - 4.8%), bleeding events (1.9% - 5.0% vs 1.2% - 2.9%), and gastrointestinal perforations (0.6% - 2.0% vs 0% - 0.3%). All these types of events had a lower frequency in the NO16966 trial than in the previous trials in mCRC.

With respect to grade 3/4 AEs of special interest for chemotherapy, small increases in the common gastrointestinal toxicities were seen in the BV arms in all three trials. In study NO16966 there was also an increase in the incidence of PPE in the BV arms compared with the chemotherapy arms (7.1% vs 3.4%), mainly driven by higher incidences of this AE in the XELOX arms.

3. Pharmacovigilance

The applicant has provided an updated RMP which replaces the second RMP dated June 2006 and include satisfactorily the current and planned pharmacovigilance and risk minimisation activities associated with the use of bevacizumab in oncology indications. The important identified and potential

risks of the clinical use of bevacizumab in Genentech- and Roche-sponsored studies, risk minimisation activities as defined in the current bevacizumab label, experience from the post-marketing setting after initial approval in the US (26 February 2004) and the EU (12 January 2005) and pharmacovigilance activities proposed and implemented in ongoing and planned studies are adequately described.

The RMP has been updated with newly available data from the following studies: NO16966 (in metastatic colorectal cancer), BO17705 (in metastatic renal cell carcinoma), AVF3135g (a dedicated drug-drug interaction study) and AVF2771n (a pilot dose-escalation study in paediatric patients). For the indications of locally recurrent or metastatic breast cancer and locally advanced and metastatic non-small cell lung cancer, for which approval is being sought, observational studies are ongoing in order to gather more and long-term safety data in a systematic manner.
In addition, ongoing clinical trials are evaluating ovarian failure, anticoagulation therapy in combination with bevacizumab containing treatments and the safety profile of bevacizumab in patients with Central Nervous System metastases and patients with squamous NSCLC. A cardiac monitoring plan has been implemented for investigational purposes together with the planned QTc study.

Specific safety assessments of events related to gastrointestinal perforations, haemorrhage (including pulmonary haemorrhage), wound healing complications, arterial thromboembolic events, hypertension, proteinuria, congestive heart failure will continue to be carried out prospectively in clinical trials.

4. OVERALL CONCLUSION AND RISK BENEFIT

This application is based on two large pivotal Phase III studies, one in patients not previously treated for their metastatic disease (first-line treatment), Study NO16966, and the other in previously treated patients (second-line treatment), Study E3200. Due to differences in the definition of the primary and secondary efficacy parameters (e.g. primary efficacy endpoint in NO16966 was PFS whereas the primary efficacy endpoint in E3200 was overall survival), and due to differences in the study population (demographics and baseline disease characteristics), no integrated comparison between the studies NO16966 and E3200 could be made.

Study NO16966
Study NO1699 is also assessed as a part of the Xeloda (capecitabine) extension of the CRC indication
In the subgroup comparison of XELOX+P and XELOX+BV a statistically significant prolongation of PFS of 57 days in favour of the bevacizumab combination was found (HR=0.77, p=0.0026). However, in the subgroup comparison of FOLFOX+P vs. FOLFOX+BV there was no significant difference between the arms (HR=0.89, p=0.1871). An imbalance with regard to an important prognostic factor (the time between primary treatment and recurrence), which was not recognized when the trial was started, can explain the seemingly superior result in the FOLFOX-P arm in part II of the trial

PFS as assessed by IRC and by On-treatment approach showed significant benefit of adding bevacizumab to chemotherapy in the overall comparison and in both treatment subgroups. However, due to the definition of event in the PFS - IRC and the PFS on-treatment approach these analyses are regarded to be of little relevance for the assessment of effect size.

