NOTE TO FILE

Study No.	ML21520 Country Germany
Study Title	Avastin® in first-line treatment of patients with advanced colorectal cancer [Avastin® first-line bis zum Progress]
Study Responsible	
TL of Study Responsible	

NOTE

Description:

In the course of recording all non-serious adverse events captured in this non-interventional study after 02.07.2012 within the Roche Safety Database a reevaluation of the events was performed by the Drug Safety Physicians. This led to a retrospective upgrading of 13 events that were listed as non-serious in the final study report dated 12.12.2016. This affects the following events:

AER	LRN	Study	Drug	upgraded event	onset	Patientennummer
1814468	2965068	ML21520	Avastin	Thromboembolie	26.06.2009	503
1814811	2965444	ML21520	Avastin	Lungenembolie	15.06.2010	2444
1814827	2965463	ML21520	Avastin	pulmonary embolism	02.04.2009	1041
1814852	2965503	ML21520	Avastin	pulmonary embolism	17.07.2010	2748
1814948	2965632	ML21520	Avastin	Hypertension>200mmHg	13.12.2009	1741
1815074	2965782	ML21520	Avastin	pulmonary embolism	30.05.2011	3218
1815212	2965892	ML21520	Avastin	pulmonary embolism	15.02.2012	5242
1815267	2966129	ML21520	Avastin	pulmonary embolism		4625
1815476	2966129	ML21520	Avastin	pulmonary embolism	20. Spt 12	2774
1815490	2966110	ML21520	Avastin	pulmonary embolism	15.May 13	4267
1815043	2965760	ML21520	Avastin	Oedema of the leg	27.02.2012	3214
1815451	2966100	ML21520	Avastin	Rectal bleeding	16.09.2011	2765
1815492	2966112	ML21520	Avastin	pulmonary embolism	23.04.2013	4269

Corrective action:

The re-assessment does not lead to any new finding concerning the safety profile of AVASTIN® in the first-line therapy of advanced colorectal cancer cancer. The conclusion (CSR page 101) therefore does not need to be amended.

Preventive action:

N/A

Name and signature of Study Responsible:	[redacted]	Date dd/mon/yy:	[redacted]
Name and signature of Team Lead of Study Responsible:	[redacted]	Date dd/mon/yy:	[redacted]

Original: Trial Master File

based on gcp_for001776
version 2

TITLE PAGE

FINAL RESEARCH REPORT

NIS INFORMATION

Title	Avastin® in first-line treatment of patients with advanced colorectal cancer [Avastin® first-line bis zum Progress]
Version identifier of the final study report	1.7
Date of last version of the final study report	12 December 2016
EU PAS register number	ML21520
Active substance	Bevacizumab [ATC code L01XC07], (Avastin®)
Medicinal product	NA
Product reference	NA
Procedure number	NA
Marketing authorisation holder(s)	
Clinical Phase	Post-Marketing
Research question and objectives	Documentation of usage, effectiveness and safety of Avastin® (bevacizumab) as part of first-line systemic (combination) treatment of metastatic colorectal cancer in current clinical routine practice in Germany, according to the label extensions including the combination with oxaliplatin.
Country(-ies) of study	Germany
Author	

MARKETING AUTORISATION HOLDER(S)

Marketing authorisation holder(s)	
MAH contact person	Head EU/International Regulatory

1. ABSTRACT

Title

Avastin® in first-line treatment of patients with advanced colorectal cancer [Avastin® first-line bis zum Progress]

Keywords

Avastin®, colorectal cancer, Non-interventional study

Rationale and background

In randomised controlled trials, the VEGF antibody bevacizumab led to increased progression-free survival (PFS) and overall survival (OS), when added to mono or combination chemotherapy (CT) for metastatic colorectal cancer (mCRC). For this reason this post authorisation non-interventional study was planned in 2008 as a prospective cohort study to collect and document data on the safety and effectiveness of bevacizumab in combination with chemotherapy regimens in the first-line treatment of patients with metastatic colorectal cancer (mCRC) in daily routine.

Research question and objectives

The objective was to evaluate the usage, safety and effectiveness of bevacizumab in a first-line routine setting. Main focus was directed on the clinical routine (induction and maintenance setting), whether patient's age, further prognostic factors influencing the efficacy of bevacizumab, as well as resectability with first-line usage of bevacizumab. The treatment combinations could include the combination with oxaliplatin.

Study design

Multicentre, non-interventional study.

Setting

Patients with diagnosis of metastatic colorectal cancer without previous systemic palliative treatment, and intended to receive systemic therapy with bevacizumab.

Subjects and study size, including dropouts

3.557 patients were registered; for these, 3.398 Case Report Forms were returned. 369 cases had to be excluded from analysis due to incomplete documentation, or prior palliative cytostatic therapy, resulting in 3.029 patients eligible for analysis.

Variables and data sources

Case report forms were issued to participating centres in order to document baseline characteristics, course of treatment, safety and efficacy results for every patient.

Results

3,029 eligible patients were enrolled between 2008 and 2012 (data cut-off February 2015). The patients were predominantly male (63%), median age was 67 years (range from 20–99 years). 1,205 pts (40%) were elderly, i.e. ≥70 years. ECOG performance status was favourable (0–1) in 89% of the patients. In 1,725 patients with known KRAS status (exon 2), mutations were present in 26%. 30% of the patients had received previous adjuvant CT.

In 97% of patients, bevacizumab was given in standard combinations with either fluoropyrimidine (FP) alone (14%; contrasting to 37% in the elderly, 70 years or older), FP/irinotecan (49%), or FP/oxaliplatin (34%), with a small remaining subgroup of patients receiving either bevacizumab as monotherapy (1%) or in combination with other CT (2%), not in accordance with SmPC despite this being a prerequisite – yet reflecting daily practice. Median treatment duration was 6.1 months for the whole population. Treatment interruption and/or delay of bevacizumab therapy were reported in 13% of all evaluable treatment cycles, corresponding to 44% of patients with ≥ 1 interruption. More than half of treatment cycles were delayed for administrative reasons, about one third due to non-hematologic toxicity. 69% of patients did not experience a dose

modification of therapy with bevacizumab or the combined CT. The reason for a dose modification was non-hematologic toxicity in nearly half of the respective treatment cycles (49%).

No major unexpected findings were identified with respect to the safety of the drug. Treatment was stopped due to an adverse drug reaction (ADR) in 10% of the patients; however, the rates of patients with an ADR (19%) or serious adverse drug reaction (SADR) (6%) were comparable to the results of other large observational trials. Specific bevacizumab-related ADRs were observed within the expected frequencies, with gastrointestinal perforation in 21 patients (1%), arterial thrombotic events in 91 (3%) and only 1 patient with reversible posterior leukoencephalopathy. Bevacizumab-related hypertension was recorded in 16% of the patients (any grade), hypertension of CTC grade 3-4 in 2.3%. No correction for patients on antihypertensive medication at baseline or de-novo hypertension was applied.

51% of patients stopped treatment with bevacizumab because of tumour progression or death caused by tumour. About one quarter of patients stopped therapy for administrative reasons, mostly due to planned surgery. The 60-days mortality from start of treatment (of any cause) was 1.6%. In all patients with follow-up data available, 57% received ≥ 1 further line treatment. Combination of fluoropyrimidine/irinotecan was the predominantly chosen regimen in second-line; it was also re-induced in 36% of patients with available follow-up data who had received this regimen in the first-line. 505 patients received bevacizumab as second-line treatment, corresponding to 20% of patients with available follow-up data.

The overall best response rates were 52% for the entire population (95% CI: 50-54%), but distinctly lower in the FP-only cohort (39%), compared to the main patient cohorts receiving the triple combination FP/oxaliplatin/bevacizumab (ORR 53%) or FP/irinotecan/bevacizumab (ORR 54%). Secondary metastasis resections were performed in 7% of all patients, but only in treatment cohorts with combination treatment (range 3-11%). R0 status was reached in 59% of all cases with secondary resection. Based on 2,461 observed events (81%), the median PFS was 10.3 months (95% CI: 9.6 – 10.7), not markedly lower in the less intensively treated elderly group (9.0 months). The median OS (1,822 deaths observed, 60%) was 23.2 months (22.2 – 24.1). The shorter median OS in the elderly (19.1 months) is potentially due to the higher baseline mortality of this age group. The data did not allow for differentiation of CRC-related or -related deaths.

Age, ECOG status at baseline, the number of involved organ sites, alkaline phosphatase and CEA were identified as the most important prognostic factors for PFS and OS. The prognostic score (Köhne) was highly discriminative ($p<0.0001$) both for PFS and OS, with OS medians of 13.2, 22.1 and 25.4 months in the high, intermediate and low risk groups, respectively.

Discussion

The therapy results of bevacizumab observed in the controlled studies were reproducible in the scope of routine clinical practice. In this unselected, routinely treated cohort, the median age of 67 years was slightly higher than in first line randomised pivotal studies of bevacizumab (59.5 years in AVF2107g[1], 60 years in NO16966[3]). The known long-term anti-tumour results and the favourable safety profile of the antibody in the treatment of mCRC could be confirmed. High age per se does not seem to be a limiting factor for a bevacizumab-containing treatment approach.

Marketing Authorisation Holder(s)

Names and affiliations of principal investigators

TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

5-FU	5-Fluorouracil (anti-cancer drug)
ADR	Adverse Drug Reaction
AE	Adverse event
AIO	„Arbeitsgemeinschaft internistische Onkologie in der Deutschen Krebsgesellschaft e.V“ – Working group for Medical Oncology in the German Cancer Society
ALAT	Alanine aminotransferase / Alinine transaminase
AMG	„Arzneimittelgesetz“ – German Drug Law
ANC	Absolute neutrophile count
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
BID / BD	Twice a day (bis in die)
BP	Blood pressure
BSA	Body Surface Area
BW	Body Weight
C/O	Complaining of
C/W	Continue With
Ca	Cancer; carcinoma
Ca	Calcium
cc	Cubic centimetre
CCR	Continuous complete remission
CEA	Carcinoembryonic Antigen (tumour marker)
CI	Confidence interval
cm	Centimetre - 0.01 meters
CNS	Central nervous system - the brain and spine
CPM	Cyclophosphamide (anti-cancer drug)
CR	Complete remission / complete response
CRA	Clinical Research Associate
CRC	Colorectal carcinoma
CRF	Case Report Forms
CRO	Contract Research Organisation
CSF	Colony-stimulating Factor
CT	Chemotherapy
CTC	Common Toxicity Criteria
CVA	Cardiovascular Accident (stroke)
D/C	Discharge
D/H	Drug History
D/W	Discussed With
DFI	Disease Free Interval
DFS	Disease Free Survival - time without disease prior to relapse or last follow-up
dl	Decilitre - 0.1 litres
DLS	Date last seen
DLT	Dose limiting toxicity - determined by phase 1 studies
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group (USA)
EFS	Event Free Survival - time from diagnosis to defined events (e.g. relapse or death)

EJC	European Journal of Cancer
EORTC	European Organisation for Research and Treatment of Cancer
FAS	Full Analysis Set
FBC	Full Blood Count
FDA	Food and Drug Administration (USA)
FP	Fluoropyrimidine
FU	Follow Up
g	Gram - unit of weight
G-CSF	Granulocyte colony stimulating factor promotes production of white blood cells
GCP	Good Clinical Practice (guidelines)
GI	Gastrointestinal
Gy	Grays (units of radiation)
Hb	Haemoglobin
HD	High dose
HDC	High Dose Chemotherapy
HR	Hazard Ratio
IB	Investigators Brochure
ICD	International Classification of Diseases (coding system)
INN	International Nonproprietary Name
ITT	Intention To Treat
IU	International units
IV	Intravenous - into a vein
JCO	Journal of Clinical Oncology
K+	Potassium
KRAS	Kirsten rat sarcoma viral oncogene homolog
kg	Kilogram - a thousand grams
l	Litre - unit of volume
LDH	Lactate dehydrogenase
LN	Lymph Node
m	Meter (unit of length)
MAB - mAb	Monoclonal antibody
mCRC	Metastatic colorectal cancer
MDR	Multi drug resistant
mEq/l	Milliequivalent per litre
mets	Metastases
Mg	Magnesium
mg	Milligram - 0.001 gram
ml	Millilitre 0.001 litre
mM	Millimole
mm	Millimetre - 0.001 meters
MTX	Methotrexate (anti-cancer drug)
Na+	Sodium
NCI	National Cancer Institute (USA)
ng	Nanogram - 0.000000001 gram
NE	Not evaluable
NIS	Non interventional study
NK	Not known
ORR	Overall response rate

OS	Overall Survival
PASS	Post Authorisation Safety Study
PD	Progressive disease
PFS	Progression Free Survival
pg	Picogram - 0.000000000001 gram
pH	Hydrogen-ion concentration - acid / alkaline
pM	Pathological metastasis stage
pN	Pathological lymph node stage
pT	Pathological primary tumour stage
PR	Partial response
QoL	Quality of Life
RBC	Red blood cell / red blood count
RCT	Radio-Chemo Therapy
RFS	Relapse-free survival
RFA	Radiofrequncy ablation
RNA	Ribonucleic acid
RT	Radiotherapy
SA	Surface area (see BSA)
SAE	Serious Adverse Event
SADR	Serious Adverse Drug Reaction
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Stable Disease
SDV	Source Data Verification
SGOT	Serum glutamic oxalacetic transaminase - a liver function test
SGPT	Serum glutamic pyruvic transaminase - a liver function test
SIRT	Selective internal radiation therapy
SmPC	Summary of Product Characteristics
TNM	Staging system - primary tumour
µg	Microgram - 0.000001 gram
UICC	Union Internationale Contre le Cancer - International Union Against Cancer
ULN	Upper Limits of Normal
vs	Versus
WBC	White blood cell count
WCC	White cell count
WHO	World Health Organisation

3. INVESTIGATORS

Principal investigator („Medizinischer Studienleiter“) was [redacted], Centrum für Tumormedizin, Charité Berlin, Germany. The complete list of all participating centres and investigators is provided as Annex 1 No. 3.

4. OTHER RESPONSIBLE PARTIES

5. MILESTONES

An overview of study milestones is presented in Table 1.

Table 1 Study milestones

Milestone	Planned Date	Actual Date
Start of data collection	March 2008	April 2008
End of patient recruitment	April 2012	April 2012
1st FU data collection	August 2013	August 2013
2nd FU data collection	September 2014	September 2014
End of data collection	September 2014	February 2015
Interim statistical report	January 2014	April 2014
Final statistical report	January 2015	April 2015
Final research report	February 2016	April 2016

6. RATIONALE AND BACKGROUND

6.1 RATIONALE

The present post authorisation non-interventional study was planned in 2008 as a prospective cohort study enrolling patients with metastatic colorectal cancer (mCRC) to collect and document data on the safety and effectiveness of Avastin® (INN: bevacizumab) in combination with chemotherapy regimens, including combinations with oxaliplatin, in the first-line treatment of patients with metastatic colorectal cancer (mCRC) in daily routine.

Bevacizumab has become a mainstay of the current treatment against metastatic CRC in combination with standard chemotherapy regimens to prolong progression-free and overall survival compared with chemotherapy alone[1, 2, 3] and is now established as one standard-of-care in the first-line and second-line treatment of metastatic disease.

This local non-interventional study was performed to examine and reproduce the effectiveness and safety of bevacizumab in the real life setting of a large, unselected patient population. It was also the aim to identify further prognostic factors influencing the efficacy of bevacizumab, as well as resectability with first-line usage of bevacizumab. Initiated to assess the efficacy and safety of bevacizumab with various chemotherapy regimens used in a routine setting, it aimed at documenting how induction and maintenance regimens are applied outside a randomised clinical trial setting. It should be evaluating how the use of bevacizumab affects PFS and OS in a broad patient population and especially elderly patients (≥ 70 years), which represents a different demographic setting than the one commonly encountered in registration trials.

6.2 BACKGROUND

After decades of relative stagnation, in the years since the turn-of-the-century the systemic therapy of colorectal tumours has undergone a virtually revolutionary development. After the development of new, highly effective, respectively easy to use cytostatic agents, even newer types of agents based on an extended understanding of molecular biology are being introduced in the practice of clinical oncology.[4, 5] Those do not only directly attack the tumour cell, but are increasingly directed towards the conditions in the stromal "micro environment", which has proven important for the development and growth of tumours and their metastases. In this concept, the blood supply of the neoplastic lesions plays a significant role.

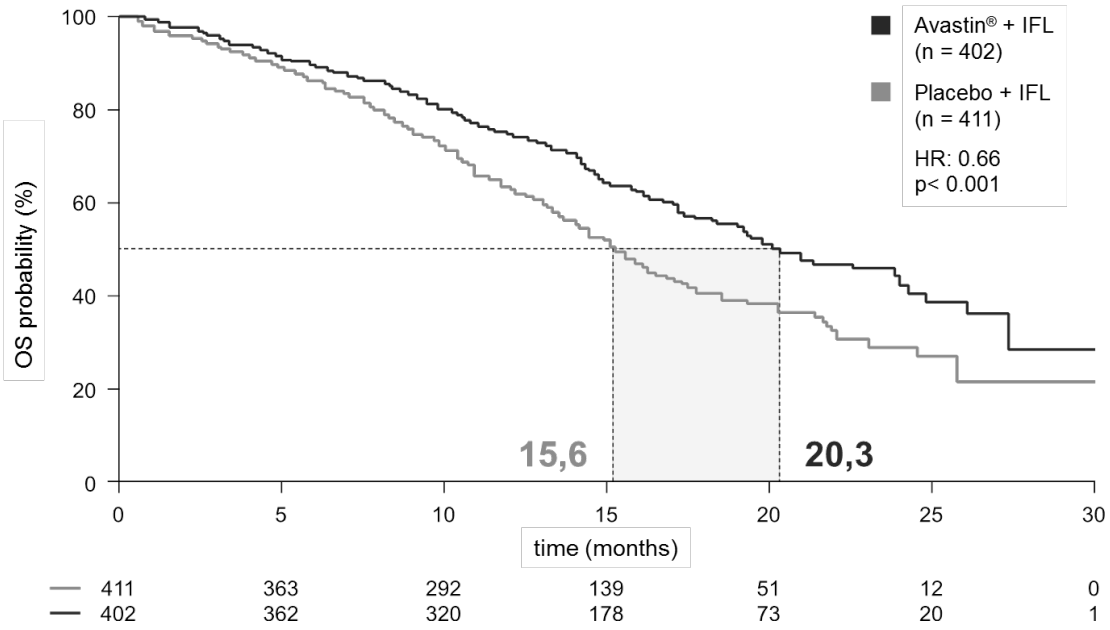
As soon as tumour lesions exceed a size of one to two millimetres, a further step takes place that is decisive for the malignant growth: the developing hypoxia and other factors trigger a signal cascade leading to neoangiogenesis. Excessive release of VEGF (vascular endothelial growth factor) through the tumour cells, a protein that is already essential during foetal development, plays a key role. Overexpressed in numerous tumour types, it often correlates with an unfavourable prognosis. Through binding to specific receptors on vascular endothelial cells, this growth factor causes a vascularisation of the tumour.[6]

With the humanised monoclonal anti-VEGF antibody bevacizumab (Avastin®), an active substance is available that is specifically directed against this growth factor. Bevacizumab inhibits the binding of VEGF to its receptors on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.

Bevacizumab was initially approved in Europe and USA for the treatment of metastatic colorectal carcinoma. Meanwhile the marketing authorisation also extends to mammary, bronchial, renal, ovarian and cervix carcinomas (market authorisation status from September 2016).

In a large-scale, double-blind, controlled Phase III study (AVF2107g)[1] on the first-line treatment of metastatic colorectal carcinoma, 402 patients received a combination consisting of irinotecan, 5-FU as bolus and bevacizumab at a dosage of 5 mg per kilogram body weight, repeated every 2 weeks. 411 patients received a placebo instead of bevacizumab. Regarding the primary target criterion overall survival, with a median time of 20.3 compared to 15.6 months a highly significant superiority of the verum resulted ($p < 0.001$, HR 0.66, see Figure 1).

Figure 1 Overall survival curve from the clinical trial AVF2107g comparing 5-FU/leucovorin/irinotecan plus bevacizumab vs. placebo[1]



The median progression free survival was nearly doubled with 10.6 vs. 6.2 months ($p < 0.001$, HR 0.54). Also the objective tumour remission rate (CR+PR) under bevacizumab was significantly higher with 44.8% vs. 34.8%. The therapeutic advantage was evident in all subgroups differentiated according to age, gender, and tumour type and similar, even though partially to a different extent.[1] The only relevant and significantly more frequently occurring adverse reaction compared to the control group was found to be an increase of the blood pressure occurring in 22% of the patients. Compared to the placebo group, the rates of

proteinuria, bleeding and thromboembolic events were only slightly elevated. In addition to this gastrointestinal perforations occurred with an incidence of approximately 2%. Also with the second cytostatic agent established in the fluoropyrimidine-based combination therapy of colorectal cancer, oxaliplatin, results are meanwhile available from two randomised studies that substantiate the effectiveness of bevacizumab. Firstly in 829 patients previously treated with a regimen containing irinotecan it was shown in the E3200 trial[7] that the second-line combination consisting of FOLFOX4 and bevacizumab, in comparison to the sole treatment with FOLFOX4, leads to a statistically highly significant improvement of the median survival by more than two months (p=0.0011, HR = 0.75). Also for progression free survival (p<0.0001, HR = 0.61), as well as the objective response (23% vs. 9%) the application of the antibody led to superior results that were highly significant.

Data from an international phase III marketing authorisation study for bevacizumab with FOLFOX/XELOX (NO16966)[3] was presented with a total of more than 2,000 patients on the first line therapy of metastatic colorectal carcinoma with oxaliplatin in combination with 5-FU/LV, respectively capecitabine as well as bevacizumab. In 1,400 of these patients a randomisation was undertaken between bevacizumab and a placebo. The dosage of the antibody was 5 mg/kg body weight, every two weeks, in combination with FOLFOX4, respectively 7.5 mg/kg, every three weeks, within the framework of the capecitabine combination XELOX. With application of the antibody median progression free survival was extended from 8.0 to 9.4 months (HR 0.83), corresponding to a reduction of the early progression risk by 17% (p = 0.0023). A pre-specified secondary analysis of on-treatment PFS (i.e. only progression and/or death events were taken into account which occurred within 28 days from the last dose of any component of study treatment), indicated that the advantage by adding the antibody is distinctly greater when it is given consistently until progression and not discontinued earlier, which may be triggered by other influences like adverse reactions or patient's wish. Regarding overall survival, numerous observations were still censored at the interim analysis, so that with medians of 21.3 vs. 19.9 months the conventional significance level was not yet reached (p = 0.077, HR 0.73). Results of a planned follow-up exploratory analysis were published in 2011 and confirmed the interim analysis: median overall survival for the combination FOLFOX4-bevacizumab was 21.0 months, respectively 21.6 months for XELOX-bevacizumab. Median overall survival times for the placebo arms amounted to 18.9 months for FOLFOX4 and 19.0 for XELOX.[8] In this study serious proteinuria, wound healing disorders and gastrointestinal perforations were observed in less than 1% of the cases, bleeding as well as arterial thromboembolic events in 2%, as well as grade 3/4 hypertension in 4%.

First results from a German multi-centre, randomised AIO study (AIO-KRK0604) showed a good practicability not only for the combination capecitabine/oxaliplatin/bevacizumab, but also for the antibody with capecitabine/irinotecan in a three-week regimen with 7.5 mg/kg bevacizumab, 200 mg/m² irinotecan, both on day 1, as well as 800 mg/m² BID capecitabine on day 1-14.[9] In both study arms a comparable, high anti-tumour efficacy (Capox/Bev vs. CapIri/Bev) was observed with a median PFS of 10.4 vs. 12.1 months (p=0.30, HR 0.93) and median OS of 24.4 vs. 25.5 months (p=0.45, HR 0.90). In a randomised Phase II study 209 patients (AVF2192g) who did not

come into consideration for an initial combination chemotherapy with irinotecan or oxaliplatin, were additionally treated with bevacizumab (5 mg/kg bodyweight every 2 weeks) or placebo until progression of the disease. Bevacizumab led to an increased remission rate (CR and PR) from 15% to 26% ($p = 0.055$), an extended median progression free time from 5.5 to 9.2 months ($p < 0.001$, HR 0.50), as well as a numerically extended median overall survival from 12.9 to 16.6 months ($p = 0.16$, HR 0.79).

A monotherapy of colorectal carcinoma with bevacizumab (10 mg/kg bodyweight every 2 weeks) is regarded as being less effective than a combination therapy with other cytotoxic agents. In the only randomised study with a bevacizumab arm without cytostatic agents (2nd-line according to regimen containing irinotecan), compared to the arms with chemotherapy a lower remission rate and a shorter time until progression was actually shown (E3200).[7] Regarding the overall survival this arm was however only marginally less favourable in comparison to FOLFOX4 with an OS of 10.2 vs. 10.4 months.

7. RESEARCH QUESTIONS AND OBJECTIVES

The objective of this non-interventional study ("Anwendungsbeobachtung", i. e. application observation, according to § 4 section 23, 3 AMG) was the documentation of data on the effectiveness and tolerability of a first-line treatment of metastatic colorectal carcinoma with bevacizumab (Avastin®) with approved combinations in routine clinical practice.

The following questions were explicitly specified in the observation plan:

- Which dosages, drug combinations and application regimens are used in routine practice?
- How often before occurrence of a tumour progression is the therapy partially or completely interrupted and what are the reasons for this?
- Are the therapy results observed in the controlled studies reproducable within the scope of the wide routine clinical practice?
- Is the demographic composition of the patient collective investigated here different from the populations that have been investigated until now within interventional phase II/III studies?
- Does the type of the applied therapy combination have an influence on the therapeutic effectiveness?
- Which conventional prognostic factors are predictive for the achieved therapy results?
- Which treatment is (re)-introduced on relapse after a therapy break without progression?
- Which reasons lead to modifications of the medication or to interruption/discontinuation of the treatment?
- How does the discontinuation of the therapy with bevacizumab relate to tumour progression?
- Which adverse drug reactions occur that have not been reported until now, if applicable with the therapy schemes applied in everyday practice?

- Are the reported frequencies of adverse reaction comparable with the previously described adverse reaction profile?
- Are there indications for interactions between the bevacizumab therapy results and prognostic subgroups?
- How large is the proportion of patients with secondary metastases resection, and what is the surgical result and which complications occur?
- Which results in the subgroup of older patients are clinically different from those in the total sample?

8. AMENDMENTS AND UPDATES TO PROTOCOL

The following points were changed, respectively complemented with the latest protocol amendment (Version 4.1)

- Contact details
- Length of patient documentation
- Specification of the long-time monitoring of overall survival / progression status as well as the subsequent therapies
- Specification of the investigation of the KRAS mutation status
- Reimbursement of expenses and rewards

Table 2 Summary of Protocol Amendments

Protocol version no	Date	Amendment or Update	Reason
1.6	December 10.2007		
2.1	June 26.2009	Amendment 1	Prolongation of the documentation period from 1 year to 2 years follow-up to cover also the progression events of the calculated 10-20% of the patients who progress after more than 12 months
3.2	July 08.2010	Amendment 2	Increasing of the patient number from 2000 to 3000 patients in order to improve the power of patients who would be secondary resectable under the treatment combination of mAb and CT and the effect of a mAb based therapy for patients ≥75 years
4.1	March 04.2013	Amendment 3	Adaption of documentation duration, specification of the long-term survey of OS/PFS and tumour specific follow-up therapy, specification of the KRAS-status

9. RESEARCH METHODS

9.1 STUDY DESIGN

This study was non-interventional in the therapeutic and diagnostic sense. The routine procedures of the participating physicians were not influenced by this study. The physician was completely free in his decision-making which patient he treats with the medication selected for documentation in this study, which dosages he selects, which diagnostic measures he undertakes, how he monitors the course of the treatment or which accompanying or additional medication he prescribes. The appointments for the physician/patient contacts were determined by the treating physician himself. The time points for the documentation were specified in the observation schedule.

9.2 SETTING

The study was performed at 438 participating centres (hospitals and private practices), qualified in the treatment of mCRC, throughout Germany. Recruitment for this study ranged from the beginning of March 2008 to the end of March 2012.

In order to collect data from routine clinical practice, patients with metastasized colorectal carcinoma without previous palliative cytostatic treatment, and intended to receive a systemic treatment with bevacizumab, could be included in the observational study. Exclusion criteria were defined by the contraindications mentioned in the current SmPC, section 4.3.

The total documentation period for each patient was 48 months. First patient, first visit (informed consent signed) was on April 24th 2008; end of follow-up period for the last patient was on February 09th 2015.

Patients were to be treated with bevacizumab according to the current SmPC section 4.2. However, the individual decision about dosage and duration of treatment with bevacizumab was at the discretion of the physician and was independent from participation in this non-interventional study. Consequently, the documentation of routine clinical practice depicted a wide variety of combinations, some of them not in accordance with the SmPC. We report all gathered data for reasons of transparency.

The data documentation followed the observation schedule below (Table 3).

Table 3 Observation schedule

Type of assessment	Start of observation	ongoing (every 2-8 weeks)	Final examination	Follow-Up
Demographic data (year of birth, gender)	X			
Cancer history (Initial diagnosis, recurrence tumour stage, metastasis)	X			
Pre-treatment (surgery, radiotherapy, chemotherapy)	X			
Relevant pre- and coexisting conditions	X			
Vital signs (body weight, height, blood pressure)	X			
Laboratory parameters	X			
General condition (ECOG-Score)	X	X	X	
Systemic therapy (therapy administered, dose deviation, therapy interruption)		X		
Combination therapy		X		
Other tumour therapy (metastasis resection, other)		X		
Current tumour status		X		
Adverse Events (toxicity)		X		
(Serious) Adverse Drug Reactions (Bevacizumab-related)		X		
End of therapy (date, reason)			X	
Best tumour response			X	
Subsequent therapy			X	X
KRAS Status (at baseline)				X
Current tumour and survival status				X

All patients were to be observed until progression or intolerable toxicity, whichever occurred first. If none of these events occurred until the end of observation period a final examination of the patient should be performed 2 years at the latest after study start.

Two follow-up assessments were conducted in August 2013 and September 2014 by fax in order to obtain the actual patient status. Overall, updated information could be retrieved in 2,465 of 3,029 patients (81%). In addition, investigators were asked to provide information about the KRAS status, if treatment with bevacizumab was continued after the end of observation period, and if any further-line cytostatic treatments after progression were administered.

The final number of case report forms received by the data centre that are eligible according to the observational plan of this non-interventional trial amounts to 3,029. Only complete documentation files that had been registered at the CRO WiSP by October 1st, 2014 were taken into account.

9.3 SUBJECTS

Patient selection for this observational study was performed at oncology centres representative for standard diagnosis and treatment of patients with mCRC. These centres included both hospitals and private practices across Germany. The centres were selected in order to obtain a collective of mCRC patients, representing clinical practice in Germany.

The statistical analysis plan (SAP) for this trial defined three different analysis sets of patients. The “Full Analysis Set” comprises all patients who:

- fulfilled the criterion of advanced colorectal cancer
- fulfilled the criterion of no systemic palliative pre-treatment, and
- were 18 years of age or older at baseline

The "Per-Protocol Analysis Set" was defined as all subjects who fulfilled additionally the following criterion:

- received at least one full dose application of bevacizumab therapy

Finally, all patients who received at least one application of bevacizumab – regardless of applied dosage – were included in the “Safety Analysis Set”.

All analyses were performed on the total group of patients and in subgroups defined by the concomitant cytostatic treatment administered in the first cycle, as described in section 7.1 of the observation plan (Version 4.1, March 2013). This includes patients with bevacizumab used as monotherapy or in combinations other than with 5-FU or capecitabine by choice of treating physician, thus diverging from the SMPC (denoted by an asterisk in the list below):

- with fluoropyrimidine (e.g. 5-FU, capecitabine) + oxaliplatin
- with fluoropyrimidine (e.g. 5-FU, capecitabine) + irinotecan
- with fluoropyrimidine (e.g. 5-FU, capecitabine) alone

- with any other cytotoxic drug or drug combination*
- without any chemotherapy, i.e. bevacizumab monotherapy*

9.4 VARIABLES

9.4.1 Overview on variables used in this trial

The non-interventional study focused on the recording of data on the safety and effectiveness of bevacizumab in combination with or without chemotherapy. The following parameters were collected within the observational study as part of the clinical routine:

Baseline data

- Demographic data (year of birth, gender)
- Cancer history (initial diagnosis, tumour stage, recurrence, current status, distant metastases)
- Pre-treatment (surgery, radiotherapy, chemotherapy)
- Relevant pre-and coexisting conditions
- Vital signs:
  - Body weight, height, body surface area, ECOG performance score, blood pressure
- Laboratory parameters:
  - Haemoglobin, platelets, leukocytes, granulocytes, creatinine, SGPT, SGOT, bilirubin, alkaline phosphatase, CEA)

Current tumor status

- Staging
- KRAS status at baseline (evaluated retrospectively within follow-up assessment)

Systemic therapy:

- Description of therapy with bevacizumab (dosage, duration)
- Description of other combination partner(s)
- Dose deviations
- Therapy interruption(s)

Adverse Drug Reactions (including toxicity based on NCI/CTC (Version 3.0)

Incidence rate of the following specifically assessed adverse drug reactions:

- Gastrointestinal perforation/fistula
- Arterial thrombotic events
- Reversible posterior leukoencephalopathy

Best tumour response

Progression free survival (PFS)

Overall survival (OS)

Other parameters:

- Duration of the observation (stop date)

- General condition (ECOG performance score) at end of observation
- Number of death(s)
- Subsequent therapy

9.4.2 Appropriateness of measurements

All effectiveness and safety parameters evaluated in this observational study are accepted standard measurements used in clinical practice for mCRC. According to the observational character of this trial missing visits or missing single data items were accepted and not assessed as protocol deviations.

9.4.3 Main effectiveness variables

Effectiveness endpoints were:

- Tumour response – disease control rate
- Progression-free survival (PFS) defined as time between start of therapy and progression or death, whichever occurred first
- Overall survival (OS) defined as time between start of therapy and date of death

9.4.4 Safety variables

Safety parameters included the occurrence, frequency, nature and severity of adverse drug reactions and specifically assessed ADRs. The type and severity of adverse drug reactions were to be assessed according to NCI-CTCAE criteria (version 3.0) to allow a standardised documentation.

9.4.5 Adverse drug reactions

Starting with the first therapy cycle and every visit thereafter, the investigators had to document all adverse drug reactions in the CRF giving the following informations:

- Description of event
- Severity
- Seriousness
- Causal relationship to bevacizumab therapy

A serious adverse event (SAE) was defined as any adverse medical occurrence or effect at any dose that:

- Resulted in death
- Was life-threatening
- Required hospitalization or prolongation of an existing hospitalization
- Resulted in persistent or significant disability or infirmity
- Was a congenital abnormality or birth defect, or
- Constituted a different medically important condition

Adverse drug reactions and medical history were coded by the project manager of CRO WiSP GmbH (Andreas Kutscheidt), using MedDRA Version 15.1.

9.5 DATA SOURCE AND MEASUREMENT

All source data were to be recorded by the investigators according to local clinical practice, i.e. hospital charts, patient files, or electronic health records. All relevant data for this observational study had to be transferred into the CRF folder. A verification of source data was not performed. All CRFs were reviewed by the CRO, and missing or inconsistent data were queried by the data management. Only data recorded in the CRFs as well as in the separate forms used for the follow-up evaluations were captured into the clinical database. Appropriate data checks and quality control procedures were applied to each stage of data entry and data handling to ensure that all data were reliable and have been processed correctly. The SOP systems of the Sponsor and WiSP GmbH were applied.

9.5.1 Case report forms

All steps related to the selection, enrolment and treatment of the patients were performed in the responsibility of the investigators and should be performed in accordance with standard medical care and the current SmPC of bevacizumab. Each site received a case report form (CRF) entitled “Dokumentationsmappe für Nicht-interventionelle Studie (NIS) Avastin® first-line bis zum Progress – NIS beim metastasierten kolorektalen Karzinom”, to document baseline characteristics, the treatment, as well as treatment results for each patient. Relevant missing information and data discrepancies were queried by the central monitoring / data management. The investigators were obliged to confirm the accuracy of the data by signature.

9.5.2 Data management

The Microsoft® Visual FoxPro 7 based database for this study was developed and maintained by the CRO WiSP GmbH, Langenfeld, Germany. The database was validated according to the corresponding validation SOP of the WiSP GmbH. Data handling including description of processes such as handling of CRFs, data cleaning, coding references, SAE tabulation following CIOMS II format and SAE reconciliation with Roche drug safety, and database lock was conducted according to WiSP GmbH SOP´s.

Data recorded in the CRFs were entered manually into the database by data entry staff of WiSP GmbH using single data entry. Detailed guidelines for the data entry staff were documented using a data entry convention manual and a correction sheet for obvious, self-evident errors was implemented. Plausibility checks and listings for manual and automated data review were described in the respective “Data Validation Plan”.

Data handling and storing was done using a Microsoft®XP SP3 environment. Data regarding adverse events and concomitant diseases were coded using NCI CTC and the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1.

Medications were coded using internal WiSP GmbH coding lists. The coding was subsequently checked by qualified personnel. Queries resulting from the automated plausibility checks and the manual data review were forwarded to the investigational sites for clarification. The database was corrected according to filed answers to queries, all data alterations were followed by an audit trail implemented in the clinical database.

9.5.3 Biometrics

All statistical analyses were performed by WiSP GmbH using the software S-PLUS 2000 - Professional Release 3 and following the Statistical Analysis Plan (SAP), version 2.0 (section 9.8.5). The outputs of the statistical programs were controlled for validity by the project statistician.

9.5.4 Data review meeting

A data review meeting (DRM) was held prior to database lock. Representatives of WiSP GmbH and sponsor checked and assessed the data for the purpose of finalizing the planned analysis. Unclear data issues were clarified and the analysis populations were defined.

Several patients were excluded from the analysis populations. The data of these patients was stored in the clinical and safety databases, but no further data processing was performed. Further

protocol deviations, such as missing data issues were discussed. The assignment of patients to the respective analysis sets is described in detail in section 10 Figure 2.

Furthermore, the decision to omit a separate per protocol analysis was made, due to the fact that the full analysis set and the per protocol population differ only by one patient. Therefore it was decided to perform all analysis on the full analysis set only.

Further data issues included the handling of inconsistent or incomplete documentation of bevacizumab doses and adverse events. Explanatory footnotes for these cases are included in the respective tables of the statistical report (Annex 1 No 2).

9.6 STUDY SIZE

Due to the descriptive / explorative nature of the study no formal hypotheses were formulated. The sample size calculation of the NIS was primarily determined in order to draw conclusions on the effectiveness of different therapy approaches (i.e. different combination partners of bevacizumab [Avastin®]), if applicable also for different prognostic subgroups. On the basis of available publications at the time of sample size planning, it was anticipated that bevacizumab might be used in the following variants in this observational study, not all of which would be in accordance with the SmPC at the time, despite the clear statement in the inclusion criteria:

- with Fluoropyrimidine (FP) + oxaliplatin
- with FP + irinotecan
- with FP without further cytostatic agent
- other combination with chemotherapy
- without chemotherapy

The following parameters recorded within the scope of the NIS were presumed to possibly have prognostic/predictive relevance:

- Age (< 70 years vs. ≥ 70 years [var1] and < 75 years vs. ≥ 75 years[var2])
- Gender (male vs. female)
- Location of primary tumour (colon vs. rectum)
- Adjuvant chemotherapy (yes vs. no)
- Distant metastases (yes vs. no)
- Liver affection (yes vs. no)
- Number of metastasis sites

- Leukocytes (<10,000 /µl vs. ≥ 10,000 /µl)
- Alkaline phosphatase (<300 U/l vs. ≥ 300 U/l)
- General condition (ECOG 0 vs. ≥1)

The prognosis score published by Köhne et al.[10] can be derived from the last four parameters, which permits a differentiated formation of risk groups. The sample size of the whole population was to be chosen large enough to allow valid statistical comparisons between subgroups, which represent 20% or less of the whole group.

The significance and reliability of possible statistical comparisons between subgroups regarding the effectiveness criterion PFS is presented in Table 4. The following assumptions were made: α-error = 0.05, two sided test; observation period of at least 1 year, or until progression; 1-year-PFS-rate of approximately 45%, as observed in the marketing authorisation study in combination with IFL, or slightly higher (as in the first-line study [47%] on the combination with FOLFOX/XELOX1). Table 4 shows that with a total sample size of n= 2,000 to n= 3,000 patients, relevant differences between subgroups that constitute around 20% of the whole collective (i.e. n = 400 to n= 600), can be detected with high statistical power. Especially for the subgroup of older patients ≥ 75 years, which was expected to build approximately 12% of the total collective, a whole sample size of 3,000 patients would allow conclusions with acceptable statistical quality also for this subgroup (corresponding to 360/3,000 patients).

Table 4 Statistical considerations for calculation of sample size

Rate free from progression after 1 year			
Favourable subgroup	Unfavourable subgroup	Power	Patient number per subgroup*
50%	40%	80%	371
50%	40%	90%	496
45%	35%	80%	353
45%	35%	80%	473

*assuming an equal distribution of cases in each subgroup

Furthermore, the calculation of sample size was determined by the possibility to significantly detect clinically relevant differences in the conversion rates (i.e. proportion of initially not resectable patients, who become resectable under therapy), respectively actual resection rates (Table 5).

Table 5 Conversion rate/ resection rate

Conversion rate / Resection rate			
Favourable subgroup	Unfavourable subgroup	Power	Patient number per subgroup*
10%	5%	80%	474
8%	4%	80%	602

As in principle only about one third of all patients included in the observational study are potential candidates for a conversion, with a total collective of 3,000 patients this results in a sample size of approximately n = 1,000, i.e. approximately 500 per subgroup. According to Table 5 this allows the substantiation of the mentioned, clinically relevant differences.

Regarding the relative frequencies of therapy and diagnosis characteristics (e.g. type of the chemotherapy, dosage, frequency of deviations from the recommendations etc.) the significance can be assessed on the basis of the confidence intervals: with an assumed rate of 50%, the exact 90% confidence interval would range from 48.5 to 51.5%, the 95% confidence interval from 48.2 to 51.8%. With rates deviating up or down from 50% the size of the confidence interval decreases.

For the detection of rare adverse reactions, the planned sample size of 3,000 patients was sufficient to observe a rare adverse drug reaction or interaction with a true incidence rate of 0.5%, at least five times with a probability of more than 99%. A rare adverse reaction with a true incidence rate of only 0.1% would have been observed at least once with a probability of 95%. Even with a true incidence rate of only 0.05%, the probability of observing such a rare adverse reaction at least once amongst 3,000 patients was still approximately 77%.[11]

9.7 DATA TRANSFORMATION

No data transformations were performed.

9.8 STATISTICAL METHODS

All observed parameters were assessed descriptively and exploratively. Continuous characteristics are presented with the number of the observations, the mean value, the standard deviation, the minimum, the median and the maximum. Categorical characteristics are presented with absolute and relative frequencies within the individual categories. The main explorative statistics are supplemented by the calculation of confidence intervals and hypothesis generating p-values if applicable, especially regarding the assessment of prognostic/predictive factors.

Due to the long follow-up periods required for the retrieval of mature data on progression-free survival (PFS) and overall survival (OS), interim analyses of selected parameters were performed.

These were based on an "ad hoc" status of the database at a respective time point, albeit clearly defined by the date of "freezing" for the interim analysis. As there were no prospectively defined formal hypotheses in this NIS, no statistical error adjustments were required. The same holds for any covariate adjustment.

9.8.1 Main summary measures

All analyses were performed for the total group of patients and for subgroups defined by concomitant chemotherapy (or without chemotherapy), according to section 7.1 of the observational study protocol version 4.1, dating from March 2013:

- with fluoropyrimidine (e.g. 5-FU, capecitabine) + oxaliplatin
- with fluoropyrimidine (e.g. 5-FU, capecitabine) + irinotecan
- with fluoropyrimidine (e.g. 5-FU, capecitabine) without additional chemotherapy (leucovorin is not taken into account)
- with any other cytotoxic drug or drug combination
- without any chemotherapy

The subgroups were defined according to the concomitant treatment administered during the first treatment cycle.

9.8.2 Main statistical methods

The statistical analysis was carried out by Andreas Kutscheidt, WiSP GmbH, in accordance with WiSP Management SOP´s. The specification of the complete analysis is laid down in detail in the final version 2.0 of the SAP, dating from April 2nd, 2014, approved in writing by Roche Pharma AG. The SAP was finalized prior to data base lock.

All analyses were performed for the full analysis/safety analysis set, respectively. All parameters were evaluated in an explorative or descriptive manner, providing means, medians, interquartile and total ranges, standard deviations and/or confidence intervals, as appropriate for the respective data types. Percentages in the result tables are rounded.

If explorative p values for differences between subgroups (e.g. prognostic) were calculated for selected items, they are presented explicitly without referring to pre-specified hypotheses or a significance level. No error adjustment for multiple testing was performed. Thus the p values reflect the comparison-wise error and not the experiment-wise error. All reported p values are two-sided. The statistical methods described in this section are suitable for the data and distributions usually expected in this type of trials.

Categorical data such as response rates or toxicity grades were analysed by Fisher´s exact test for 2x2 tables. Continuous data were analysed by the Wilcoxon test.