Mature overall survival (OS) data from part II of NO16966 (62.5% patients have died) are now available after an analysis performed with an additional 12 months of follow-up (34% of patients had died at the cut-off for the primary analysis).
The result shows a trend for longer OS with BV compared with placebo (median 92.3 weeks vs. 86.6 weeks, HR=0.89) however statistical significance was not reached (p=0.0769). Two key factors may have reduced the magnitude of OS benefit observed:

- Early discontinuation of BV therapy
- The impact of a cohort with an outlying efficacy result: patients with previous adjuvant treatment in the FOLFOX+P arm had a more favourable baseline characteristic (longer time from start of adjuvant therapy to randomisation) than the cohorts of adjuvant-treated patients in the other treatment arms. This may explain the unexpectedly good outcome in

the FOLFOX-4+P arm. A Cox regression model confirmed that time from start of adjuvant chemotherapy to randomization (recurrence) has an influence on OS.

Three exploratory analyses, aimed at reducing the impact of this cohort on OS, show a significant OS benefit of BV vs. Placebo in the 2x2 factorial part II of NO16966. Moreover, an exploratory analysis of OS including all patients in NO16966 (from part I and II) shows a similar result. An overall survival benefit has therefore also been shown in this study.

No increase in BOR was observed when adding bevacizumab to chemotherapy, neither in the investigator nor IRC analyses. The highest discordance between investigator and IRC assessments was due to partial responses by investigators being classified as stable disease by IRC. Time to response was similar between treatment arms and the majority of responses (70 %) occurred between week 6 and week 18. In the overall comparison the duration of response was longer for patients who received bevacizumab in combination with chemotherapy compared with patients who received chemotherapy alone (HR=0.82, p=0.031) while duration of response was not significantly prolonged in either of the treatment subgroups. The time to treatment failure increased in the overall comparison analyses (26 days, HR=0.84, p=0.003) and the XELOX treatment subgroup (32 days, HR=0.80, p=0.007), while there was no significant benefit of adding bevacizumab to FOLFOX-4. It seems quite plausible that the imbalance with regard to an important prognostic variable (not recognized when the trial was started) gave rise to the unexpected result in the subgroup of patients treated with FOLFOX-4. Analyses correcting (partially) for this imbalance clearly point in that direction.

A multivariable analysis adjusting for prognostic factors, stratification variables and geographic region was performed and the results confirmed the robustness of the results of the PFS primary efficacy analyses for the overall comparison and in each treatment subgroup. Sensitivity analyses were performed to investigate whether or not delays in tumour assessments had any effect on the outcome of the primary analyses for PFS, and the results confirm the primary analysis in the overall comparison and the treatment subgroup comparisons, and thus indicate that delays in tumour assessments did not affect the outcome of the primary analysis of PFS. A superiority analysis which combined all patients in the trial (patients in 2-arm part plus patients in 2x2 factorial part of the study) was specified in the protocol in case of borderline results. This analysis was performed, and demonstrated superiority for the BV-containing arms versus the chemotherapy alone arms in the overall comparison and the XELOX treatment subgroup, and in addition significant improvement of adding bevacizumab to FOLFOX-4 was obtained (HR=0.82, p=0.0080). However, the validity of combining the two parts of the study may be questioned, and does not alter conclusions based on the primary analysis. A clear distinction between patients who received prior adjuvant chemotherapy and those who did not was demonstrated in the subgroup analysis of the FOLFOX-4 treatment subgroup. Therefore additional exploratory analyses were performed and these analyses showed that removing the subgroup of patients that may have slower tumour progression, improved the results, and even the subgroup analysis of FOLFOX-4 became significant in favour of addition of bevacizumab. As mentioned previously, an imbalance with regard to an important prognostic factor (the time between primary treatment and recurrence), which was not recognized when the trial was started, can explain these results. However, this is a post-hoc analysis which must be assessed with great caution.

Taken together, the PFS and OS for the overall comparison shows that adding bevacizumab to chemotherapy is superior to chemotherapy alone.