Event related data like progression-free and overall survival were estimated by the product limit method[12] and eventually compared using the log rank test. If the Peto log rank test [13,14] was not appropriate because of violation of the proportional hazard assumption[15], Gehan's generalization of the Wilcoxon rank sum test for censored data[16] was alternatively applied, preferably in its modification by Peto[13] and Prentice.[17]

An additional multivariate analysis was performed by using suitable regression models (i.e. proportional hazard regression model[18] for event data).

9.8.3 Missing values

In general, missing values for single items were not taken into account. All analyses and calculations were performed on the basis of the data actually available for each item (observed case analyses). In the case of missing values the analysed population size deviates from the FAS. Thus, the sample size actually analysed (100%) is provided in each table of the statistical report and in section 10, accordingly. If not stated as footnote in the respective table, all percentages were calculated with exclusion of missing values.

9.8.4 Sensitivity analyses

According to the SAP it was planned to repeat the main effectiveness analyses (progression-free survival and overall survival, total group [i.e. not in subgroups]) on the per-protocol analysis set as a sensitivity analysis. During the framework of the data review meeting the decision to omit a separate per protocol analysis was made, due to the fact that the full analysis set and the per protocol population differ only by one patient.

9.8.5 Amendments to the statistical analysis plan

The statistical analysis plan 1.1 based on the version 4.1 of the observational study protocol dated March 2013 and provided the guidelines for the descriptive or explorative analysis of all parameters. Additional analyses were incorporated in the amended versions of the SAP as shown in Table 6. All amendments of the SAP were made before the final analysis of the study.

Table 6 Summary of SAP Amendments

Number	Date	Amendment or Update	Reason / added items
1.1	July 07.2013		
1.2	January 02.2014	Amendment 1	Baseline & Effectiveness: second age category , Köhne score; Treatment: chemotherapy drugs added during observation; Toxicity/Safety: assessment of adverse drug reactions with respect to expectedness, as derived from the current SmPC; Effectiveness: result of secondary metastasis resection
2.0	April 04.2015	Amendment 2	Baseline & Effectiveness: synchronous vs. metachronous metastasation, leukocytes, alkaline phosphatase Effectiveness: comparison of FP/Ox vs. FP/Iri vs. FP treatment groups within the subgroups defined by KRAS status: wild type vs. mutated; ORR, PFS, OS; multivariate prognostic analysis/model for PFS/OS

9.9 QUALITY CONTROL

CRF forms were automatically and manually checked for completeness and plausibility and unreported adverse drug reactions. Discrepancies were addressed and usually corrected by mail or phone contact with the investigator or centre.

10. RESULTS

The following sections represent a summary of the results of the data analyses performed in February 2015.

10.1 PARTICIPANTS

Patient registrations have been reported from 438 centres. Annex 1 No 1 Fig. 2 shows the cumulative course of recorded registration forms and complete case report forms over time.

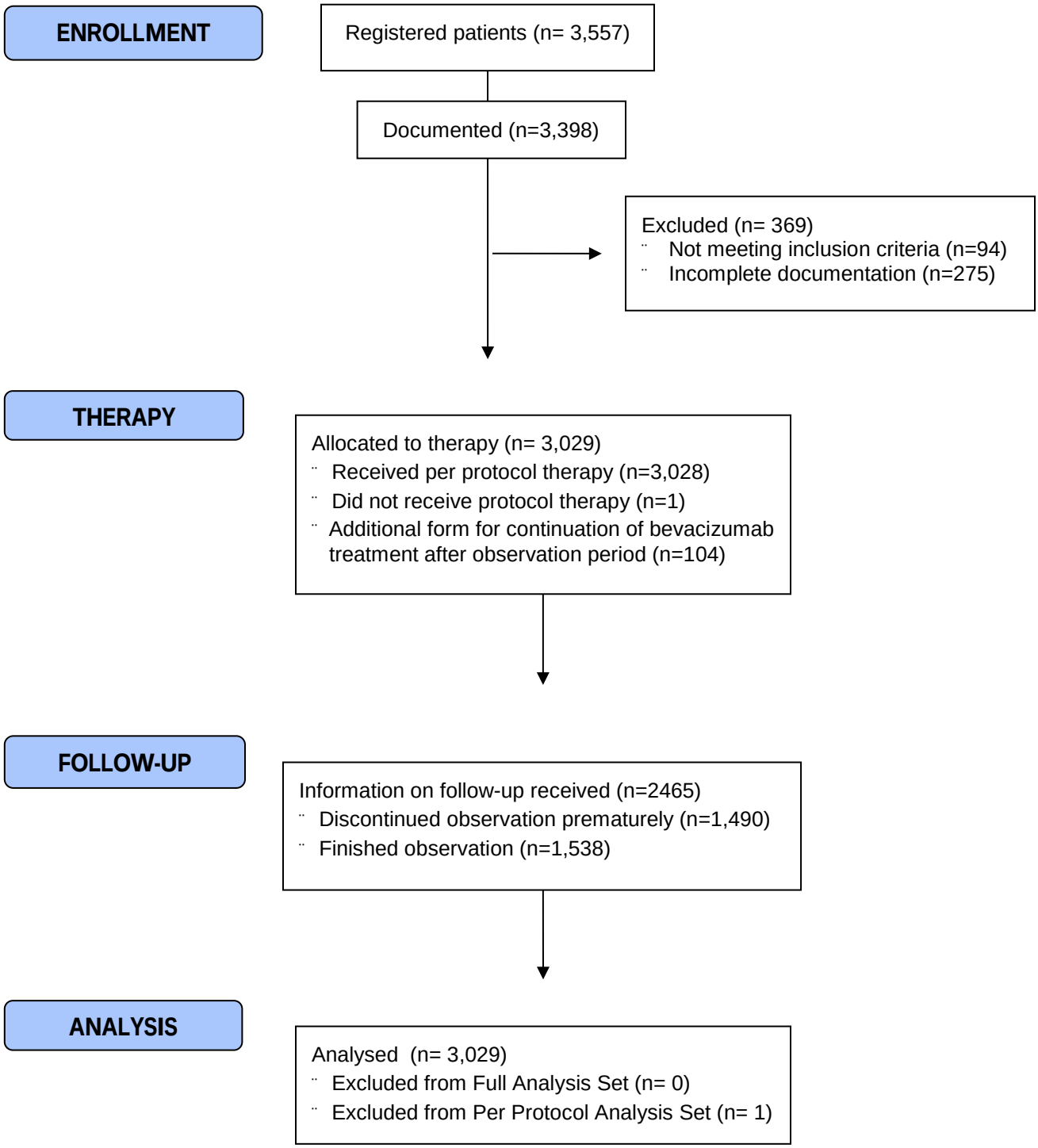
A total of 3,557 patients provided written consent for collection and processing of their data, and were therefore registered in the observational study. For 159 registered patients no documentation was sent to the data management centre, resulting in 3,398 patient documentations available. Of these, 94 documentations were categorised as non-eligible, mainly because the patients had received prior palliative cytostatic treatment. Furthermore, for 275 patients incomplete documentations were provided, usually consisting only of anamnestic baseline data, collected together with the registration form. Thus, 369 patients were excluded from analysis due to incomplete documentation, or not meeting the inclusion criteria, respectively. The resulting 3,029 patients represent the population included in the full analysis set (FAS), as well as the safety set (SAF).

One patient of the FAS was excluded from the per protocol sample (PPS) due to early withdrawal. An additional case report form used to document if treatment with bevacizumab was continued after the end of observation period for up to one consecutive year is available for 104 patients.

All patient numbers enrolled and analysed in the study are summarized in Figure 2 also providing the reasons for exclusion from the respective analysis sets.

The first patient was included in the study on April 24th, 2008 (date of enrolment, first patient on registration fax) and last patient last follow-up visit was on February 9th, 2015.

Figure 2 Study flowchart



10.2 DESCRIPTIVE DATA

10.2.1 Demographic data and general health condition

The patient population is predominantly of male gender (63%), 37% were female (Table 7). The proportion of male patients ranges from 54% to 65% in the subgroups, and is a little higher in groups with a triple combination e.g. bevacizumab with a fluoropyrimidine and either oxaliplatin or irinotecan, compared to the other subgroups.

Median age of all patients was 67 years, ranging from 20 to 99 years. Thus, according to the median, the patient population of this observational study is seven years older compared to the first-line registration study.[3]

Table 7 Baseline demographic data

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,042	1,479	424	55	3,029 (100%)
Gender distribution						
Male (%)	17 (59%)	674 (65%)	966 (65%)	228 (54%)	30 (55%)	1,915 (63%)
Female (%)	12 (41%)	368 (35%)	513 (35%)	196 (46%)	25 (45%)	1,114 (37%)
Age (years)						
Mean ± SD	69.9 ± 10.2	64.0 ± 10.0	64.6 ± 9.7	72.8 ± 9.9	62.7 ± 12.5	65.6 ± 10.3
Median	70	66	66	74	65	67
Quartiles (1st and 3rd)	65 - 74	58 - 71	58 - 72	68 - 80	53.5 - 72.5	59 – 73
Range	44 - 91	23 - 88	20 - 87	21 - 99	29 - 85	20 – 99
Age groups, var 1						
< 70 years	14 (48%)	693 (67%)	957 (65%)	125 (29%)	35 (64%)	1,824 (60%)
≥ 70 years	15 (52%)	349 (33%)	522 (35%)	299 (71%)	20 (36%)	1,205 (40%)
Age groups, var 2						
< 75 years	22 (76%)	901 (86%)	1283 (87%)	213 (50%)	46 (84%)	2,465 (81%)
³ 75 years	7 (24%)	141 (14%)	196 (13%)	211 (50%)	9 (16%)	564 (19%)

40% of the patients are 70 years and older, nearly one fifth (19%) of the study population was 75 years or older. Annex 1 Fig. 04 shows the distribution of the percentage of patients in 5 year increments (within each treatment subgroup). The analysis of age distribution shows that investigators seem to choose to apply bevacizumab monotherapy, or the double combination with fluoropyrimidine only, in elderly patients more often than the more aggressive triple combinations.

Table 8 and Table 9 present further data on the general condition of the patients at baseline. With respect to the ECOG performance status, 39% of the whole population had a normal performance status at baseline. 50% of the patients had an ECOG performance status 1 at the start of treatment, while 11% of the patients exhibited a distinctly reduced performance status of ECOG 2 or 3. There were only slight differences in the distribution of performance status between the treatment groups treated with the triple combinations of fluoropyrimidine/oxaliplatin/bevacizumab, or fluoropyrimidine/irinotecan/bevacizumab, respectively. Corresponding to the results of age distribution, the data shows that patients with less favourable ECOG status (≥ ECOG 1) are overrepresented in the treatment groups with the fluoropyrimidine only combination and bevacizumab monotherapy.

The median body weight at baseline was 75 kg in the total population, with no significant differences over all treatment subgroups (Table 9).

Table 8 ECOG performance status (baseline)

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	27	1,018	1,417	409	53	2,924 (100%)
Grade 0	11 (41%)	432 (42%)	548 (39%)	128 (31%)	29 (55%)	1,148 (39%)
Grade 1	12 (44%)	500 (49%)	720 (51%)	215 (53%)	20 (38%)	1,467 (50%)
Grade 2	3 (11%)	79 (8%)	142 (10%)	62 (15%)	3 (6%)	289 (10%)
Grade 3	1 (4%)	7 (1%)	7 (<1%)	4 (1%)	1 (2%)	20 (1%)

Table 9 Weight distribution (baseline)

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,039	1,477	422	55	3,022
Mean ± SD	73.2 ± 14.6	76.3 ± 15.9	77 ± 15.9	73.1 ± 14.6	74.8 ± 14.2	76.1 ± 15.7
Median	74.2	75	75.2	72	74	75
Quartiles (1st and 3rd)	65 - 83	65 - 85	66 - 86	63 - 82	64 - 84.3	65 – 85
Range	47 - 105	42 - 160	37 - 143	38 - 157	39.6 - 110	37 – 160

10.2.2 Anamnestic data

The sections 10.2.2.1 to 10.2.2.7 summarize the anamnestic data of patients.

10.2.2.1 Disease history

1,959 of 3,029, patients were diagnosed with distant metastases or an inoperable local relapse at their primary diagnosis of colorectal cancer, or within less than two weeks thereafter. This means that 65% of the whole patient population were treated in an initially palliative situation in this observational study (Table 10). The proportion of patients in palliative situation at diagnosis in the treatment arms FP/oxaliplatin/bevacizumab and FP/irinotecan/bevacizumab were 76% and 60%, respectively.

The time from primary diagnosis to relapse/distant dissemination ranged from >2 weeks to less than 1 year for 10%, and from 1 to 4 years for 19% of the whole population. For 6% of the patients this period was longer than 4 years (data shown in Annex 1 No. 2, Tab. 9).

Table 10 Time from primary diagnosis to relapse/distant dissemination [weeks]

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,042	1,479	424	55	3,029
Mean ± SD	52.5 ± 102.7	34.6 ± 96.6	47.5 ± 88.0	60.1 ± 100.1	65 ± 118.1	45.2 ± 93.9
Median	0	0	0	0	0	0
Quartiles (1st and 3rd)	0 – 22	0 – 0	0 – 69	0 – 86	0 – 75	0 – 53
Range	0 – 371	0 – 905	0 – 946	0 – 708	0 – 567	0 – 946
n	29	1,042	1,479	424	55	3,029 (100%)
Initially palliative	19 (66%)	793 (76%)	890 (60%)	223 (53%)	30 (55%)	1,955 (65%)

The occurrence of metastases was categorized as synchronous or metachronous dependant on their time point of detection in relation to the time of primary diagnosis of colorectal cancer. If the detection of metastases took place within 8 weeks after initial diagnosis, they were considered as being synchronous. Outside this time frame, they were categorized as metachronous. The data on synchronous/metachronous metastasization is shown in Table 11. In almost two thirds of all cases, patients were diagnosed with synchronous metastases. Patients with synchronous metastases were more frequently treated with the triple combination containing oxaliplatin, while in the treatment subgroup with bevacizumab/fluoropyrimidine the proportion of patients with metachronous metastases is distinctly higher compared to the whole population.

Table 11 Synchronous / metachronous metastasization

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,042	1,479	424	55	3,029
Synchronous	20 (69%)	806 (77%)	904 (61%)	226 (53%)	30 (55%)	1,986 (66%)
Metachronous	9 (31%)	236 (23%)	575 (39%)	198 (47%)	25 (45%)	1043 (34%)

10.2.2.2 Staging and grading at baseline

Table 12 to Table 15 present the data of tumour staging (pTNM status) and grading at baseline. These data could be assessed for nearly all patients of the FAS, there are only few cases of missing values for each parameter. The majority of patients presented with a pathological tumour stage of pT3 or pT4 at the initial diagnosis (Table 12). Stage pT3 was present in 55% of all patients, 28% were assessed as stage pT4. The distribution of pT staging shows no major differences between treatment subgroups.

In 68% of all cases the patients were diagnosed with positive lymph node involvement at primary diagnosis, compared to 20% of patients with status pN0 (Table 13). Distant metastases at the time point of initial diagnosis were present in 59% (Table 14). The rate of patients with distant metastases at initial diagnosis was distinctly higher in the triple combination groups (FP/oxaliplatin/bevacizumab and FP/irinotecan/bevacizumab) compared to the other treatment combination subgroups (Table 14).

Table 12 Tumour stage at initial diagnosis – primary tumour (pT)

pT	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,039	1,470	424	55	3,017 (100%)
pTis	-	9 (1%)	2 (<1%)	1 (<1%)	-	12 (<1%)
pT1	-	16 (2%)	25 (2%)	10 (2%)	2 (4%)	53 (2%)
pT2	-	69 (7%)	85 (6%)	36 (8%)	4 (7%)	194 (6%)
pT3	17 (59%)	540 (52%)	814 (55%)	241 (57%)	35 (64%)	1,647 (55%)
pT4	8 (28%)	296 (28%)	415 (28%)	126 (30%)	13 (24%)	858 (28%)
pTx	4 (14%)	109 (10%)	129 (9%)	10 (2%)	1 (2%)	253 (8%)

Table 13 Tumour stage at initial diagnosis – lymph nodes (pN)

pN	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,039	1,471	424	55	3,018 (100%)
pN0	6 (21%)	207 (20%)	278 (19%)	100 (24%)	14 (25%)	605 (20%)
pN1	8 (28%)	264 (25%)	446 (30%)	151 (36%)	15 (27%)	884 (29%)
pN2	10 (34%)	430 (41%)	575 (39%)	152 (36%)	24 (44%)	1191 (39%)
pNx	5 (17%)	138 (13%)	172 (12%)	21 (5%)	2 (4%)	338 (11%)

Table 14 Tumour stage at initial diagnosis – distant metastases (M)

pT	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,039	1,474	424	55	3,021 (100%)
M0	11 (38%)	204 (20%)	489 (33%)	177 (42%)	22 (40%)	903 (30%)
M1	15 (52%)	728 (70%)	807 (55%)	206 (49%)	28 (51%)	1,784 (59%)
Mx	3 (10%)	107 (10%)	178 (12%)	41 (10%)	5 (9%)	334 (11%)

About two thirds (62%) of the patients exhibited a well or moderately differentiated tumour (G1-2), while 29% were diagnosed with undifferentiated disease (G3-4) (Table 15).

Table 15 Tumour grading at initial diagnosis

Grading	without CT	FP with oxaliplatin	FP with irinotecan	only FP	other CT	total
n	28	1,038	1,470	424	55	3,015 (100%)
G1	-	13 (1%)	21 (1%)	7 (2%)	2 (4%)	43 (1%)
G2	16 (57%)	594 (57%)	941 (64%)	264 (62%)	37 (67%)	1,852 (61%)
G3	11 (39%)	329 (32%)	397 (27%)	119 (28%)	12 (22%)	868 (29%)
G4	-	3 (<1%)	2 (<1%)	-	-	5 (<1%)
Gx	1 (4%)	99 (10%)	109 (7%)	34 (8%)	4 (7%)	247 (8%)

10.2.2.3 Location of disease at study registration

In total 56% patients (1,697 cases) of the full analysis set (FAS) were diagnosed with positive locoregional tumour at baseline. Of these, 1,448 patients were positive for local primary tumour in the colon/rectum, corresponding to 48% of the FAS. 580 patients (19%) showed a tumour involvement of the regional lymph nodes. Nearly all patients (97%) had distant metastasis at the start of the observation period in this study (Table 16).

Table 16 Patients with distant metastases at baseline and metastasis location

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,042	1,479	424	55	3,029 (100%)
Distant metastasis	25 (86%)	1,017 (98%)	1,428 (97%)	404 (95%)	53 (96%)	2,927 (97%)
Involved organ system / site of metastases*						
Liver	18 (62%)	784 (75%)	1,029 (70%)	254 (60%)	38 (69%)	2,123 (70%)
Lung	13 (45%)	299 (28%)	502 (34%)	141 (33%)	16 (29%)	971 (32%)
Ascites	1 (3%)	30 (3%)	40 (3%)	11 (2%)	1 (2%)	83 (3%)
Bones	1 (3%)	29 (3%)	44 (2%)	18 (4%)	-	92 (3%)
Pleuratic effusion	-	13 (1%)	15 (1%)	8 (2%)	-	36 (1%)
CNS	-	4 (<1%)	7 (<1%)	3 (1%)	-	14 (<1%)
Other	8 (28%)	233 (22%)	355 (24%)	97 (23%)	10 (18%)	703 (23%)

* Percentages refer to the total patient number of 3,029, multiple answers were possible

In total, 3,914 lesions were documented, with multiple answers for the involved organ system being possible. The organ systems predominantly involved by distant metastasis were the liver (70%, range in the treatment subgroups 62 - 75%) and the lung (32%, 28 – 34%, Table 16). With regard to other sites of metastatic lesions, most frequently documented locations or organ systems were not-regional lymph nodes (6%), involvement of the peritoneum and retroperitoneum (9%), and peritoneal carcinomatosis (4%).

10.2.2.4 KRAS status

As data on the KRAS status was not initially included in the CRF, a retrospective request for this information was included in the (optional) assessment of updated follow-up data by fax and compiled in August 2013 and September 2014. Therefore this data item is available in only 1,725 of 3,029 patients (57%). For 23% of patients the information on KRAS mutation status is unknown, e.g. due to inappropriate biological material, in 618 patients (20%) no data on KRAS status at all could be obtained. A KRAS wild type is present in 31% of the patients, while 26% of the patients were KRAS mutated (Table 17).

Table 17 KRAS status

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,042	1,479	424	55	3,029
KRAS wild type	5 (17%)	332 (32%)	478 (32%)	97 (23%)	24 (44%)	936 (31%)
KRAS mutated	4 (14%)	258 (25%)	414 (28%)	104 (25%)	9 (16%)	789 (26%)
Unknown	10 (34%)	223 (21%)	312 (21%)	133 (31%)	8 (15%)	686 (23%)
No data	10 (34%)	229 (22%)	275 (19%)	90 (21%)	14 (25%)	618 (20%)

10.2.2.5 Vital signs at baseline: blood pressure

It is noteworthy that blood pressure measurements (systolic as well as the diastolic values) at baseline were not available in 26.4% of the patients (almost 800 patients). With respect to the distribution of the blood pressure measurements among the WHO categories, there are considerable differences in the semi-quantitative assessment of the systolic and diastolic values (Table 18). Based on the systolic values 35% of the patients are to be considered as being hypertensive (782 / 2,228, Annex 1 No. 2, Tab. 21, 22), compared to 17% (389 / 2,228) to be considered as hypertensive based on the diastolic values. The median value of the systolic and diastolic blood pressure (130/80) is the same for all treatment subgroups (Table 18).

Table 18 Blood pressure at baseline [mm Hg]

Parameter	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
Systolic value [mmHg]						
n	23	753	1,107	300	45	2,228
Mean ± SD	132.3 ± 15.6	131.8 ± 17.0	131.7 ± 17.5	133.8 ± 17.1	129.3 ± 13.1	132 ± 17.2
Median	130	130	130	130	130	130
Quartiles (1st and 3rd)	122.5 - 140	120 - 140	120 – 140	120 - 141.2	120 - 140	120 - 140
Range	100 - 166	80 - 200	64 – 270	90 - 194	108 - 165	64 - 270
Diastolic value [mmHg]						
Mean ± SD	78.6 ± 6.3	78.8 ± 10.6	78.4 ± 10.6	77.3 ± 10.4	78.2 ± 8.4	78.4 ± 10.5
Median	80	80	80	80	80	80
Quartiles (1st and 3rd)	71.5 - 80	70 - 85	70 – 85	70 - 80	73 - 80	70 - 85
Range	70 - 90	15 - 120	20 – 140	50 - 115	60 - 97	15 - 140

10.2.2.6 Köhne score

Patients were allocated to three distinct “risk-groups” based on the methods described by Köhne et al.[10] The Köhne score is built upon the following parameters: ECOG performance status (section 10.2.1), the number of involved organ sites, white blood count (Table 19) and level of alkaline phosphatase (AP, Table 20).