Study E3200

Study E3200 (an open-label, randomised, multicenter, active-controlled Phase III trial to evaluate the safety and efficacy of FOLFOX-4+bevacizumab versus FOLFOX-4 versus bevacizumab alone in patients with advanced CRC who have failed therapy with irinotecan and 5-fluorouracil) showed that overall survival was significantly longer for patients in the FOLFOX+BV arm (13.0 months) compared with patients in the FOLFOX-4 arm (10.8 months). (Stratified HR=0.751, p = 0.0012). The difference in median PFS was 3 months in favour of the FOLFOX-4 + BV patients, which is both statistically and clinically significant. The objective response rate was 13.6 % higher in the FOLFOX-4+BV arm than in the FOLFOX-4 arm, as a result of increased partial response among the

patients. There was no difference in median duration of objective response, 6.2 months vs. 6.0 monts in the FOLFOX-4 + BV arm and FOLFOX-4 arm, respectively.

The results of the subgroup analyses were consistent with those for the randomised population as a whole. There was an overall consistent trend for prolonged duration of survival for patients in the FOLFOX-4 + BV arm compared with those in the FOLFOX-4 arm regardless of the baseline risk factor examined. Additionally, after adjusting for important prognostic factors for overall survival, the estimated hazard ratio indicated an approximately 30% reduction in the hazard of death among patients who received FOLFOX-4 + BV treatment compared with those who received FOLFOX-4, and thus support the primary analysis (HR=0.693 p<0.0001). Sensitivity analyses were performed using two definitions of lost to follow-up: last contact date > 3 months and > 6 months prior to the date of the final database. Results from stratified analyses showed that duration of survival was improved in the FOLFOX-4+bevacizumab arm compared with the FOLFOX-4 arm (HR=0.740, p=0.0004 and HR= 0.736, p=0.0004, respectively), supporting the results of the primary analysis.

Exploratory analyses of duration of survival, PFS, and objective response were performed for the bevacizumab monotherapy arm, which was closed for enrolment 11 March 2003. The stratified hazard ratio for death for bevacizumab monotherapy relative to FOLFOX-4+BV was 1.327, p=0.0021. However, it is notable that median OS in the BV monotherapy arm was not significantly different from the FOLFOX-4 arm (10.2 months and 10.8 months, respectively (p=0.7631)). In addition, there seemed to be less toxicity in the BV monotherapy arm in comparison to FOLFOX-4. The PFS in the BV arm was 2 months (p<0.0001) and 5 months (p<0.0001) shorter than the PFS in FOLFOX-4 and FOLFOX-4+BV arm, respectively. Additionally, the ORR was significantly lower (p=0.0121) in the BV monotherapy treatment arm. Symptomatic deterioration, which was assessed for the treated patients, was equally distributed across the three treatment arms. However, there were significantly more patients who experienced symptomatic deterioration without disease progression in the FOLFOX-4 + bevacizumab (67.5%) arm compared to the other treatment arms, FOLFOX-4 (50.0%) and BV monotherapy (42.4%). The results of a supportive Bayesian analysis were in line with the results of the primary analysis and indicated that it is highly likely that FOLFOX-4 + bevacizumab is superior both to FOLFOX-4 and to bevacizumab monotherapy as measured by duration of survival.

In conclusion, adding bevacizumab to FOLFOX-4 has benefit compared to FOLFOX-4 alone when given as second line therapy.

Overall; the benefit derived through the addition of BV to oxaliplatin-containing chemotherapy, in terms of prolonged PFS on treatment (studies NO16966 and E3200), and overall survival (study E3200) is in line with previous experience with other combinations (5FU/LV and irinotecan plus 5FU) in mCRC. Statistically significant and clinical meaningful efficacy with regards to a prolongation of PFS has been demonstrated in combination with oxaliplatin-based therapy. A superior survival benefit has also been demonstrated in patients previously treated with irinotecan for whom no other therapeutic option with a proven survival benefit exists (study E3200).

The data further support the consistent benefit of BV seen in combination with a variety of cytotoxic agents in a number of indications. The lack of substantial potentiation of chemotherapy-related toxicity (owing to the different mechanism of action and non-overlapping toxicity profile) makes BV a favorable and well-tolerated partner to cytotoxic therapy. Despite continual improvements in outcome with cytotoxic therapies and new and improved combinations of these agents, BV is still able to provide additional benefit without significantly impacting overall tolerability.