The three risk groups according to the Köhne Score are defined as follows:

- Low risk: ECOG 0/1, one tumour site only
- Intermediate risk: ECOG 0/1, > 1 tumour site, AP < 300 U/l, or
  ECOG > 1, < 10.0 /nl, one tumour site only
- High risk: ECOG 0/1, > 1 tumour site, AP ≥ 300 U/l, or
  ECOG > 1, > 1 tumour site or WBC count ≥ 10.0 /nl

Data on WBC count and alkaline phosphatase are provided in Table 19 and Table 20, respectively. Median WBC count for all patients was 7.3 /nl, 17% of patients had a WBC count of ≥ 10 /nl. Median value for AP is 105 U/l for the total population, 11% of patients exhibited a value for AP equal to or above 300 U/l. Significant differences between the treatment subgroups regarding these parameters were not detectable.

Table 19 WBC count at baseline [/nl]

Parameter / Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	28	1,016	1,423	408	54	2,929
Mean ± SD	7.8 ± 2.6	8.2 ± 5.0	8 ± 5.5	7.7 ± 5.4	7.4 ± 3.2	8 ± 5.2
Median	8.1	7.6	7.2	7.1	7	7.3
Quartiles (1st and 3rd)	6 - 9.2	5.9 - 9.2	5.7 - 9	5.6 - 8.6	5.5 - 8.6	5.7 – 9
Range	1.4 - 12.7	1.5 - 77.4	1.6 - 90.6	0.5 - 97.5	2.8 - 20.8	0.5 - 97.5
< 10 /nl	23 (82%)	832 (82%)	1,169 (82%)	352 (86%)	48 (89%)	2,424 (83%)
≥ 10 /nl	5 (18%)	184 (18%)	254 (18%)	56 (14%)	6 (11%)	505 (17%)

Table 20 Alkaline phosphatase [U/l]

Parameter / Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	24	882	1,188	357	51	2,502
Mean ± SD	166.8 ± 129.6	172.9 ± 180.9	157.3 ± 161.7	139.3 ± 136.3	172.0 ± 181.1	160.6 ± 165.9
Median	100.5	108	104	101	104.4	105
Quartiles (1st and 3rd)	77.3 - 242.2	80 - 186	76.2 - 159.2	77 - 145	69.5 - 135.5	77.4 – 165
Range	54 - 470	0.9 - 1659	0.8 - 1587	6.1 - 1351	1.6 - 760	0.8 – 1659
< 300 U/l	20 (83%)	768 (87%)	1,064 (90%)	334 (94%)	41 (80%)	2,227 (89%)
≥ 300 U/l	4 (17%)	114 (13%)	124 (10%)	23 (6%)	10 (20%)	275 (11%)

Applying the Köhne score to the available data for the population of the present trial results in 92% (2,785 patients) being allocated to the three risk groups; the majority of patients were assigned to the low risk group (65%, Table 21); 27% of patients were at intermediate risk and only 8% of patients had to be assigned to high risk. There are no major differences between the treatment subgroups regarding the allocation to risk groups (Table 21).

Table 21 Köhne score

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	27	975	1,334	397	52	2,785 (100%)
Low risk group	12 (44%)	663 (68%)	842 (63%)	254 (64%)	40 (77%)	1,811 (65%)
Intermediate risk group	10 (37%)	240 (25%)	379 (28%)	111 (28%)	8 (15%)	748 (27%)
High risk group	5 (19%)	72 (7%)	113 (8%)	32 (8%)	4 (8%)	226 (8%)

10.2.2.7 Pre-treatment

The analysis of pre-treatment before enrolment into the present study shows that the primary tumour was dissected in the majority of patients (88%, Table 22). A prior radiotherapy had been performed in 15% of the patients (Table 23).

Table 22 Surgery of the primary tumour

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,040	1,479	424	55	3,027
No	5 (17%)	178 (17%)	169 (11%)	21 (5%)	4 (7%)	377 (12%)
Yes	24 (83%)	862 (83%)	1,310 (89%)	403 (95%)	51 (93%)	2,650 (88%)

Table 23 Radiotherapy

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,041	1,478	424	55	3,027
No	27 (93%)	904 (87%)	1,245 (84%)	347 (82%)	50 (91%)	2,573 (85%)
Yes	2 (7%)	137 (13%)	233 (16%)	77 (18%)	5 (9%)	454 (15%)

Before treatment with bevacizumab 43% of the patients had received one or more cycles of previous cytotoxic therapy. In total, 1,627 therapies were documented for 1,340 patients (44%, Table 24), mostly as neoadjuvant or adjuvant treatment.

Patients with palliative cytostatic pre-treatment did not qualify for this non-interventional study and therefore were not included in the analysis. However, the population includes cases in which the investigators decided to administer initial cycles of chemotherapy at a timepoint when bevacizumab was contraindicated, e.g. due to a short time interval since surgery, and added bevacizumab in the following cycles. In these cases investigators were asked to document the chemotherapy without administration of bevacizumab as palliative pre-treatment (12% of the whole population, Table 24). Percentages given in Table 24 refer to number of patients with previous chemotherapy / and total patient numbers, respectively.

Information about the application period of the preceding (neo)/adjuvant treatment is available for 949 of the 1,315 patients (corresponding to 72%). In 28% of the patients the treatment with bevacizumab started within six months after end of the (neo)/adjuvant treatment, in 17% the treatment-free interval ranged from seven to twelve months. In 37% of patients bevacizumab therapy was initiated between one and three years after end of the (neo)/adjuvant treatment, in 18% the treatment-free period was three years and above.

Table 24 Number of previous chemotherapies*

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n (pts with previous CTx/ all pts)	9 / 29	380 / 1,024	732 / 1,479	191 / 424	28 / 55	1,340 / 3,029
No data	-	1 (<1% / <1%)	8 (1% / <1%)	2 (1% / <1%)	-	11 (1% / <1%)
Adjuvant	5 (56% / 56%)	141 (37% / 14%)	522 (71% / 35%)	129 (68% / 30%)	19 (68% / 35%)	816 (61% / 27%)
Neoadjuvant	-	54 (14% / 5%)	53 (7% / 4%)	26 (14% / 6%)	2 (7% / 4%)	135 (10% / 4%)
Palliative	4 (44% / 44%)	184 (48% / 18%)	149 (20% / 10%)	34 (18% / 8%)	7 (25% / 13%)	378 (28% / 12%)

* Percentages refer to number of patients with previous therapy/ total number of patients

10.2.2.8 Relevant concomitant diseases

About half of the patients suffered at baseline from at least one concomitant disease apart from colorectal cancer. Table 25 shows the types of relevant concomitant diseases as documented, which are known to potentially interfere with bevacizumab application, and therefore possibly relevant for the course of therapy.

The proportion of patients with any documented relevant concomitant disease is highest (36%) in the treatment subgroup with fluoropyrimidine/bevacizumab. The most frequent concomitant disease in all subgroups is hypertension in 39% of all patients, followed by diabetes mellitus in 14% of the whole population. The occurrence of arterial embolic events is of only minor relevance (3%).

Table 25 Relevant concomitant diseases

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,042	1,479	424	55	3,029 (100%)
Any conc. disease	9 (31%)	513 (49%)	754 (51%)	273 (64%)	21 (38%)	1,570 (52%)
Type of concomitant disease* [multiple answers possible]						
Hypertension	8 (28%)	390 (37%)	557 (38%)	202 (48%)	15 (27%)	1,172 (39%)
Diabetes mellitus	3 (10%)	127 (12%)	213 (14%)	74 (17%)	5 (9%)	422 (14%)
Arterial embolic event	2 (7%)	22 (2%)	53 (3%)	19 (4%)	-	96 (3%)
Other disease	10 (34%)	261 (25%)	378 (26%)	148 (35%)	11 (20%)	808 (27%)

* Percentages refer to the total number of patients

10.2.3 Treatment with bevacizumab

The duration of bevacizumab treatment was calculated as the interval between the date of the first application of the antibody and the date of the end-of-treatment or end-of-observation report, respectively. The results are presented in Table 26. Median duration of the bevacizumab treatment was 6.1 months. However, in 17% of patients of the whole population the duration of treatment was more than 12 months, mostly due to treatment interruptions, treatment delay, or delayed scheduling of the final examination after treatment. Furthermore, for 104 of 3,029 patients (3%) the bevacizumab treatment was continued after the first year, which was evaluated on a separate CRF page included in the requests on updated follow-up data by fax.

The median treatment duration of patients treated with bevacizumab in combination with oxaliplatin (5.8 months) is notably shorter compared to patients treated in combination with irinotecan (6.7 months, Table 26). This may explain the difference in treatment duration of the present observational study in comparison to the preceding non-interventional study ML18664 (median duration 7.0 months).[19,20] In ML18664 bevacizumab was more frequently applied in combination with irinotecan (64%) than in combination with oxaliplatin (18%). This relation is more balanced in the present trial: irinotecan 49%, oxaliplatin 34% of patients.

Table 26 Duration of documented bevacizumab therapy (months)

Parameter	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,042	1,479	424	55	3,029
Mean ± SD	5.8 ± 4.2	6.8 ± 4.9	7.9 ± 5.6	6.8 ± 5.2	7.6 ± 4.8	7.3 ± 5.3
Median	5.3	5.8	6.7	5.7	6.8	6.1
Quartiles (1st and 3rd)	2.3 - 7.1	3.2 - 8.9	3.7 - 10.9	2.8 - 9.3	4.3 - 10.9	3.4 - 10.1
Range	0.4 - 15.7	0 - 36.2	0 - 55.2	0 - 35.2	0.2 - 25.6	0 - 55.2

For 48% of all patients the treatment duration with bevacizumab was documented for up to six months, further 41% of the patients received bevacizumab for up to 14 months. In only 10% of the patients bevacizumab was applied for a longer time period of up to more than two years (data shown in Annex 1 No. 2, Tab. 35).

Due to the fact that the choice of the cytotoxic agents administered in combination with bevacizumab was at discretion of the investigator, treatment regimens with different cycle lengths and schedule were used. Therefore no homogenous definition of cycle duration can be applied; the CRF was flexibly designed, in order to allow documentation of each therapy cycle with a frequency of bevacizumab applications every two or three weeks. Thus, the documented median number of nine cycles or therapy periods for the whole population corresponds to a median of eleven applications of bevacizumab (Table 27). More than half of the patients (52%) received between six and 15 bevacizumab applications. Taken into account that also treatment delays occurred with respect to the therapy period, an exact correspondence to the duration in months cannot be expected.

Table 27 Number of documented bevacizumab cycles and applications

Parameter / Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
Number of documented cycles						
n	29	1,042	1,479	424	55	3,029
Mean ± SD	9.3 ± 6.6	10.7 ± 7.6	12.1 ± 8.7	10.4 ± 7.9	12.8 ± 9.1	11.3 ± 8.3
Median	8	9	10	8	10	9
Quartiles (1st and 3rd)	4 - 14	6 - 13	6 - 17	4.8 - 14	7 - 17.5	5 - 15
Range	1 - 22	1 - 52	1 - 52	1 - 52	1 – 52	1 - 52
Number of documented applications						
Mean ± SD	9.7 ± 6.4	11.6 ± 7.7	13.1 ± 8.9	11.1 ± 8.3	13.5 ± 8.8	12.3 ± 8.4
Median	8	10	11	9	11	11
Quartiles (1st and 3rd)	5 - 14	6 - 15	6 - 18	5 - 15	8 - 18	6 – 16
Range	1 - 22	1 - 52	1 - 71	1 - 58	1 - 50	1 – 71
1-5 appl.	8 (28%)	208 (20%)	271 (18%)	110 (26%)	9 (16%)	606 (20%)
6-10 appl.	9 (31%)	321 (31%)	410 (28%)	129 (30%)	15 (27%)	884 (29%)
11-15 appl.	6 (21%)	275 (26%)	318 (22%)	84 (20%)	12 (22%)	695 (23%)
16-20 appl.	3 (10%)	111 (11%)	193 (13%)	45 (11%)	7 (13%)	359 (12%)
21-25 appl.	3 (10%)	69 (7%)	122 (8%)	27 (6%)	6 (11%)	227 (7%)
> 25 appl.	-	58 (6%)	165 (11%)	29 (7%)	6 (11%)	258 (9%)

Table 28 shows the calculated duration between the first and the second bevacizumab cycle. The 222 patients who received only one treatment cycle were excluded from this analysis. In nearly two thirds of the patients (65%) a bi-weekly regime was chosen. In 24% of the evaluable cases an application of bevacizumab took place every three weeks. A shorter administration schedule of weekly bevacizumab administrations was rarely applied (1% of all patients). Cycle duration of four weeks and more occurred in 4%, due to the respective treatment interruptions.

Table 28 Calculated duration of first bevacizumab cycle

Parameter / Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	24	959	1,377	394	53	2,807 (100%)
Mean ± SD	15.8 ± 4.5	16.5 ± 6.6	17.4 ± 9.8	18.5 ± 7.3	17.9 ± 11.2	17.3 ± 8.5
Median	14	14	14	15.5	14	14
Quartiles (1st and 3rd)	14 - 20.2	14 - 16	14 - 15	14 - 21	14 - 16	14 - 20
Range	6 - 28	1 - 83	2 - 100	6 - 84	7 - 86	1 - 100
£ 1 week	1 (4%)	9 (1%)	9 (1%)	7 (2%)	1 (2%)	27 (1%)
>1 - £2 weeks	15 (62%)	656 (68%)	956 (69%)	173 (44%)	33 (62%)	1,833 (65%)
>2 - £3 weeks	7 (29%)	202 (21%)	270 (20%)	169 (43%)	12 (23%)	660 (24%)
>3 - £4 weeks	1 (4%)	61 (6%)	57 (4%)	31 (8%)	4 (8%)	154 (5%)
>4 - £5 weeks	-	16 (2%)	21 (2%)	4 (1%)	1 (2%)	42 (1%)
> 5 weeks	-	15 (2%)	64 (5%)	10 (3%)	2 (4%)	91 (3%)

The distribution of bevacizumab dosage was analysed for the first observation cycle (i.e. within the first four weeks of therapy), and is presented in Table 29. In all subgroups the patients received in median the recommended dosage of 5 mg/kg bodyweight (BW). Nevertheless, a higher single dose of 7.5 mg/kg BW was applied especially in the combination of bevacizumab with fluoropyrimidine only (39% of n = 424, compared to 13% with application of 7.5 mg/kg BW for the whole population). A higher dosage from 10 to 15 mg/kg BW occurred only in a minority of cases (54 patients, corresponding to 2%).

Table 29 Dosage of bevacizumab in the first treatment cycle [mg/kg BW]

Parameter / Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,042	1,479	424	55	3,029
Mean ± SD	5.8 ± 1.5	5.5 ± 1.3	5.2 ± 0.7	6.2 ± 1.7	5.2 ± 0.9	5.4 ± 1.2
Median	5	5	5	5	5	5
Quartiles (1st and 3rd)	5 - 6	5 - 5	5 - 5	5 - 7.5	5 - 5	5 - 5
Range	5 - 10	3 - 15	2.5 - 10	4 – 15	5 - 10	2.5 - 15

10.2.3.1 Cytostatic agents applied in combination with bevacizumab

A total of 59,172 chemotherapeutic co-medications were reported in overall 33,857 documented treatment cycles of all eligible patients. This means that on average two cytostatic medications were combined with bevacizumab (Table 30). Applications of folic acid were ignored in order to identify the combination of cytotoxic agents more precisely. As expected triple combinations of bevacizumab with 5-FU and either irinotecan or oxaliplatin prevail (43% or 22%, respectively). The use of capecitabine instead of 5-FU in this combinations was generally rare (5% of all cycles, Table 30). Capecitabine is more frequently combined with bevacizumab alone, without addition of oxaliplatin or irinotecan (9% of all cycles).

Table 30 Type of cytostatic agent as co-medication (all therapy cycles)

Category	n / (%)
n (total documented therapy cycles)	33,857 (100%)
Irinotecan / 5-FU	14,530 (43%)
Oxaliplatin / 5-FU	7,518 (22%)
5-FU	4,235 (13%)
Capecitabine	2,880 (9%)
Bevacizumab monotherapy	2,348 (7%)
Irinotecan / capecitabine	793 (2%)
Oxaliplatin / capecitabine	835 (2%)
Irinotecan	342 (1%)
Oxaliplatin / 5-FU / irinotecan	161 (<1%)
Oxaliplatin	92 (<1%)
5-FU / capecitabine / irinotecan	37 (<1%)
Mitomycin / irinotecan	19 (<1%)
Oxaliplatin / 5-FU / capecitabine	16 (<1%)
5-FU / capecitabine	15 (<1%)
Oxaliplatin / irinotecan	12 (<1%)
Tegafur	8 (<1%)
Ralitrexed / irinotecan	6 (<1%)
Oxaliplatin / capecitabine / irinotecan	4 (<1%)
5-FU / irinotecan / cetuximab	3 (<1%)
Oxaliplatin / 5-FU / capecitabine / irinotecan	2 (<1%)
Oxaliplatin / 5-FU / cetuximab	1 (<1%)

If each cytostatic agent applied as co-medication is counted only once per patient, a total of 5,893 chemotherapeutic co-medications results for all documented treatment cycles in 3,029 eligible patients; the results are presented in Table 31. Independent from the therapy regime, 85% of the patients received at least one dose of 5-FU, followed by irinotecan (54%) and oxaliplatin (38%).

Table 31 Cytostatic co-medication (all therapy cycles): each cytotoxic agent counted once per patient

Category	n / (%)
Number of co-medications	(5,893)
Number of patients	3,029 (100%)
5-FU	2,563 (85%)
Irinotecan	1,632 (54%)
Oxaliplatin	1,138 (38%)
Capecitabine	553 (18%)
Cetuximab	2 (<1%)
Mitomycin	2 (<1%)
Ralitrexed	1 (<1%)
Tegafur	1 (<1%)
Zoledronat	1 (<1%)

Table 32 presents the documented types of cytostatic compound (combinations) during the first treatment cycle with bevacizumab for the whole population of this observational trial. The combination of 5-FU with irinotecan and bevacizumab is the most common combination (46%), followed by the combination of bevacizumab with 5-FU and oxaliplatin (30%). Table 32 forms the basis for the allocation of all eligible patients in the present study to the treatment subgroups generally applied in all analyses.

Table 32 Type of therapy combinations with bevacizumab during the first cycle

Category	n / (%)	Allocation to treatment subgroup n (%)
Number of patients	3,029 (100%)	3,029 (100%)
No data	29 (1%)	Without CT 29 (1%)
Irinotecan	28 (1%)	Other CT 55 (2%)
Oxaliplatin / 5-FU / irinotecan	17 (1%)	
Oxaliplatin	8 (<1%)	
Oxaliplatin / 5-FU / cetuximab	1 (<1%)	
Tegafur	1 (<1%)	
Capecitabine	219 (7%)	5-FU or capecitabine only 424 (14%)
5-FU	202 (7%)	
5-FU / capecitabine	2 (<1%)	
Mitomycin / irinotecan	1 (<1%)	
Oxaliplatin / 5-FU	917 (30%)	FP with oxaliplatin 1,042 (34%)
Oxaliplatin / capecitabine	124 (4%)	
Oxaliplatin / 5-FU / capecitabine	1 (<1%)	
5-FU / irinotecan	1,382 (46%)	FP with irinotecan 1,479 (49%)
Capecitabine / irinotecan	91 (3%)	
5-FU / capecitabine / irinotecan	5 (<1%)	
5-FU / irinotecan / cetuximab	1 (<1%)	

10.2.3.2 Dose deviations

The analysis of dose deviations of bevacizumab or chemotherapy includes all treatment cycles in which the applied dose deviated from the dosage administered during the first cycle for each patient. The data were analyzed with respect to the total number of documented treatment cycles as well as to the number of eligible patients. Overall, a dose deviation occurred in 13% of all applied treatment cycles, which corresponds to an absolute number of 2,268 cycles (Table 33). No dose deviation was recorded in 2,086 patients (69%) of the whole population. At least one dose deviation was required in 31% of the total group. Since patients could have several dose deviations during the course of their therapy, the total of 2,268 documented deviations occurred in 943 patients with no distinct differences between the therapy subgroups. In 278 patients (9%) a dose deviation in comparison to the first treatment cycle was recorded at least three times or more (Table 33).

Table 33 Dose deviations (by treatment cycles, by patient)

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
Number of cycles	140	5,760	9,188	2,298	365	17,751 (100%)
No dose deviation	134 (96%)	5,014 (87%)	7,985 (87%)	2,008 (87%)	342 (94%)	15,483 (87%)
Dose deviation present	6 (4%)	746 (13%)	1,203 (13%)	290 (13%)	23 (6%)	2,268 (13%)
Dose deviations (by patient):						
n	29	1,042	1,479	424	55	3,029 (100%)
No dose deviation	25 (86%)	700 (67%)	1,015 (69%)	305 (72%)	41 (75%)	2,086 (69%)
1 dose deviation	2 (7%)	158 (15%)	223 (15%)	64 (15%)	8 (15%)	455 (15%)
2 dose deviations	2 (7%)	88 (8%)	97 (7%)	19 (4%)	4 (7%)	210 (7%)
≥ 3 dose deviations	-	96 (9%)	144 (10%)	36 (8%)	1 (2%)	278 (9%)

The main reason for the occurrence of dose deviations was to be documented and categorized by the investigators in the CRF. The results are presented in Table 34. In almost half of the cases (49%) the dosage was adjusted because of non-haematological toxicities. Dose deviations caused by hypertension were rare (<1%).

Table 34 Reasons for dose deviations, (cycles, by categories)

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
Number of dose deviations	6	746	1,203	290	23	2,268 (100%)
Hematotoxiciy	1 (17%)	85 (11%)	151 (13%)	5 (2%)	2 (9%)	244 (11%)
Hypertension	-	-	3 (<1%)	-	-	3 (<1%)
Non-haematological toxicities	4 (67%)	387 (52%)	544 (45%)	175 (60%)	12 (52%)	1,122 (49%)
Other	1 (17%)	157 (21%)	274 (23%)	63 (22%)	4 (17%)	499 (22%)
Unknown	-	117 (16%)	231 (19%)	47 (16%)	5 (22%)	400 (18%)

10.2.3.3 Treatment interruptions / delays

An interruption or delay of the bevacizumab therapy was documented in 13% of all evaluable treatment cycles (corresponding to 2,343 of 17,746 cycles). These interruptions or delays were reported for 1,339 patients (44%) of the whole patient population. In the treatment subgroup flouropyrimidine/oxaliplatin/bevacizumab an interruption/delay occurred in 40%, in the treatment subgroup flouropyrimidine/irinotecan/bevacizumab in 48% of patients. In 815 cases of the whole population the bevacizumab treatment was interrupted or delayed once (27%), in 294 patients an interruption/delay occurred twice (10%), and for 230 patients (8%) three or more delays of bevacizumab application were reported.

The main reasons for the treatment interruptions / delays of bevacizumab therapy are listed by categories in Table 35. In more than half of the cases of interruptions / delays (56%) the time points of bevacizumab application were adjusted for other reasons and not due to toxicity of the treatment.

Table 35 Reasons for interruptions/delays of bevacizumab therapy, (cycles, by categories)

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	15	646	1352	276	54	2,343 (100%)
Haematotoxicity	1 (7%)	76 (12%)	85 (6%)	2 (1%)	9 (17%)	173 (7%)
Hypertension	-	12 (2%)	16 (1%)	6 (2%)	1 (2%)	35 (1%)
Non-haematological toxicities	5 (33%)	213 (33%)	439 (32%)	111 (40%)	20 (37%)	788 (34%)
Other	9 (60%)	338 (52%)	788 (58%)	154 (56%)	23 (43%)	1,312 (56%)
Unknown	-	7 (1%)	24 (2%)	3 (1%)	1 (2%)	35 (1%)

The results for the frequency of treatment interruptions or delays with regard to the cytostatic agents applied in combination treatment were similar to the results shown for bevacizumab. An interruption or delay of any cytostatic co-medication occurred in 17% of all documented cycles (3,000 of 17,725 cycles). These interruptions / delays were reported for 1,572 patients (52%) of the whole population, and were slightly more frequent in patients treated with irinotecan (54%), compared to patients receiving oxaliplatin (51%, in combination with FU/bevacizumab).

In general, with regard to any treatment compound including bevacizumab, 80% of all evaluable treatment cycles (14,286 of 17,763 cycles) could be administered without interruption or delay.

10.2.3.4 Adaptations of therapy regimens in the course of treatment

In order to obtain information whether the cytotoxic therapy regimens applied in addition to bevacizumab were changed during the course of treatment, and whether any correlation to the time point of disease progression is evident, the cytotoxic agents applied in the first and last cycle were compared for each patient. The results are presented in Table 36.

According to the analysis findings, patients were allocated to one of four categories:

1) No difference in number of cytotoxic agents (incl. patients with bevacizumab mono-therapy); also: substitution of one cytotoxic compound against another with constant total number of agents combined with bevacizumab,
2) Cytotoxic therapy stopped during course of treatment (i.e. all applied agents stopped completely),
3) Cytotoxic therapy reduced during course of treatment (i.e. stop of one or more compounds, but no stop of whole treatment),
4) Cytotoxic agent(s) added during course of treatment.

Table 36 Adaptations of therapy regimens in the course of treatment

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,042	1,479	424	55	3,029 (100%)
No difference	21 (72%)	720 (69%)	1,162 (79%)	358 (84%)	30 (55%)	2,291 (76%)
Complete stop of CT	-	93 (9%)	99 (7%)	41 (10%)	10 (18%)	243 (8%)
Partial stop of CT	-	218 (21%)	203 (14%)	2 (<1%)	11 (20%)	434 (14%)
CT added	8 (28%)	11 (1%)	15 (1%)	23 (5%)	4 (7%)	61 (2%)

In the next step the results for treatment adaption or treatment continuation without changes were correlated to information regarding disease progression. Progression events were taken into account if they occurred within 28 days after the last documented bevacizumab application. Patients with addition of a cytotoxic agent during the course of the treatment were allocated to the “bevacizumab + CT until PD” category if an event for disease progression occurred. Complete data regarding this analysis was obtained for 2,950 patients, in 42% (1,238 patients) a disease progression occurred until end of the observation period or within 28 days thereafter. In most cases all cytotoxic agents were applied until disease progression (31%, 913 patients). In 4% (128 patients) the cytotoxic agents were completely stopped before progression, in 7% (197 patients) they were partially stopped. In all patients, application of bevacizumab was continued until disease progression (data shown in Annex 1 No. 2, Tab. 56).

10.2.4 Other treatment related data

10.2.4.1 Secondary metastasis resection

According to the research questions and objectives of the observational study (section 7) data on the frequency of secondary metastasis resection was obtained and analysed. A secondary metastasis resection during the course of the bevacizumab treatment was performed in 201 patients (7%, Table 37). Of these, 195 patients had one secondary resection (6%), six patients (<1%) had two resections each, leading to a total number of 207 secondary resections performed for the whole trial collective.

The results of these 207 resections are also provided in Table 37. In 59% of all cases a R0 resection was achieved. However, for 20% of the performed resections investigators provided no data regarding the residual margin.

Table 37 Frequency of secondary metastasis resection (by patient), and resection results

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,042	1,479	424	55	3,029 (100%)
No sec. met. resection	29 (100%)	960 (92%)	1,377 (93%)	413 (97%)	49 (89%)	2,828 (93%)
Sec. met. resection	-	82 (8%)	102 (7%)	11 (3%)	6 (11%)	201 (7%)
Result of secondary metastasis resection, by number of resections:						
Number of resections	0	84	106	11	6	207 (100%)
R0	-	53 (63%)	60 (57%)	6 (55%)	3 (50%)	122 (59%)
R1	-	13 (15%)	9 (8%)	3 (27%)	-	25 (12%)
R2	-	5 (6%)	11 (10%)	2 (18%)	-	18 (9%)
Rx	-	13 (15%)	26 (25%)	-	3 (50%)	42 (20%)

For the majority of the patients a secondary resection of liver metastases was performed (70% of all resections). Furthermore, secondary resections involved predominantly the lung (15%), or other sites/organ systems (15%). Complications during the secondary resection were reported occasionally; one patient in the FP/oxaliplatin/bevacizumab group (2% of resections in this group), and four patients in the FP/irinotecan/bevacizumab group (4%). However, information regarding complications is missing in 20% of the cases (42 patients).

10.2.4.2 Additional tumour-related therapy

Out of the 3,029 evaluable cases only 74 patients received an additional tumour-related therapy during the observation period (2%, Table 38). The number of applied additional therapies per patient ranged from one to nine. This amounts to a total of 166 therapies, which were applied in the 47 patients. The additional tumour-related therapies predominantly consisted of therapy with bisphosphonate (40% of the applied therapies), and radiotherapy (15% of the applied therapies, Table 39).

Table 38 Number of additional tumour-related therapies (by patient)

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,042	1,479	424	55	3,029 (100%)
No add. therapy	29 (100%)	1,010 (97%)	1,447 (98%)	415 (98%)	54 (98%)	2,955 (98%)
1	-	20 (2%)	23 (2%)	4 (1%)	-	47 (2%)
2	-	7 (1%)	2 (<1%)	2 (<1%)	-	11 (<1%)
4	-	1 (<1%)	2 (<1%)	1 (<1%)	1 (2%)	5 (<1%)
5	-	1 (<1%)	-	-	-	1 (<1%)
≥ 6	-	3 (<1%)	4 (<1%)	2 (<1%)	-	9 (<1%)

Table 39 Type of additional tumour-related therapies

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
Number of documented therapies	0	63	75	24	4	166 (100%)
Bisphosphonate	-	11 (17%)	42 (56%)	14 (58%)	-	67 (40%)
Radiation	-	10 (16%)	15 (20%)	-	-	25 (15%)
Hyperthermia	-	8 (13%)	6 (8%)	6 (25%)	-	20 (12%)
Mistletoe therapy	-	11 (17%)	1 (1%)	-	4 (100%)	16 (10%)
Other medication	-	11 (17%)	5 (7%)	1 (4%)	-	17 (10%)
No data	-	4 (6%)	2 (3%)	-	-	6 (4%)
Other	-	3 (5%)	-	3 (12%)	-	6 (4%)
Resection, other surgery	-	4 (6%)	1 (1%)	-	-	5 (3%)
RFA / SIRT	-	1 (2%)	3 (4%)	-	-	4 (2%)

10.2.5 Documentation at the end of the observation period

10.2.5.1 Performance status

Information about the performance status at the end of the observation period was obtained in 2,535 patients (84% of the evaluable patients). The result is presented in Table 40.
29% of all patients presented with an unreduced performance status at the end of the observation. Half of the patients exhibited a slightly reduced performance status of ECOG 1. For 20% of the whole population a distinctly reduced performance status was reported, with an ECOG ranging from 2 to 4 (Table 40).
Compared to baseline, with 89% of patients being ECOG 0-1, and 11% of patients being ECOG 2-3 (no patient ECOG 4), it seems that the performance status of the patients at the end of the observation has generally worsened compared to baseline, which is consistent with the fact that for most patients the observation period ended with progression of their disease.

Table 40 ECOG performance status (end of therapy)

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	25	894	1,224	344	48	2,535 (100%)
ECOG 0	9 (36%)	270 (30%)	366 (30%)	69 (20%)	20 (42%)	734 (29%)
ECOG 1	9 (36%)	458 (51%)	622 (51%)	165 (48%)	17 (35%)	1,271 (50%)
ECOG 2	5 (20%)	131 (15%)	189 (15%)	84 (24%)	9 (19%)	418 (16%)
ECOG 3	2 (8%)	26 (3%)	35 (3%)	23 (7%)	2 (4%)	88 (3%)
ECOG 4	-	9 (1%)	12 (1%)	3 (1%)	-	24 (1%)

10.2.5.2 Reasons for discontinuation of bevacizumab treatment

1,350 out of the 3,029 evaluable patients discontinued the therapy with bevacizumab due to disease progression (45%). For 261 patients (9%) the documentation period after one or two years ended without having progressed. Of these, information about therapy continuation after the end of the observation period was obtained for 245 cases; in 82% (200 patients) of them investigators planned to continue the treatment, only in 45 patients (18%) the therapy was terminated.

In a total of 1,418 patients (47%) the treatment with bevacizumab was stopped prematurely for other reasons than progression or regular end of observation period. The detailed reasons are given in Table 41, in which multiple reasons for treatment discontinuation were allowed. In most cases, administrative/miscellaneous reasons were documented to have caused the discontinuation of bevacizumab.

Table 41 Reasons for discontinuation (multiple answers possible, percentage by patients)

Reason	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,042	1,479	424	55	3,029 (100%)
Progression	15 (52%)	456 (44%)	652 (44%)	205 (48%)	22 (40%)	1,350 (45%)
End of observation after one year	1 (3%)	64 (6%)	147 (10%)	31 (7%)	4 (7%)	247 (8%)
End of observation after two years	-	1 (<1%)	9 (1%)	3 (1%)	1 (2%)	14 (<1%)
Administrative reasons / miscellaneous	8 (28%)	296 (28%)	390 (26%)	86 (20%)	17 (4%)	797 (26%)
Serious adverse drug reaction	3 (10%)	115 (11%)	137 (9%)	44 (10%)	2 (4%)	301 (10%)
Refusal of treatment / non-compliance	2 (7%)	74 (7%)	96 (6%)	39 (9%)	3 (5%)	214 (7%)
Death due to tumour	2 (7%)	70 (7%)	91 (6%)	27 (6%)	4 (7%)	194 (6%)
Loss of contact to patient	3 (10%)	38 (4%)	64 (4%)	23 (5%)	5 (9%)	133 (4%)
Death due to other cause*	-	26 (2%)	30 (2%)	7 (2%)	-	63 (2%)

* The detailed list for deaths due to other cause is provided in Annex 1 No. 2, Tab. 93.

With regard to the 797 patients who discontinued therapy for administrative/miscellaneous reasons, further details for the type of reason and the respective proportions are given in Table 42. The predominant reasons were planned surgery (22%), and end of documentation (15%). No explicit reason was provided in 8% of the cases.

Table 42 Administrative reasons for discontinuation of bevacizumab treatment

Reason	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
Patients with administrative reasons / misc.	8	296	390	86	17	797 (100%)
Surgery planned	2 (25%)	77 (26%)	83 (21%)	7 (8%)	5 (29%)	174 (22%)
Documentation end	2 (25%)	43 (15%)	54 (14%)	19 (22%)	3 (18%)	121 (15%)
Patient's wish	-	36 (12%)	50 (13%)	14 (16%)	5 (29%)	105 (13%)
Best response achieved	1 (12%)	31 (10%)	56 (14%)	8 (9%)	1 (6%)	97 (12%)
Stop of planned therapy by physician	-	37 (12%)	37 (9%)	3 (3%)	2 (12%)	79 (10%)
Therapy-free interval	2 (25%)	16 (5%)	44 (11%)	8 (9%)	1 (6%)	71 (9%)
Deterioration of health status	-	26 (9%)	19 (5%)	17 (20%)	-	62 (8%)
No statement	1 (12%)	20 (7%)	36 (9%)	9 (10%)	-	66 (8%)
Other reasons	-	10 (3%)	11 (3%)	1 (1%)	-	22 (3%)

If the patient numbers for the category „death due to tumour" (Table 41) are also assessed as disease progressions, the end of therapy was associated with progression of colorectal cancer in overall 1,544 / 3,029 (51%) patients. If, in addition "deterioration of health status" (according to Table 42) is assessed as disease progression, the numbers and rate amount to 1,606 / 3,029 (53%).

In Table 43 the patient disposition at the end of the study and reasons for the discontinuation of bevacizumab therapy are shown again, counting each patient only once with the main reason for the discontinuation. For patients with multiple reasons for discontinuation according to the documentation of the investigator, the main reason was determined according to the hierarchical order given in the left column in the table (top to bottom). The reference list for the hierarchical order was provided by Roche CTg.

The results of this analysis show that more than half of the patients (53%) have completed the study according to the observational plan, with similar proportions of patients in the two main subgroups (FP/oxaliplatin 50%, FP/irinotecan 55%). Regarding the patients with premature discontinuation of treatment, administrative/miscellaneous reasons for discontinuation are reported in most cases (23%); 9% of all patients have stopped the treatment due to serious adverse drug reactions, 5% have died due to colorectal cancer, 2% (n=48) of the whole population have died due to other cause. The detailed list of the free text entries for cause of death of these 48 patients is provided in Annex 1 No. 2, Tab. 93.

Table 43 Patient disposition at the end of observation period (by patients, main reason for treatment discontinuation in hierarchical order)

Category / reason*	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n (A+B+C)	29	1,042	1,479	424	55	3,029 (100%)
Study completed (A)	16 (55%)	521 (50%)	808 (55%)	239 (56%)	27 (49%)	1,611 (53%)
Serious adverse drug reaction (b1)	3 (10%)	105 (10%)	119 (8%)	41 (10%)	2 (4%)	270 (9%)
Death due to tumour (b2)	2 (7%)	55 (5%)	73 (5%)	19 (4%)	3 (5%)	152 (5%)
Death due to other cause (b3)	-	21 (2%)	21 (1%)	6 (1%)	-	48 (2%)
Refusal of treatment / non-compliance (b4)	2 (7%)	54 (5%)	78 (5%)	34 (8%)	3 (5%)	171 (6%)
Administrative reasons /misc. (b5):	6 (20%)	260 (25%)	339 (23%)	68 (16%)	15 (27%)	688 (23%)
Best response achieved	*1 (3%)*	*31 (3%)*	*53 (4%)*	*7 (2%)*	*1 (2%)*	*93 (3%)*
Surgery planned	*2 (7%)*	*72 (7%)*	*74 (5%)*	*6 (1%)*	*4 (7%)*	*158 (5%)*
End of planned therapy by physician	*-*	*35 (3%)*	*36 (2%)*	*3 (1%)*	*2 (4%)*	*76 (3%)*
Deterioration of health	*-*	*18 (2%)*	*14 (1%)*	*12 (3%)*	*-*	*44 (1%)*
Therapy-free interval	*1 (3%)*	*14 (1%)*	*30 (2%)*	*7 (2%)*	*1 (2%)*	*53 (2%)*
Patient´s wish	*-*	*28 (3%)*	*44 (3%)*	*10 (2%)*	*4 (7%)*	*86 (3%)*
Other reasons	*-*	*8 (1%)*	*10 (1%)*	*1 (<1%)*	*-*	*19 (1%)*
No statement	*1 (3%)*	*20 (2%)*	*33 (2%)*	*5 (1%)*	*-*	*59 (2%)*
Documentation end	*1 (3%)*	*34 (3%)*	*45 (3%)*	*17 (4%)*	*3 (5%)*	*100 (3%)*
Loss of contact to patient (C)	-	26 (2%)	41 (3%)	17 (4%)	5 (9%)	89 (3%)

* Explanations: n = A+B+C; B = ∑ (b1 ... b5); category b5 is further divided in subcategories marked in *italic*. Percentages refer to the total number of patients.

10.2.5.3 60-Days-mortality

During the observation period of this trial, in total 194 patients were reported with death due to underlying disease (according to Table 41, multiple reasons possible). For these patients the time period between date of death and date of treatment start was analysed. The majority of deaths happened more than 60 days after treatment start (84%). 31 cases (16% of patient deaths caused by tumour) occurred within 60 days after start of therapy (Table 44).
Out of the 63 patients who died because of other cause than tumour, the death occurred in 29% of patients within 60 days after the start of the therapy (Table 44). With respect to the total patient population in this study the overall 60-days-mortality amounts to 49 of 3,029 patients, corresponding to 1.6%.

Table 44 60-Days-mortality

Category	Death by tumour	Death by other cause	Total
n	194	63	257 (100%)
> 60 days after therapy start	163 (84%)	45 (71%)	208 (81%)
≤ 60 days after therapy start	31 (16%)	18 (29%)	49 (19%)

10.2.6 Further-line treatments

As described in section 9.2, two assessments of follow-up data after the end of the individual regular observation period were performed in August 2013 and September 2014.
The follow-up assessments included data on the actual patient status, information about KRAS status at baseline (if test was performed), as well as information whether the antibody treatment with bevacizumab was continued after the end of the observation period. Finally, informations about second and further-line treatments in case of disease progression were included in the follow-up questionnaires.
Additional data on 2,153 patients could be retrieved in the first follow-up request in 2013, and data on 857 patients during the second update in 2014, leading to overall 2,465 cases with at least one time point of additional follow-up information. Of these, 1,417 (57%) cases were reported to have received one or more further-line treatment (Table 45).

Table 45 Further-line chemotherapy (available follow-up data)

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	20	837	1,226	341	41	2,465 (100%)
No further-line treatment	15 (75%)	348 (42%)	482 (39%)	187 (55%)	16 (39%)	1,048 (43%)
≥ 1 further-line treatment	5 (25%)	489 (58%)	744 (61%)	154 (45%)	25 (61%)	1,417 (57%)

Altogether 2,742 treatment regimens were documented for the 1,417 patients with any further-line therapy: 1,415 documented regimes were applied in second-line, i.e. for two patients no data on the type of the second-line treatment was provided. With respect to the total number of evaluable patients in this study, in 47% of the total population a second-line therapy was reported.
806 patients received at least a third-line treatment, corresponding to 29% of the reported further-line treatments, and 27% of all patients, respectively. Further 364 patients received at least treatment in fourth-line (13% of regimes, 12% of patients). Overall up to eight further treatment lines are documented for the whole patient population in this study (Table 46).
All analyses on further-line treatments were focused on treatments in second and third-line; only the detailed results for second-line treatments are presented here. The results concerning third-line treatment are to be found in Annex 1 No. 2, section 7.

Table 46 Number of further-line chemotherapies (number of reported regimes)

Further-line therapy	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n (regimens)	9	951	1,452	286	44	2,742 (100%)
1 (2^{nd} -line)	5 (56%)	491 (52%)	742 (51%)	152 (53%)	25 (57%)	1,415 (52%)
2 (3^{rd} -line)	2 (22%)	278 (29%)	429 (30%)	84 (29%)	13 (30%)	806 (29%)
3 (4^{th} -line)	2 (22%)	122 (13%)	195 (13%)	39 (14%)	6 (14%)	364 (13%)
4 (5^{th} -line)	-	39 (4%)	53 (4%)	10 (3%)	-	102 (4%)
5 (6^{th} -line)	-	15 (2%)	20 (1%)	1 (<1%)	-	36 (1%)
6 (7^{th} -line)	-	6 (1%)	8 (1%)	-	-	14 (1%)
7 (8^{th} -line)	-	-	3 (<1%)	-	-	3 (<1%)
8 (9^{th} -line)	-	-	2 (<1%)	-	-	2 (<1%)

The regimes reported for treatment in second-line were assessed according to the same categories generally used in this analysis report, i.e. as for the cytostatic co-medications documented for the first treatment cycle with bevacizumab in this study.

The correlation between treatment subgroup and treatment regime for second-line chosen by the investigator, is presented in Table 47 to Table 49. For 9% of the patients with documented second-line treatment no data on the type of second-line regimen is available. It is remarkable that in 66% of the patients treated in first-line with the combination FP/oxaliplatin/bevacizumab, the triple combination with irinotecan was chosen, whereas only 40% of patients treated with FP/irinotecan/bevacizumab in first-line changed to the combination with oxaliplatin. For patients treated with FP/irinotecan/bevacizumab in first-line, the re-initiation of this combination is more frequent (36%), compared to patients receiving oxaliplatin in first-line (14%, Table 47).

Table 47 Second-line chemotherapy regimens

Further-line therapy	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	5	491	742	152	25	1,415 (100%)
FP with oxaliplatin	2 (40%)	69 (14%)	295 (40%)	42 (28%)	7 (28%)	415 (29%)
FP with irinotecan	2 (40%)	324 (66%)	264 (36%)	53 (35%)	8 (32%)	651 (46%)
Only FP	-	56 (11%)	98 (13%)	34 (22%)	1 (4%)	189 (13%)
Other CT	1 (20%)	6 (1%)	24 (3%)	5 (3%)	-	36 (3%)
No data / unknown	-	36 (7%)	61 (8%)	18 (12%)	9 (36%)	124 (9%)

Table 48 and Table 49 show the data of second-line therapies separated for the patient subgroups with KRAS wild-type and KRAS mutation, respectively.

Table 48 Second-line chemotherapy regimens – patients with KRAS wild type

Further-line therapy	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	2	239	350	58	17	666 (100%)
FP with oxaliplatin	1 (50%)	29 (12%)	122 (35%)	17 (29%)	6 (35%)	175 (26%)
FP with irinotecan	1 (50%)	164 (69%)	143 (41%)	22 (38%)	5 (29%)	335 (50%)
Only FP	-	23 (10%)	34 (10%)	12 (21%)	-	69 (10%)
Other CT	-	2 (1%)	7 (2%)	-	-	9 (1%)
No data / unknown	-	21 (9%)	44 (13%)	7 (12%)	6 (35%)	78 (12%)

Table 49 Second-line chemotherapy regimens - patients with KRAS mutation

Further-line therapy	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	1	168	252	52	6	479 (100%)
FP with oxaliplatin	-	29 (17%)	120 (48%)	19 (37%)	-	168 (35%)
FP with irinotecan	-	112 (67%)	74 (29%)	20 (38%)	3 (50%)	209 (44%)
Only FP	-	18 (11%)	32 (13%)	6 (12%)	1 (17%)	57 (12%)
Other CT	1 (100%)	3 (2%)	16 (6%)	2 (4%)	-	22 (5%)
No data / unknown	-	6 (4%)	10 (4%)	5 (10%)	2 (33%)	23 (5%)

Regarding the second-line treatment, the application of an antibody or a targeted therapy agent is documented for 964 of the 1,415 applied treatments (68%). In 515 cases (36% of all second-line treatments) a re-initiation of the treatment with bevacizumab in second-line is reported. The application of another antibody or inhibitor within second-line treatment is documented for 449 patients (32% of all second-line treatments).