Safety

A total of 2864 patients with mCRC were exposed to at least one dose of bevacizumab in the two studies; N016966 and E3200. In study NO16966, the median duration of chemotherapy treatment was similar between the BV arms and their corresponding placebo arms (approx. 6 months) whereas in study E3200 the median duration was longer in the BV arm.

The overall safety profile of BV in combination with oxaliplatin/fluoropyrimidine-containing therapy is comparable to that observed in previous phase II and III studies in combination with other 5-FU-

based therapies (5-FU/LV and IFL). No significant new safety concerns have been identified. Many of the observed adverse events are typically described in patients who receive chemotherapy e.g. constipation, diarrhoea, arthralgia, alopecia, rash, fatigue/asthenia, nausea and vomiting. Similar to other bevacizumab studies, the higher incidence of bleeding, hypertension, epistaxis, headache and proteinuria is observed with bevacizumab treatment.

In study NO16966, there were more AEs (all grades) in the chemotherapy+BV arms compared with the chemotherapy+P arms (≥ 5% absolute difference: anorexia, hypertension, PPE, epistaxis and dysphonia). The incidences of Grade 3/4 gastrointestinal disorders, vascular disorders, cardiac disorder and pulmonary embolism were increased in both BV arms whereas PPE was mainly increased in the XELOX+BV arm. Gastrointestinal perforations, proteinuria and wound healing complications were rare in both treatment arms. There were no major differences between the pooled treatment arms for the most commonly occurring individual SAEs, with the exception of pulmonary embolism and deep vein thrombosis. A higher proportion of patients discontinued all study treatment due to AEs in the BV treatment arms mainly due to chemotherapy-related toxicity; however, only 5% of the patients in the BV treatment arms and 2% in the placebo arms discontinued all study treatment due to AEs of special interest for BV. With respect to the non-PD related deaths, the causes were generally similar between groups; however, more deaths in the chemotherapy+BV arm than in the chemotherapy+P group were related to cardiac etiologies (10 patients, 1.4% vs. 2 patients, 0.3%, respectively) or gastrointestinal obstruction (4 patients, < 1% vs. no patients).

In study E3200, grade 3/4 hypertension, grade 3-5 bleeding, and grade 3-5 gastrointestinal perforation were the most commonly reported AEs of special interest for BV (all grades), all of which were experienced by a higher proportion of patients in the FOLFOX-4+BV arm. There was no appreciable increase in the incidence of grade 3–5 venous thromboembolic events with the addition of BV to FOLFOX-4. Proteinuria, arterial thromboembolic events, and wound healing complications were either rare or absent in both treatment arms.

The incidences of Grade 3 and 4 sensory neuropathy events were higher in the FOLFOX-4+BV arm compared with the FOLFOX-4 arm. Sensory neuropathy is an adverse event known to be associated with oxaliplatin and the higher incidence in the FOLFOX-4+BV arm is probably due to the increased oxaliplatin exposure in this arm compared with the arm without BV. In study NO16966 there was no difference in the observed sensory neuropathy between the chemotherapy+BV arms and the chenmotherapy+P arms. The proportion of patients who discontinued all protocol therapy for toxicity was similar between the treatment arms. Cardiac-related deaths (9 patients) and infections (7 patients) were the most frequent causes of non-PD related deaths in the chemotherapy+BV arms while infections (5 patients) were the most frequent cause in the chemotherapy+P arms.

Pharmacovigilance

A risk management plan had been submitted and assessed in parallel for both indications of Renal Cell Carcinoma and metastatic colorectal cancer. A summary of the known identified safety concerns, along with the PhV proposed activities and proposed risk minimization activities is provided in the table below:

Safety concern	**Proposed PhV activities**	**Proposed Risk minimization activities**
1. Haemorrhage including:	-prospective data collection on the use of aspirin and other anti-platelet prophylactic anticoagulation therapy -evaluation of the effect of anticoagulation in several studies -yearly update report	Warning in section 4.4 of the SPC