The time interval from end of the observation period to start of second-line treatment ranged from an immediate initiation to a start of second-line 3 to 5 years after end of the observation period (Table 50). The second-line treatment was started within 2 weeks or less after end of the observation for 32% of all patients. In 36% of the patients the second-line therapy started within 6 months after the documented end of observation in this study. In Table 51 similar results are shown for the time period between end of observation and start of second-line treatment with re-initiation of the antibody bevacizumab.

Table 50 Time interval from end of NIS observation period to start of second-line therapy

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	5	486	731	147	25	1,394 (100%)
Directly	1 (20%)	114 (23%)	199 (27%)	46 (31%)	7 (28%)	367 (26%)
< 2 weeks	-	41 (8%)	43 (6%)	5 (3%)	1 (4%)	90 (6%)
2-4 weeks	-	35 (7%)	44 (6%)	12 (8%)	3 (12%)	94 (7%)
1 month - 6 months	1 (20%)	148 (30%)	206 (28%)	45 (31%)	7 (28%)	407 (29%)
7 months - 1 y.	1 (20%)	89 (18%)	151 (21%)	32 (22%)	6 (24%)	279 (20%)
1-2 y.	1 (20%)	43 (9%)	70 (10%)	7 (5%)	1 (4%)	122 (9%)
2-3 y.	-	13 (3%)	11 (2%)	-	-	24 (2%)
3-5 y.	1 (20%)	3 (1%)	7 (1%)	-	-	11 (1%)

Table 51 Time interval from end of NIS observation period to start of second-line bevacizumab therapy

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	0	172	269	57	7	505 (100%)
Directly	-	51 (30%)	82 (30%)	16 (28%)	5 (71%)	154 (30%)
< 2 weeks	-	11 (6%)	12 (4%)	1 (2%)	-	24 (5%)
2-4 weeks	-	4 (2%)	12 (4%)	5 (9%)	-	21 (4%)
1 month - 6 months	-	46 (27%)	67 (25%)	17 (30%)	1 (14%)	131 (26%)
7 months - 1 y.	-	36 (21%)	58 (22%)	15 (26%)	1 (14%)	110 (22%)
1-2 y.	-	19 (11%)	29 (11%)	3 (5%)	-	51 (10%)
2-3 y.	-	4 (2%)	6 (2%)	-	-	10 (2%)
3-4 y.	-	1 (1%)	3 (1%)	-	-	4 (1%)

With regard to other antibodies or targeted agents documented to be administered in second-line, the EGFR targeting antibodies cetuximab and panitumumab were most frequently documented (Table 52). In Table 53 and Table 54 again the distribution of antibodies/targeted therapies in relation to the KRAS mutation status is provided.

Table 52 Other additional antibodies/inhibitors used in second-line therapies

Category	without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	3	170	232	25	16	446 (100%)
Cetuximab	3 (100%)	121 (71%)	177 (76%)	16 (64%)	9 (56%)	326 (73%)
Panitumumab	-	33 (19%)	48 (21%)	9 (36%)	7 (44%)	97 (22%)
Aflibercept	-	11 (6%)	6 (3%)	-	-	17 (4%)
Ramucirumab	-	3 (2%)	-	-	-	3 (1%)
Denosumab	-	1 (1%)	-	-	-	1 (<1%)
Rituximab	-	-	1 (<1%)	-	-	1 (<1%)
Sorafenib	-	1 (1%)	-	-	-	1 (<1%)

Table 53 Other additional antibodies/inhibitors used in second-line therapies - KRAS wild type

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	2	141	195	21	15	374 (100%)
Cetuximab	2 (100%)	106 (75%)	153 (78%)	13 (62%)	9 (60%)	283 (76%)
Panitumumab	-	27 (19%)	42 (22%)	8 (38%)	6 (40%)	83 (22%)
Aflibercept	-	5 (4%)	-	-	-	5 (1%)
Ramucirumab	-	2 (1%)	-	-	-	2 (1%)
Sorafenib	-	1 (1%)	-	-	-	1 (<1%)

Table 54 Other additional antibodies/inhibitors used in second-line therapies - KRAS mutation

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	0	10	14	1	0	25 (100%)
Aflibercept	-	5 (50%)	5 (36%)	-	-	10 (40%)
Cetuximab	-	2 (20%)	6 (43%)	-	-	8 (32%)
Panitumumab	-	2 (20%)	2 (14%)	1 (100%)	-	5 (20%)
Ramucirumab	-	1 (10%)	-	-	-	1 (4%)
Rituximab	-	-	1 (7%)	-	-	1 (4%)

10.3 OUTCOME DATA

10.3.1 Tumour response

While on treatment, the investigators were asked to document the current response status of patients on each treatment form. Based on these results, the best response category achieved on treatment was evaluated for each patient and the result is presented in Table 55. According to this evaluation, a disease remission or at least stable disease (SD) was achieved in 73% of the patients. The objective response rate of complete and partial remissions (CR+PR) amounts to 47%.

Table 55 Best response during therapy (based on all treatment forms per patient)

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,042	1,479	424	55	3,029 (100%)
CR	-	60 (6%)	97 (7%)	11 (3%)	3 (5%)	171 (6%)
PR	7 (24%)	445 (43%)	630 (43%)	131 (31%)	28 (51%)	1,241 (41%)
SD	6 (21%)	274 (26%)	380 (26%)	117 (28%)	14 (25%)	791 (26%)
PD	4 (14%)	120 (12%)	155 (10%)	67 (16%)	5 (9%)	351 (12%)
NE	2 (7%)	39 (4%)	40 (3%)	26 (6%)	3 (5%)	110 (4%)
No restaging available	10 (34%)	104 (10%)	177 (12%)	72 (17%)	2 (4%)	365 (12%)

In addition, the „best overall response“-finding had to be documented once per patient on the end-of-treatment/observation form, according to investigators assessment. The results for best tumour response achieved according to this data item are summarised in Table 56. This information is available for nearly all patients (3,024), only in five cases the overall investigator assessment is missing. The results of the investigators assessment at the end of treatment are in good agreement with the evaluation over the course of treatment, at least regarding complete as well as partial remissions, both for the whole population and the main treatment subgroups (Table 56).

Table 56 Best response (assessment on end-of-therapy/observation form)

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
N	29	1,039	1,479	422	55	3,024 (100%)
CR	2 (7%)	65 (6%)	94 (6%)	14 (3%)	4 (7%)	179 (6%)
PR	8 (28%)	436 (42%)	616 (42%)	131 (31%)	27 (49%)	1,218 (40%)
SD	11 (38%)	312 (30%)	429 (29%)	142 (34%)	12 (22%)	906 (30%)
PD	1 (3%)	123 (12%)	175 (12%)	64 (15%)	5 (9%)	368 (12%)
NE	7 (24%)	103 (10%)	165 (11%)	71 (17%)	7 (13%)	353 (12%)

Finally, the best response categories achieved were summarized for each patient, based on all available documentation forms. The results are presented in Table 57; the percentages provided in this table follow methodically the intent-to-treat principle, i.e. all patients with insufficient or missing restaging information are assessed as failures (=non-responders).

According to the best response evaluation based on both sources, the objective (overall) remission rate amounts to 52 % for the whole population (exact 95% confidence interval: 50-54%), with 7% of patients achieving a complete remission. Whereas in the subgroups treated with bevacizumab in combination with oxaliplatin and irinotecan the objective remission rate (CR+PR) amounts to 53% and 54%, respectively, the overall response rate is 39% in the cohort of patients treated with bevacizumab plus fluoropyrimidine only (Table 57).

Table 57 Best response (all sources, ITT, by combination regimen)

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,042	1,479	424	55	3,029 (100%)
CR	2 (7%)	78 (7%)	112 (8%)	16 (4%)	4 (7%)	212 (7%)
PR	9 (31%)	478 (46%)	687 (46%)	148 (35%)	31 (56%)	1,353 (45%)
SD	10 (34%)	297 (29%)	403 (27%)	140 (33%)	11 (20%)	861 (28%)
PD	2 (7%)	108 (10%)	144 (10%)	60 (14%)	5 (9%)	319 (11%)
NE	6 (21%)	81 (8%)	133 (9%)	60 (14%)	4 (7%)	284 (9%)

A test with regard to the 2x2 contingency table for the main treatment subgroups (FP/oxali-platin/bevacizumab and FP/irinotecan/bevacizumab) and responders vs non-responders reveals no significance ($p = 0.75$, Fisher's exact test).

For comparison to other published data concerning the overall response rate see discussion in section 11.

The response rate was also analysed regarding the influence of several prognostic factors which were pre-defined in the SAP.
Minor influence on the overall remission rate (difference < 5%) could be observed for the prognostic subgroups defined by gender (ORR, male: 53% vs female: 50%), number of distant metastasis (< 2 metastases: 53% vs ≥ 2 metastases: 49%), CEA value at baseline (< 20 ng/ml: 55% vs ≥ 20 ng/ml: 51%), previous adjuvant chemotherapy (no adjuvant pre-treatment: 53% vs adjuvant pre-treatment: 50%), and time point of dissemination of metastases (synchronous: 51% vs metachronous: 52%; complete data shown Annex 1 No. 2, section 4.1).
In contrast, a trend towards higher response rate became apparent for younger patients (< 70 years: 54% vs ≥ 70 years: 48%; Table 58), patients with lower WBC at baseline (< 10 /nl: 54% vs ≥ 10 /nl: 45%; Table 59), as well as patients with lower levels of alkaline phosphatase at baseline (< 300 U/l: 54% vs ≥ 300 U/l: 47%; results shown in Annex 1 No. 2, Tab. 72). A distinctly higher response rate was observed for patients exhibiting good or slightly reduced performance status (ECOG < 2, ORR: 53%) compared to patients with ECOG ≥ 2 (ORR: 40%, Table 60). Also the prognostic subgroups according to the Köhne score show a clear correlation between risk assessment and response rate (ORR: low risk 54%, intermediate risk 50%, high risk 40%; full data shown in Annex 1 No. 2, Tab. 73).

Table 58 Best response (all sources, ITT), by age

Category	< 70 years	≥ 70 years	Total
n	1,824	1,205	3,029 (100%)
CR	148 (8%)	64 (5%)	212 (7%)
PR	836 (46%)	517 (43%)	1,353 (45%)
SD	513 (28%)	348 (29%)	861 (28%)
PD	184 (10%)	135 (11%)	319 (11%)
NE	143 (8%)	141 (12%)	284 (9%)

Table 59 Best response (all sources, ITT), by WBC at baseline

Category	< 10 /nL	≥ 10 /nL	Total
n	2424	505	2,929 (100%)
CR	185 (8%)	20 (4%)	205 (7%)
PR	1,106 (46%)	208 (41%)	1,314 (45%)
SD	689 (28%)	140 (28%)	829 (28%)
PD	252 (10%)	57 (11%)	309 (11%)
NE	192 (8%)	80 (16%)	272 (9%)

Table 60 Best response (all sources, ITT), by ECOG status at baseline

Category	ECOG < 2	ECOG ≥ 2	Total
n	2,615	309	2,924 (100%)
CR	184 (7%)	20 (6%)	204 (7%)
PR	1,202 (46%)	105 (34%)	1,307 (45%)
SD	748 (29%)	86 (28%)	834 (29%)
PD	266 (10%)	43 (14%)	309 (11%)
NE	215 (8%)	55 (18%)	270 (9%)

10.4 MAIN EFFICACY RESULTS

The analysis of progression-free survival and overall survival is based on the complete primary documentation available, i.e. the forms included in the initial CRF covering the main observation period, as well as the data retrieved by the two requests for follow-up data performed in August 2013 and September 2014. The main results and key figures regarding PFS (and OS) are presented in the following sections. Full data and additional figures are included in the Annex 1 No. 1, Figures 12 a-o and Figures 13 a-o.

10.4.1 Progression-free survival (PFS)

Since the patient recruitment for this trial was stopped in early 2012, and the information about a progression event is available for 81% of the patients (2,461 of 3,029 patients), the estimation for PFS reflects a mature data situation. Patients without information of a progression event were censored at the time point of last observation.

The Kaplan-Meier estimation for progression-free survival currently amounts to a median PFS time of 10.3 months for the whole population (95%-CI: 9.6 – 10.7 months, Table 61 and Figure 3). The narrow 95% confidence interval also indicates the maturity and reliability of the Kaplan-Meier estimation. 19% of the patients were reported as being progression-free at the time point of analysis. The rate of patients with an observed event is above 80% in all treatment subgroups.

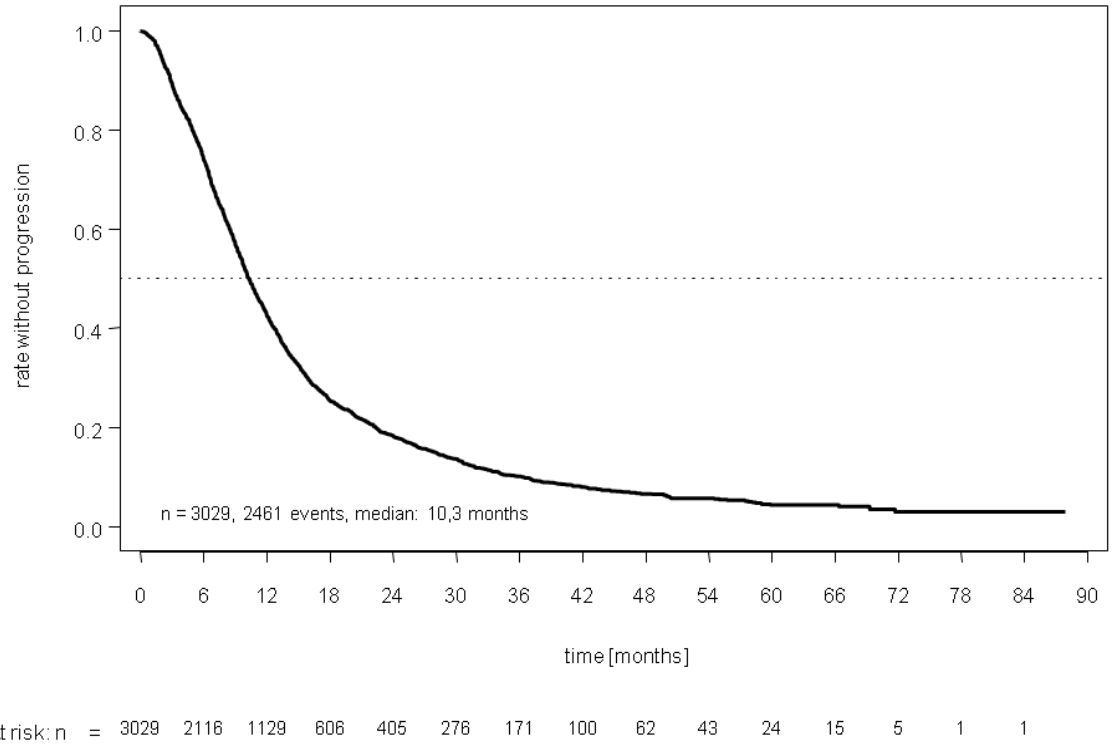
The findings for progression-free survival in this study are consistent with the results of the previous observational study of bevacizumab in advanced colorectal cancer (ML18664, median PFS 10.2 months).[19]

The comparison of progression-free survival between subgroups reveals that the longest median progression-free survival time of 11.3 months is observed for the patients treated with the combination FP/irinotecan/bevacizumab. The median PFS of patients treated with oxaliplatin instead of irinotecan is nearly two months less, i.e. 9.5 months (Table 61).

Table 61 Progression-free survival (PFS)

Parameter	without CT	FP with oxaliplatin	FP with irinotecan	only FP	other CT	total
n	29	1,042	1,479	424	55	3,029 (100%)
Number of events (%)	25 (86%)	843 (81%)	1,198 (81%)	350 (83%)	45 (82%)	2,461(81%)
Median progression-free survival time [months]	8.9	9.5	11.3	8.5	10.9	10.3
95% -confidence interval of PFS [months]	6.5 – 15.9	9.1 – 10.2	10.7 – 12.0	7.9 – 10.0	10.5 –13.0	9.6 – 10.7

Figure 3 Kaplan-Meier estimation of progression-free survival (PFS)



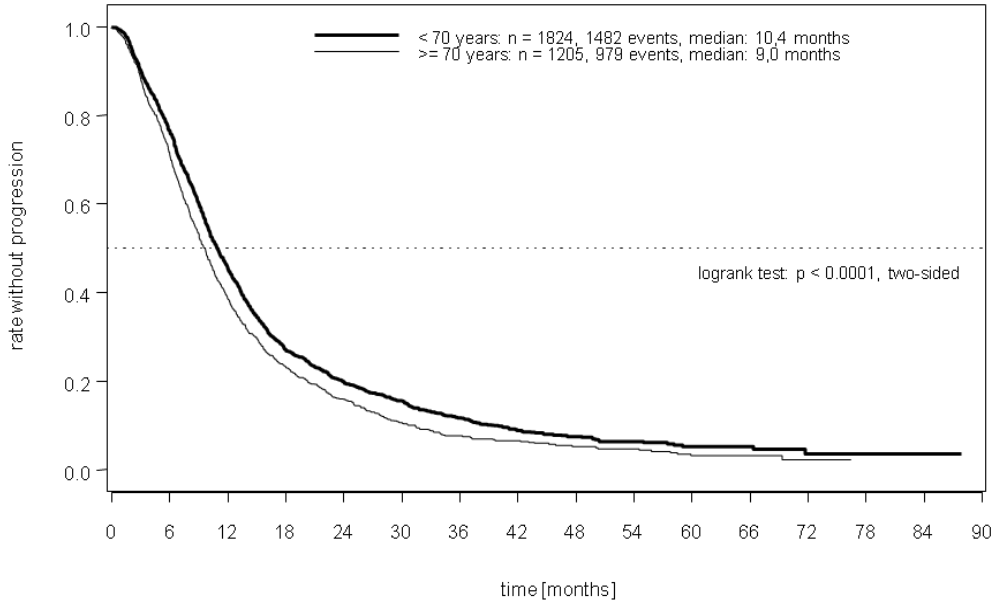
A univariate analysis regarding the potential influence of prognostic factors on progression-free survival was performed, using the same prognostic subgroups as for tumour response (see section 10.3.1, or section 3.2 of the SAP, respectively). The complete Kaplan-Meier plots for all prognostic subgroups are provided as Annex 1 No. 1 (Figure 12a to 12o).

Prognostic factors with a statistically highly significant influence on PFS were age (Figure 4; cut-off 75 years see Annex 1 No. 1, Figure 12b), ECOG performance status (Figure 12c), number of metastatic sites (Figure 12d), as well as the laboratory parameters WBC (Figure 12f), alkaline phosphatase (Figure 12g), and CEA values (Figure 12h), each evaluated at baseline. A trend towards somewhat shorter progression-free survival for patients with synchronous metastases was also observed, but not reaching the formal limit of statistical significance of $p = 0.05$ (Figure 12o). A summary of HR values, including their 95% confidence intervals, and p values for the univariate analyses of prognostic subgroups is provided in Table 63 in section 10.5.1. Also the application of the Köhne score on the population analysed in this trial allows a distinct discrimination of prognosis between the three risk groups (Figure 12j, $p < 0.0001$, logrank test for trend).

No influence on PFS was revealed for the parameters gender, adjuvant pre-treatment, location of metastatic site, and KRAS status. However, the interpretation of the PFS results with regard to KRAS status is limited due to the incomplete data situation (Figure 12e). Within the subgroup of patients with a secondary resection, there is a trend towards shorter median PFS for patients with

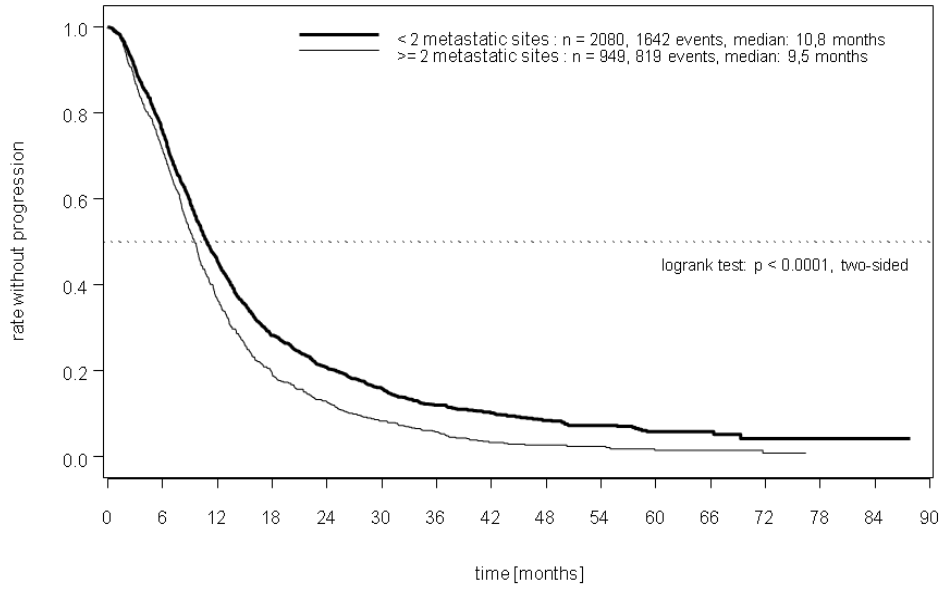
macroscopic residual tumour after surgery (R2), compared to those patients with pathologically complete resection (R0), or only microscopically positive resection margins (R1, Figure 12l), however this evidence is also limited by the small sample size.

Figure 4 Progression-free survival by age groups (cut-off 70 years)



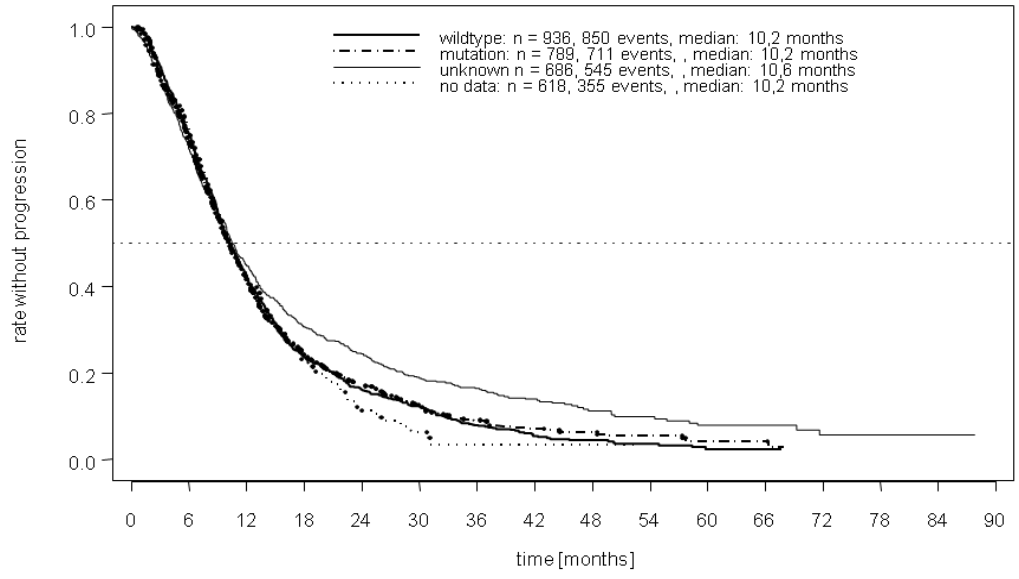
At risk: n =	1824	1320	734	396	272	198	126	66	42	27	13	8	3	1	1	(< 70 years)
n =	1205	796	395	210	133	78	45	34	20	16	11	7	2	0	0	(>= 70 years)

Figure 5 Progression-free survival by number of metastatic sites



At risk: n =	2080	1476	825	460	317	220	134	83	52	35	19	10	4	1	1	(< 2 metastatic sites)
n =	949	640	304	146	88	56	37	17	10	8	5	5	1	0	0	(>= 2 metastatic sites)

Figure 6 Progression-free survival by KRAS status



At risk: n =	936	695	383	208	134	94	50	23	16	11	4	1	0	0	0 (wildtype)
n =	789	575	324	179	124	83	48	26	18	11	5	4	0	0	0 (mutation)
n =	686	470	277	177	130	94	71	50	27	21	15	10	5	1	1 (unknown)
n =	618	376	145	42	17	5	2	1	1	0	0	0	0	0	0 (no data)

10.4.2 Overall survival (OS)

Also with regard to overall survival the current data situation is quite mature. To date, 1,822 death events were reported for the 3,029 evaluable patients, corresponding to 60% of the whole study population. The number of events and rates for each treatment subgroup are shown in Table 62. Patients without reported date of death at the time point of analysis were censored with the date of their last observation. The full results including all Kaplan-Meier plots are included as Annex 1 No. 1, Figures 13 and 13a to 13o.

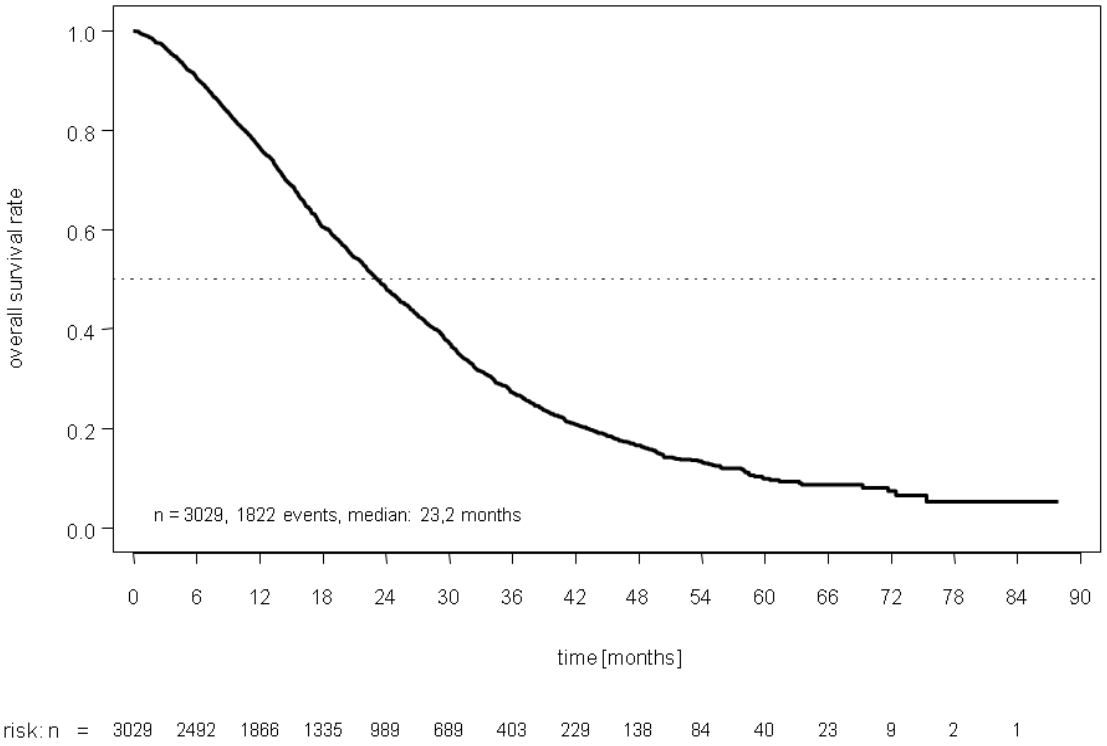
The Kaplan-Meier estimation for overall survival currently reveals a median overall survival time of almost two years (23.6 months) for the total population. The 95% confidence interval for median overall survival ranges from 22.2 to 24.1 months. Thus, the median overall survival in this study is slightly less compared to the previous non-interventional study ML18664 (median OS 24.8 months).[19]

Concerning the comparison of overall survival between subgroups, the observed trends are similar as for progression-free survival: the longest median overall survival time of 24.8 months is observed for the patients treated with the combination FP/irinotecan/bevacizumab. The median OS of patients treated with oxaliplatin instead of irinotecan is more than two months shorter, i.e. 22.2 months (Table 62 and Figure 7).

Table 62 Overall survival (OS)

Parameter	without CT	FP with oxaliplatin	FP with irinotecan	only FP	other CT	total
n	29	1,042	1,479	424	55	3,029 (100%)
Number of events (%)	18 (62%)	622 (60%)	896 (61%)	254 (60%)	32 (58%)	1,822 (60%)
Median overall survival time [months]	17.4	22.2	24.8	19.7	26.4	23.2
95% - confidence interval	15.8 – 28.2	20.7 – 24.0	23.5 – 26.3	17.6 – 22.7	20.4 – 40.8	22.2 – 24.1

Figure 7 Kaplan-Meier estimation of overall survival (OS)



Also with regard to overall survival, a univariate analysis in order to detect correlations to potential prognostic factors was performed. The complete prognostic analyses are shown in the Annex 1 No. 1, Figures 13 and 13a to 13o.

Prognostic factors with a statistically significant influence on overall survival were generally the same as described for progression-free survival. Again, the age of the patients had a highly significant influence: median OS for younger patients (< 70 years) amounts to 24.3 months, compared to a median OS of 21.6 months for patients of age 70 years and older (Figure 8). With an age cut-off of 75 years the median OS times are 23.9 months (< 75 years) vs 19.1 (≥ 75 years, Annex 1 No. 1, Figure 13b2). Further prognostic factors with a statistically highly significant influence on OS were ECOG performance status (Figure 13c), number of metastatic sites (Figure 13d), as well as the laboratory parameters WBC (Figure 13f), alkaline phosphatase (Figure 13g), and CEA values (Figure 13h), each evaluated at baseline. A summary of HR values, including their 95% confidence intervals, and p values for the univariate analyses of prognostic subgroups is provided in Table 65 in section 10.5.1. Again the Köhne score provides a highly significant discrimination of prognosis for overall survival between the three risk groups, which is even more clearly than for progression-free survival. The median OS times according to the risk groups are: 25.4 months (low risk), 22.1 months (intermediate risk), and 13.2 for the high-risk group (Figure 13j, $p < 0.0001$, logrank test for trend).

Again no significant influence on overall survival could be revealed for the factors gender (Annex 1 No. 1, Figure 13a), prior adjuvant chemotherapy (Figure 13i), result of secondary resection (Figures 13k and 13l), as well as for the KRAS status (Figure 13e).
Interestingly, the prognostic factors location of metastatic site, and time point of metastatic dissemination, which were not significant with regard to progression-free survival, become statistically significant for overall survival; median OS is 26.2 months for patients with liver metastases only, compared to median OS of 22.8 months for patients with other metastatic sites (p = 0.01, logrank test, two-sided; Figure 13m). Median OS for patients with metachronous metastases amounts to 20.3 months, compared to median OS of 18.3 months for patients with synchronous metastases (p = 0.017, logrank test, two-sided; Figure 13o). Even more important in the context of the second-line treatment, patients seem to benefit from the application of bevacizumab in second-line with regard to overall survival. The median OS time for patients with bevacizumab amounts to 29.9 months, compared to 23.0 months for patients with other agents or treatment combinations without bevacizumab. The comparison between both subgroups is highly significant (p < 0.0001, two-sided logrank test, Figure 13n).

Figure 8 Overall survival by age (cut-off 70 years)

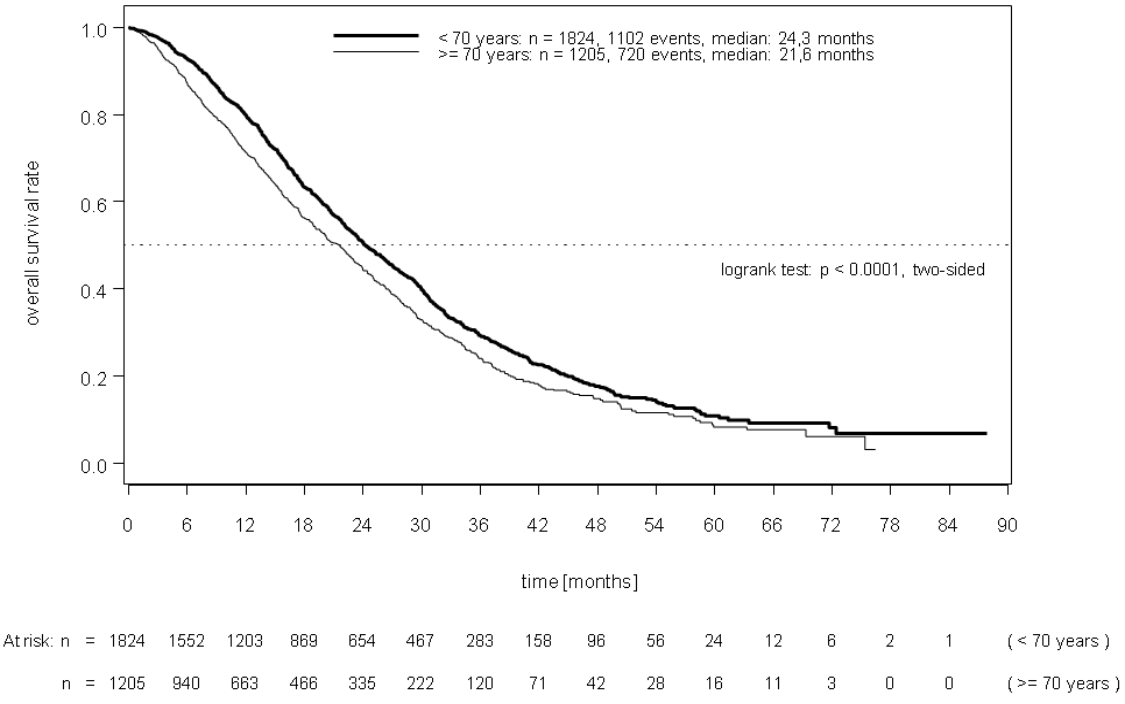
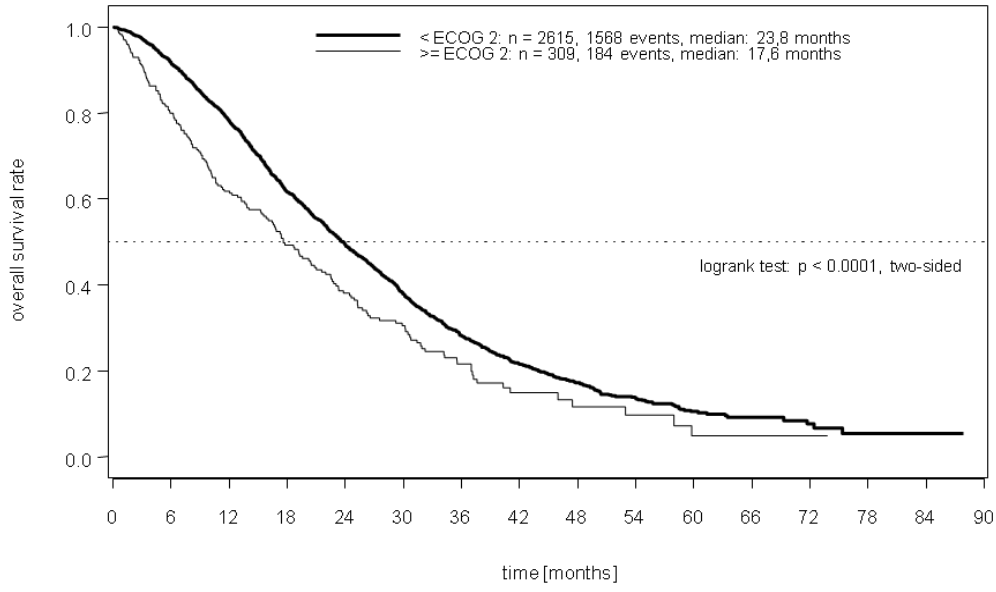


Figure 9 Overall survival by ECOG performance status at baseline



At risk: n =	2615	2192	1662	1186	882	612	359	207	124	75	37	21	8	2	1	(< ECOG 2)
n =	309	209	134	94	68	47	30	12	7	4	2	2	1	0	0	(>= ECOG 2)

10.5 OTHER ANALYSIS

10.5.1 Multivariate prognostic analysis of progression-free and overall survival

For the multivariate analysis the Cox proportional hazard model was utilized. All independent parameters from the univariate analyses regarding PFS (Table 63) and OS (Table 65) with a p-value below 0.1 were included in an initial ("full") model. Excluded from the multivariate analysis were age (<75 vs ≥ 75 years) because age is already present with another category (<70 vs ≥ 70 years); the Köhne score, because it is a combination of three independent variables which are all included in the analysis, and result of secondary resection, because it is not an independent variable, but highly correlated to a mix of parameters concerning patient health, treatment and response. Model reduction occurred by stepwise exclusion of the least significant parameter, until all remaining factors had p<0.1 (Table 64 for PFS and Table 66 for OS).

Table 63 Progression-free survival (univariate analyses)

Parameter*		n	HR*	95% confidence interval of the HR*		p-value (log rank, two-sided)
Age	< 70 years	1,824 (60%)	1.18*	1.09	1.28	< 0.0001
	≥ 70 years	1,205 (40%)				
ECOG baseline	< 2	2,615 (89%)	1.20*	1.05	1.37	0.0037
	≥ 2	309 (11%)				
Number of metastatic sites	< 2	2,080 (69%)	1.31*	1.2	1.42	< 0.0001
	≥ 2	949 (31%)				
Leucocytes	< 10 /NL	2,424 (83%)	1.28*	1.15	1.42	< 0.0001
	≥ 10 /NL	505 (17%)				
Alkaline phosphatase	< 300 U/l	2,227 (89%)	1.86*	1.63	2.12	< 0.0001
	≥ 300 U/l	275 (11%)				
CEA baseline	< 20 ng/ml	1,134 (48%)	1.46*	1.33	1.6	< 0.0001
	≥ 20 ng/ml	1,239 (52%)				
Metastases	synchronous	1,986 (66%)	0.93*	0.86	1.01	0.0885
	metachronous	1,043 (34%)				

* the group mentioned first is set as reference group, meaning that a HR > 1 relates to a higher risk in the second group and a HR <1 to a lower risk, respectively.

Table 64 Progression-free survival (multivariate analyses), complete model and final reduced model

Parameter	Comparison	Multivariate: complete model		Multivariate: final reduced model	
		n = 2,088		n = 2,102	
		p	HR	p	HR
Age	< 70 vs. ≥ years	< 0.1	1.13	< 0.1	1.13
ECOG baseline	< 2 vs. ≥ 2	< 0.1	1.19	< 0.1	1.18
Number of metastatic sites	< 2 vs. ≥ 2	< 0.0001	1.27	< 0.0001	1.27
Leucocytes	£ 10 / > 10 / nl	0.2	1.09	-	-
Alkaline phosphatase	£ 300 / > 300 U/l	< 0.0001	1.56	< 0.0001	1.58
CEA baseline	£ 20 / > 20 ng/ml	< 0.0001	1.35	< 0.0001	1.35
Metastases	synchronous / metachronous	0.38	1.05	-	-

* the group mentioned first is set as reference group, meaning that a HR > 1 relates to a higher risk in the second group and a HR <1 to a lower risk, respectively.

With regard to PFS, the parameters age, ECOG performance status at baseline, number of metastatic sites, alkaline phosphatase, as well as CEA levels at baseline appear to be the most independently predictive (Table 64).

For OS, the final reduced model reveals also the WBC at baseline as being an additional independently predictive parameter for this outcome variable (Table 66). According to the result of the multivariate analysis of prognostic factors for OS in this study, all independently predictive parameters are included in the Köhne score, except for age and CEA levels at baseline.

Table 65 Overall survival (univariate analyses)

Parameter*		n	HR	95% confidence interval of the HR*		p-value (log rank, two-sided)
Age	< 70 years	1,824	1.22	1.11	1.34	< 0.0001
	≥ 70 years	1,205				
ECOG baseline	< 2	2,615	1.42	1.22	1.66	< 0.0001
	≥ 2	309				
Number of metastatic sites	< 2	2,080	1.34	1.22	1.47	< 0.0001
	≥ 2	949				
Leucocytes	< 10 /NL	2,424	1.37	1.21	1.55	< 0.0001
	≥ 10 /NL	505				
Alkaline phosphatase	< 300 U/l	2,227	2.04	1.76	2.37	< 0.0001
	≥ 300 U/l	275				
CEA baseline	< 20 ng/ml	1,134	1.51	1.35	1.67	< 0.0001
	≥ 20 ng/ml	1,239				
Metastases	synchronous	1,986	0.86	0.78	0.95	0.0028
	metachronous	1,043				

* the group mentioned first is set as reference group, meaning that a HR > 1 relates to a higher risk in the second group and a HR <1 to a lower risk, respectively.

Table 66 Overall survival (multivariate analyses) , complete model and final reduced model

Parameter	Comparison	Multivariate: complete model		Multivariate: final reduced model	
		n = 2,088		n = 2,088	
		p	HR	p	HR
Age	< 70 vs ≥ 70 years	< 0.1	1.16	< 0.1	1.16
ECOG baseline	< 2 vs. ≥ 2	< 0.01	1.35	< 0.01	1.35
Number of metastatic sites	< 2 vs. ≥ 2	< 0.0001	1.33	< 0.0001	1.33
Leucocytes	£ 10 / > 10 / nl	< 0.1	1.15	< 0.1	1.15
Alkaline phosphatase	£ 300 / > 300 U/l	< 0.0001	1.62	< 0.0001	1.62
CEA baseline	£ 20 / > 20 ng/ml	< 0.0001	1.37	< 0.0001	1.37
Metastases	synchronous / metachronous	1.0	1.00	-	-

* the group mentioned first is set as reference group, meaning that a HR > 1 relates to a higher risk in the second group and a HR <1 to a lower risk, respectively.

10.6 ADVERSE EVENTS AND ADVERSE REACTIONS

10.6.1 Treatment toxicity (NCI)

As described in section 9.3, all patients who received at least one application of bevacizumab – regardless of the applied dosage – were included in the safety analysis set.
Several adverse events/adverse reactions to be expected under treatment within the therapeutic setting of the trial were pre-defined in the forms of the CRF and were to be answered with their grade of occurrence for each treatment cycle. If the respective adverse reaction was not present, investigators had to put in “no reaction” as their answer. With regard to MedDRA SOC terminology, these pre-defined toxicities comprised the SOCs “Blood and lymphatic system disorders”, “Gastrointestinal disorders”, and other toxicities concerning several SOCs.

10.6.1.1 SOC Blood and lymphatic system disorders / haematologic toxicity

The highest NCI grade toxicity by patient recorded during the entire observation period is shown in Table 67 for the whole study population. More than half of the patients (54%) were anaemic, with a severe anaemia (grade 3-4 NCI CTC) occurring in 2%. Leukopenia was present in about one third (34%), neutropenia in 21% of the patients. However, these reactions were not often of severe grade (leukopenia grade 3-4: 3%, neutropenia grade 3-4: 4%). Thrombopenia of any grade occurred in 20% of all patients, and was severe in 1% of all cases. A severe haemorrhaging or bleeding reaction was generally a rare event in this NIS.

Table 67 Haematological toxicity (highest NCI CTC grade per patient), total group

Toxicity	**n (%) / NCI CTC grade**					
NCI grade	n	No reaction	1	2	3	4
Anaemia	3,029	1,400 (46%)	1167 (39%)	396 (13%)	54 (2%)	12 (<1%)
Leukopenia	3,029	1,984 (66%)	597 (20%)	342 (11%)	93 (3%)	13 (<1%)
Neutropenia	3,029	2,378 (79%)	345 (11%)	176 (6%)	101 (3%)	29 (1%)
Thrombopenia	3,029	2,413 (80%)	509 (17%)	80 (3%)	19 (1%)	8 (<1%)
Haemorrhaging / bleeding	3,029	2,726 (90%)	269 (9%)	29 (1%)	4 (<1%)	1 (<1%)

Table 68 presents an overview of the observed haematological toxicities for all treatment subgroups summarized for grade 3-4 events. The detailed tables showing explicitly all toxicity grades and percentages are provided in Annex 1 No. 2, Tab. 96 to Tab. 101.
In the main treatment subgroups (i.e. the triple combination treatments with oxaliplatin or irinotecan), the rate of grade 3-4 leukopenia and /or neutropenia are slightly higher compared to the total group.

Table 68 Haematological toxicity (highest NCI CTC grade per patient), by treatment subgroups

Category		Number (%)
Without CT (n = 29)		
Anaemia	all grades grade 3-4	12 (41%) 1 (3%)
Leukopenia	all grades grade 3-4	11 (38%) 1 (3%)
Neutropenia	all grades grade 3-4	4 (17%) 2 (7%)
Thrombopenia	all grades grade 3-4	5 (17%) -
Haemorrhaging / bleeding	all grades grade 3-4	4 (14%) -
FP with oxaliplatin (n = 1,042)		
Anaemia	all grades grade 3-4	579 (56%) 25 (2%)
Leukopenia	all grades grade 3-4	404 (39%) 47 (4%)
Neutropenia	all grades grade 3-4	265 (17%) 58 (7%)
Thrombopenia	all grades grade 3-4	339 (17%) 15 (1%)
Haemorrhaging / bleeding	all grades grade 3-4	109 (14%) 2 (<1%)

Table 68 Haematological toxicity (highest NCI CTC grade per patient), by treatment subgroups, ctd.