Pulmonary haemorrhage/ Haemoptysis	-guided questionnaires - retrospective case analysis of E4599 and BO17704 - evaluation of patients with squamous NSCLC in defined studies	Listed in section 4.8
Patients with CNS metastases	-prospective data collection in ongoing trials -retrospective case analysis in BO17704	Listed as contraindication in 4.3
2. Arterial thromboembolism (ATE)	-prospective data collection on the use of aspirin and other anti-platelet as well as history of arterial disease and risk factors for ATE -guided questionnaire	Warning in section 4.4 of the SPC Listed in section 4.8
3. hypertension	-prospective data collection for evaluation of incidence and reversibility	Warning in section 4.4 of the SPC Listed in section 4.8
4. proteinuria	-prospective data collection for evaluation of incidence and reversibility	Warning in section 4.4 of the SPC Listed in section 4.8
5. congestive heart failure	-in defined studies Safety monitoring plan Sequential regular LVEF monitoring Cardiology advisory board Guided questionnaire	Warning in section 4.4 of the SPC Listed in section 4.8
6. wound healing complications	-prospective data collection to evaluate incidence and risk factors -evaluation of the safety of surgery in a defined study	
7. Gastrointestinal perforations and fistula	- in an ovarian cancer study - guided questionnaire	Warning in section 4.4 of the SPC Listed in section 4.8
8. RPLS	- routine PhV	Warning in section 4.4 of the SPC Listed in section 4.8
9. Neutropenia	- routine PhV	Warning in section 4.4 of the SPC Listed in section 4.8
10. venous thromboembolic events (VTE)	- routine PhV	Warning in section 4.4 of the SPC Listed in section 4.8
11. fistulae	-data collection in a defined study	Warning in section 4.4 of the SPC Listed in section 4.8

User testing:
The Marketing Authorisation Holder (MAH) also took the opportunity to implement editorial changes to the Package Leaflet as a result of the user testing procedure.

Benefit-Risk
In conclusion, the benefit risk profile of BV treatment remains positive based on the data generated from the studies in this submission. The current prescribing information and risk management plan adequately address the identified risks associated with BV treatment (events of special interest).

Furthermore, the MAH will provide for the study NO16966 the result of a multiple Cox regression analysis for the overall comparison of XELOX+BV/FOLFOX-4+BV versus XELOX+P/FOLFOX-4+P in the ITT in terms of PFS by end of 1Q08 and will update the prescribing information accordingly, if supported by the results of the mentioned Cox regression analysis. The model will include the following covariates 1) bevacizumab treatment (yes vs. no); 2) chemotherapy backbone (FOLFOX-4 vs. XELOX); 3) interaction of bevacizumab treatment with chemotherapy backbone; 4) CEA level (abnormal vs. normal); 5) interaction of CEA with bevacizumab treatment; 6) previous adjuvant treatment (no previous adjuvant treatment, start of previous adjuvant treatment more than 900 days before date of randomization, start of previous adjuvant treatment less or equal than 900 days before date of randomization); 7) interaction of previous adjuvant treatment with bevacizumab treatment.

In order to further explore and reassess the dose of bevacizumab in mCRC, the MAH will present the efficacy data from on going trials, that will provide information from approximately 750 patients with mCRC treated with bevacizumab at a dose of 2.5 mg/kg/wk equivalent in second line, and to compare the data from these studies with the data from study E3200 (bevacizumab 5 mg/kg/wk equivalent).

The MAH also committed to provide the data from a prospective biomarker program implemented in the Phase III randomized, placebo-controlled multicenter study, , investigating use of bevacizumab in the gastric cancer indication. The study , which started to recruit in September 2007, will compare the efficacy and safety of bevacizumab 2.5 mg/kg/wk equivalent/versus placebo in combination with capecitabine and cisplatin in 760 patients. A comprehensive biomarker program was incorporated into this study to prospectively elucidate the association of the VEGF-, neuropilin- and EGF-receptor family in gastric cancer patients.

Bevacizumab doses will be further evaluated after the results are available for the clinical NSCLC study and in a mBC study. The latter study compares the 2.5 and 5 mg/kg/wk equivalent dose with placebo and, if both bevacizumab arms are significantly active vs. placebo, an exploratory comparison between the two doses will also be made.

The MAH will also provide the data from a retrospective analysis in more than 400 samples obtained from the NO16966 trial in mCRC indication.