Category		Number (%)
FP with irinotecan (n = 1,479)		
Anaemia	all grades grade 3-4	808 (55%) 31 (2%)
Leukopenia	all grades grade 3-4	538 (36%) 57 (4%)
Neutropenia	all grades grade 3-4	340 (23%) 67 (5%)
Thrombopenia	all grades grade 3-4	198 (13%) 11 (1%)
Haemorrhaging / bleeding	all grades grade 3-4	152 (10%) 2 (<1%)
FP only (n = 424)		
Anaemia	all grades grade 3-4	204 (48%) 8 (2%)
Leukopenia	all grades grade 3-4	68 (16%) -
Neutropenia	all grades grade 3-4	28 (7%) 1 (<1%)
Thrombopenia	all grades grade 3-4	60 (14%) 1 (<1%)
Haemorrhaging / bleeding	all grades grade 3-4	33 (8%) 1 (<1%)
Other CT (n = 55)		
Anaemia	all grades grade 3-4	26 (47%) 1 (2%)
Leukopenia	all grades grade 3-4	24 (44%) 1 (2%)
Neutropenia	all grades grade 3-4	13 (24%) 2 (4%)
Thrombopenia	all grades grade 3-4	14 (25%) -
Haemorrhaging / bleeding	all grades grade 3-4	5 (9%) -

10.6.1.2 SOC Gastrointestinal disorders

With regard to this SOC the toxicities diarrhoea, nausea, and vomiting were pre-defined in the CRF forms. The frequency of occurrence of these reactions is presented in Table 69 for the whole study population, and summarized in Table 70 for each treatment subgroup.

The predominant gastrointestinal toxicity is diarrhoea, which occurred with any grade in 40% of all patients, and in 6% of all patients with severe grade 3-4. Severe nausea or vomiting was observed less frequently (2-3%). However, 44% of all patients were suffering from nausea.

Table 69 Gastrointestinal toxicities (highest NCI CTC grade per patient), total group

Toxicity	**n (%) / NCI CTC grade**					
NCI-Grade	n	no reaction	1	2	3	4
Diarrhoea	3,029	1,811 (60%)	633 (21%)	402 (13%)	146 (5%)	37 (1%)
Nausea	3,029	1,683 (56%)	799 (26%)	441 (15%)	105 (3%)	1 (<1%)
Vomiting	3,029	2,401 (79%)	333 (11%)	238 (8%)	49 (2%)	8 (<1%)

The analysis of gastrointestinal toxicities by subgroups reveals that patients who developed diarrhoea of grade 3-4 were mostly seen in the FP/irinotecan/bevacizumab triple combination subgroup (Table 70).

Table 70 Gastrointestinal toxicities (highest NCI CTC grade per patient), by subgroups

	n (%) / NCI CTC grade					
Toxicity	n	no reaction	1	2	3	4
Without CT						
Diarrhoea	29	20 (69%)	4 (14%)	4 (14%)	-	1 (3%)
Nausea	29	20 (69%)	6 (21%)	1 (3%)	2 (7%)	-
Vomiting	29	26 (90%)	2 (7%)	1 (3%)	-	-
FP with oxaliplatin						
Diarrhoea	1,042	681 (65%)	190 (18%)	120 (12%)	40 (4%)	11 (1%)
Nausea	1,042	562 (54%)	304 (29%)	142 (14%)	34 (3%)	-
Vomiting	1,042	845 (81%)	119 (11%)	67 (6%)	10 (1%)	1 (<1%)

Table 70 Gastrointestinal toxicities (highest NCI CTC grade per patient), by subgroups, ctd.

	n (%) / NCI CTC grade					
Toxicity	n	no reaction	1	2	3	4
FP with irinotecan						
Diarrhoea	1,479	786 (53%)	355 (24%)	221 (15%)	97 (7%)	20 (1%)
Nausea	1,479	772 (52%)	400 (27%)	250 (17%)	57 (4%)	-
Vomiting	1,479	1,125 (76%)	179 (12%)	138 (9%)	31 (2%)	6 (<1%)
Only FP						
Diarrhoea	424	293 (69%)	69 (16%)	51 (12%)	8 (2%)	3 (1%)
Nausea	424	301 (71%)	76 (18%)	36 (8%)	10 (2%)	1 (<1%)
Vomiting	424	365 (86%)	27 (6%)	23 (5%)	8 (2%)	1 (<1%)
Other CT						
Diarrhoea	55	31 (56%)	15 (27%)	6 (11%)	1 (2%)	2 (4%)
Nausea	55	28 (51%)	13 (24%)	12 (22%)	2 (4%)	-
Vomiting	55	40 (73%)	6 (11%)	9 (16%)	-	-

10.6.1.3 Other toxicities

Other pre-defined toxicities cover several MedDRA SOC categories as shown in the following table (Table 71). With an incidence rate of 33% for any NCI CTC grade, pain is the most frequently reported symptom. In general, the severity of most events was light to moderate. Severe cases of pain are reported with a rate of 4%, and it must be taken into account that this general disorder might also been caused by the underlying disease instead of the applied treatment.

Severe cases of cardiac function disorders and proteinuria were rarely reported (<1%). The frequency of sensory disorder and hand-foot-syndrome of any CTC grade were around 20%; severe cases of both toxicities occurred in 1% of all patients.

In order to summarize the data for other toxicities with regard to the treatment subgroups, it is noteworthy that no grade 3-4 toxicity at all was reported for the patients receiving no cytotoxic co-medication in addition to bevacizumab. Severe pain (grade 3-4) was reported for all treatment subgroups receiving FP or FP as triple combination together with oxaliplatin or irinotecan (pain grade 3-4: 4% [FP/oxaliplatin/bev]; 4% [FP/irinotecan/bev]; 4% [FP/bev]). A hypertension of higher grade was more frequently reported for the FP/oxaliplatin/bev and FP/bev cohort (4%),

compared to the FP/irinotecan/bev group (1%). The detailed data is provided in Annex 1 No. 2, Tab. 108 to 113.

Table 71 Other toxicities (highest NCI CTC grade per patient), total group

SOC / toxicity	n (%) / NCI CTC grade					
NCI-Grade	n	no reaction	1	2	3	4
Nervous system disorders						
Neuropathy, sensory	3,029	2,456 (81%)	336 (11%)	197 (7%)	40 (1%)	-
Cardiac disorders						
Cardiac function	3,029	2,997 (99%)	17 (1%)	8 (<1%)	6 (<1%)	1 (<1%)
Hypertension	3,029	2,536 (84%)	276 (9%)	146 (5%)	65 (2%)	6 (<1%)
Skin and subcutaneous tissue disorders						
Hand-foot-syndrome	3,029	2,351 (78%)	484 (16%)	169 (6%)	25 (1%)	-
Renal and urinary disorders						
Proteinuria	3,029	2,712 (90%)	264 (9%)	42 (1%)	9 (<1%)	2 (<1%)
General disorders and administration site conditions						
Fever	3,029	2,769 (91%)	126 (4%)	124 (4%)	1 (<1%)	-
Pain	3,029	2,020 (67%)	415 (14%)	456 (15%)	131 (4%)	7 (<1%)

Other toxicities which were not pre-specified in the CRF form, were to be entered as free-text entries by the investigators. These toxicities were coded by the project manager according to NCI CTCAE terms.

In total, 1,668 other toxicities were documented, 189 of these (11%) with unknown severity grade. A tabulation of the 12 most frequently reported other toxicities, including incidence rate and severity grade, is given in Table 72**.** The order of presentation follows the MedDRA terminology SOC list in internationally agreed order. The complete table with all 1,668 other toxicities is provided in Annex 1 No. 2, Tab. 114.

Table 72 Description of other toxicities (free text), coded according to NCI CTC categories (maximum grade by patient)

SOC / toxicity n / NCI CTC grade	n (%) Total	1	2	3	4	unknown
n	1,668 (100%)	818	490	156	15	189
Infections and infestations						
Infection	153 (9%)	58 (7%)	50 (10%)	23 (15%)	1 (7%)	21 (11%)
Nervous system disorders						
Neurology, other	82 (5%)	43 (5%)	29 (6%)	5 (3%)	1 (7%)	4 (2%)
Vertigo	56 (3%)	40 (5%)	10 (2%)	1 (1%)	-	5 (3%)
Vascular disordes						
Phlebitis/ thrombosis/ embolism	51 (3%)	3 (<1%)	18 (4%)	14 (9%)	2 (13%)	14 (7%)
Respiratory, thoracic and mediastinal disorders						
Dyspnea	69 (4%)	28 (3%)	32 (7%)	2 (1%)	-	7 (4%)
Gastrointestinal disorders						
Gastrointestinal, other	157 (9%)	73 (9%)	45 (9%)	18 (12%)	2 (13%)	19 (10%)
Mucositis	127 (8%)	65 (8%)	38 (8%)	12 (8%)	-	12 (6%)
Salivary gland changes	43 (3%)	26 (3%)	10 (2%)	-	-	7 (4%)
Stomatitis	56 (3%)	32 (4%)	14 (3%)	2 (1%)	2 (13%)	6 (3%)
Skin and subcutaneous tissue disorders						
Alopecia	82 (5%)	38 (5%)	28 (6%)	8 (5%)	-	8 (4%)
Skin, local	71 (4%)	37 (5%)	18 (4%)	2 (1%)	-	14 (7%)
General disorders and administration site conditions						
Fatigue	239 (14%)	127 (16%)	76 (16%)	16 (10%)	-	20 (11%)

10.6.1.4 Specifically assessed toxicities

Due to the results of the registration trial for bevacizumab, several toxicities were specifically assessed by the documentation of this observational study. These toxicities were gastrointestinal perforation, an arterial thrombotic event, and reversible posterior leukoencephalopathy. These specific events were surveyed using the toxicity form included in the CRF, and the obtained data was analysed independently from possibly related SAE events (Table 73). A gastrointestinal perforation was reported in a total of 21 patients (0.7%). For two patients this event occurred more than once during the observation period. At least one arterial thrombotic event was reported for 91 patients (3%); again, in four patients this type of event occurred two to three times. Only

one patient of the total population exhibited a reversible posterior leukoencephalopathy, but also with multiple episodes of this toxicity.

Table 73 Specifically assessed toxicities

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,042	1,479	424	55	3,029
Gastrointestinal perforation						
1 occurrence	-	5 (<1%)	12 (1%)	1 (<1%)	1 (2%)	19 (1%)
2 occurrences	-	-	1 (<1%)	-	-	1 (<1%)
4 occurrences	-	1 (<1%)	-	-	-	1 (<1%)
Arterial thrombotic event						
1 occurrence	-	35 (3%)	46 (3%)	6 (1%)	-	87 (3%)
2 occurrences	-	-	2 (<1%)	1 (<1%)	-	3 (<1%)
3 occurrences	-	1 (<1%)	-	-	-	1 (<1%)
Reversible posterior leukoencephalopathy						
3 occurrences	-	-	1 (<1%)	-	-	1 (<1%)

10.6.2 (Serious) adverse drug reactions (associated with study treatment)

Adverse drug reactions (serious and non-serious) of CTC grade 2 or higher were to be recorded during the observation period of the study. Adverse reactions which occurred several times (i.e. the duration of the reaction extended over several 4-week time periods), were to be recorded by the investigators only once with the highest toxicity grade of occurrence, according to NCI CTCAE criteria.

A total of 1,473 adverse drug reactions (ADR) of grade two or higher with causal relationship to at least one agent applied during the therapy were reported for the safety population of this trial. Thereof, 1,032 drug reactions were serious (70%), and 441 reactions have been reported as being non-serious.

Out of the in total 1,473 ADRs, 690 ADRs were reported with a positive causality assessment in relation to bevacizumab, i.e. the causality was documented as being “certain”, “probable”, or at least “possible”. Of these, 361 reactions were reported as serious (52%), and 329 as being non-serious.

The 690 reported ADRs with causal relationship to bevacizumab occurred in 586 patients, i.e. 19% of the whole population of the trial. The number of reactions per patient ranged from one to 17 ADRs. The 361 SADRs with positive causality to bevacizumab occurred in 181 patients, corresponding to 6% of all patients. The range of SADRs per patient was one to seven events.

The information in this paragraph is also summarized in the flow chart Figure 10 and in Table 74.

Figure 10 Overview about reported (S)ADRs and correlation with patient numbers

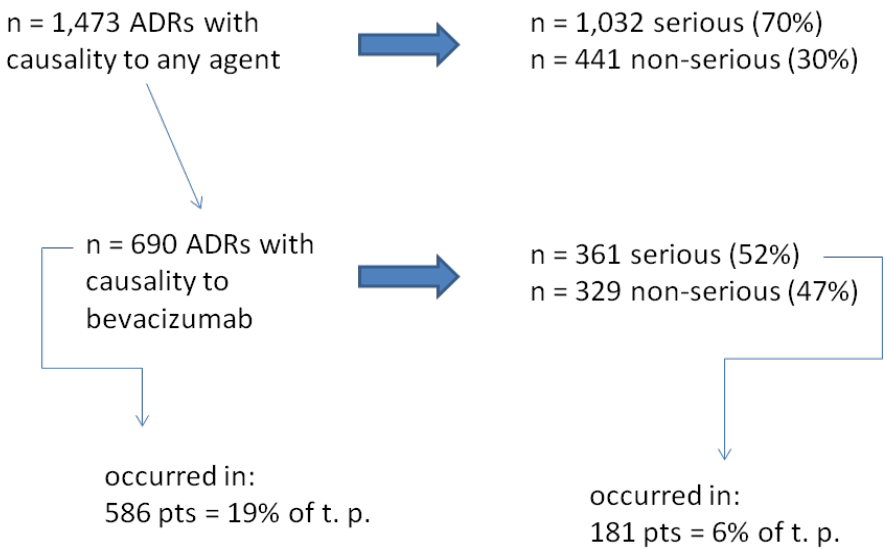


Table 74 Number of reported (serious) adverse drug reactions per patient with causal relationship to bevacizumab

Category	Without CT	FP with oxaliplatin	FP with irinotecan	Only FP	Other CT	Total
n	29	1,042	1,479	424	55	3,029 (100%)
Patients with ≥ 1 ADR	4 (14%)	198 (19%)	285 (19%)	91 (21%)	8 (15%)	586 (19%)
Patients with ≥ 1 SADR	2 (7%)	52 (5%)	102 (7%)	24 (6%)	1 (2%)	181 (6%)

All 690 ADRs of grade two or higher and possible association with the application of bevacizumab were coded according to NCI common toxicity criteria. The maximum NCI severity grade observed by category and patient was analysed. However, in 97 cases information about the severity grade is unknown. The most common ADRs with an incidence rate of at least 3% of all reported ADRs with association to bevacizumab are presented in Table 75, full results of the analysis are included in Annex 1 No. 2, Tab. 121. The ADRs mostly reported include hypertension, followed by thromboembolic events.

Table 75 Bevacizumab associated ADRs of grade 2-5 (max. grade by NCI CTC category and patient)

SOC / toxicity	n (%)					
n / NCI CTC grade	2	3	4	5	Unknown	Total
n	298	220	71	4	97	690 (100%)
Infections and infestations						
Infection	13 (4%)	14 (6%)	5 (7%)	-	4 (4%)	42 (6%)
Blood and lymphatic system disorders						
Haemoglobin	14 (5%)	4 (2%)	1 (1%)	-	-	19 (3%)
Haemorrhage (clinical)	11 (4%)	5 (2%)	4 (6%)	1 (25%)	1 (1%)	24 (3%)
Leucocytes	17 (6%)	11 (5%)	2 (3%)	-	-	30 (4%)
Cardiac disorders						
Hypertension	62 (21%)	37 (17%)	4 (6%)	-		
Vascular disorders						
Phlebitis/ thrombosis/ embolism	25 (8%)	37 (17%)	15 (21%)	1 (25%)		
Gastrointestinal disorders						
Diarrhoea	18 (6%)	18 (8%)	2 (3%)	-	11 (11%)	89 (13%)
Gastrointestinal, other	10 (3%)	10 (5%)	10 (14%)	1 (25%)		
Nausea	17 (6%)	8 (4%)	-	-	15 (15%)	46 (7%)
Vomiting	12 (4%)	10 (5%)	1 (1%)	-	6 (6%)	109 (16%)
General disorders and administration site conditions						
Pain	15 (5%)	9 (4%)	-	-		

In order to assess whether any ADR occurred during the course of the present NIS that is not yet represented in the published safety data for bevacizumab treatment, the documented ADRs reported for this trial were compared to the most common ADRs according to Tab. 1 and Tab. 2 of the investigators brochure dated December 19th 2012 (German version). The result of this comparison is presented in Table 76. Adverse drug reactions that were reported in the present trial and not yet included in the safety data profile of bevacizumab according to the IB, are highlighted in bold typography.

Table 76 Bevacizumab associated ADR (in comparison to IB, differences highlighted in bold)

ADR	n (%)	IB Table 1	IB Table 2
Haemoglobin	19 (3%)	Anaemia	
Leucocytes	30 (4%)	Leukopenia	
Granulocytes	11 (2%)	(febrile) Neutropenia	
Thrombocytes	8 (1%)	Thrombocytopenia	
Blood/bone marrow other	1 (<1%)		
Haemorrhage (clincal)	24 (3%)	Epistaxis, GI hemorrhage, hemorrhage,	
Infection	41 (6%)	Sepsis, abscess, infection	
Nausea	27 (4%)	Nausea	Nausea
Vomiting	24 (3%)	Vomiting	Vomiting
Diarrhoea	42 (6%)	Diarrhea	
Stomatitis	4 (1%)	Stomatitis	
Dysphagia, oesophagitis	1 (<1%)	Gastrointestinal perforation, ileus, intestinal obstruction, abdominal pain, colitis, constipation, fistula	
Gastritis/ulcer	5 (1%)		
Colitis	2 (<1%)		
Fistula-intestinal	2 (<1%)		
Gastrointestinal, other	46 (7%)		Anastomotic ulceration
Mucositis	5 (1%)	Mucositis	
Transaminases (SGOT/SGPT)	3 (<1%)		
Hepatic, other	3 (<1%)		
Creatinine (Serum)	1 (<1%)		
Proteinuria	9 (1%)	Proteinuria	Proteinuria
Haematuria	1 (<1%)		

Table 76 Bevacizumab associated ADRs (in comparison to IB, differences highlighted in bold), ctd.

ADR	n (%)	IB Table 1	IB Table 2
Renal failure	3 (<1%)		Renal thrombotic microangiopathy
Dysurea	1 (<1%)		
Urinary retention	1 (<1%)		
Renal/genitourinary – other	7 (1%)	Urinary tract infection	
Dyspnoea	8 (1%)	Dyspnoea	Dyspnoea
Pulmonary, other	3 (<1%)	Hypoxia	Hypoxia
Pneumonitis/pulmo-nary infiltrates	5 (1%)		
Arrhythmia	2 (<1%)	Congestive heart failure, supraventricular tachycardia, syncopy	
Aardiac function	3 (<1%)		
Ischemia	3 (<1%)		
Cardiovascular, other	12 (2%)		
Hypertension	109 (16%)	Hypertension	Hypertension
Hypotension	4 (1%)		Hypotension
Phlebitis/ thrombosis/ embolism	89 (13%)	Pulmonary embolism, deep vein thrombosis, cerebrovascular accident	
Neuropathy, sensory	8 (1%)	Sensory neuropathy	
Neuropathy, motor	5 (1%)	Weakness	
Cognitive disturbance	1 (<1%)	Confusion	
Mood alteration	1 (<1%)	Lethargy	
Headache	1 (<1%)	Headache	
Pain	29 (4%)	Myalgia, arthralgia, pain	
Vertigo	2 (<1%)		
Salivary gland changes	1 (<1%)	Dysgeusia	
Neurology, other	7 (1%)	Dysarthria	Hypertensive encephalopathy
Skin	2 (<1%)	Exfoliative dermatitis, dry skin, skin discolouration	Flush, rash/desquamation
Skin, local	4 (1%)		
Hand-foot-syndrome	5 (1%)	Hand-foot-syndrome	
Allergic reaction	3 (<1%)		

10.6.3 Non-serious adverse drug reactions

As described in section 10.6.2 30% of the reported ADRs with causal relation to any of the applied therapeutic substances were documented as being non-serious (441 of 1,473 ADR events).

The top ten of the reported non-serious ADR categories with the highest frequency of occurrence were: hypertension (24%), thromboembolic event (7%), leukopenia (7%), diarrhoea (6%), nausea (6%), anaemia (5%), clinical haemorrhage (4%), infection (4%), pain (4%), and vomiting (4%). The percentages given in parenthesis refer to the total number of non-serious adverse drug reactions (n = 441).

11. DISCUSSION

In this non-interventional observational study, the disease course and treatment with bevacizumab in a total of 3,029 metastatic colorectal cancer patients without cytotoxic pre-treatment in the palliative setting were reported. Overall, 438 physicians/centres across Germany participated in the project, registering patients mainly between 2008 and 2012.

According to the structure of the case report form, the bevacizumab treatment was routinely recorded for one year (for longer periods, according to an observation plan amendment, in a limited number of the patients). The treatment could be administered beyond that limit in case of continued response of the disease, or decision for bevacizumab treatment in multiple lines. The long-term survival was recorded by several follow-up assessments of the patients' status, after completion of the documentation forms covering the first year of treatment.

11.1 KEY RESULTS

The effectiveness criteria were tumour response, progression-free survival, and overall survival. The toxicity of the treatment regimen was assessed according to NCI CTC categories and severity grades, with a special focus on major adverse reactions particularly associated with bevacizumab treatment (gastrointestinal perforation, arterial thrombotic event, reversible posterior leukoencephalopathy). In addition, detailed data were collected on adverse reactions with pre-sumed causal relationship with the antibody.

Due to the observational character of this study, descriptive and explorative statistical methods were predominantly used, providing means, standard deviations, medians, quartiles, ranges, rates, and confidence intervals. Prognostic factors for long-term endpoints were assessed with Kaplan-Meier estimations using the log rank test, and the multivariate Cox proportional hazard model.

The majority of patients received treatment with bevacizumab in combination with other cytotoxic agents. The largest subgroups were treated using triple combinations consisting of bevacizumab combined with either fluoropyrimidine/oxaliplatin, or fluoropyrimidine/irinotecan. Based on the results of 3,029 evaluable patients, the overall response rate in this trial was 52% (exact 95% confidence interval: 50-54%). As may be expected, the ORR was higher in patients receiving bevacizumab plus either oxaliplatin- based or irinotecan-based doublet chemotherapy, compared with bevacizumab and a fluoropyrimidine alone. The median PFS for the whole study population amounted to 10.3 months (95% CI: 9.6 – 10.7 months). The Kaplan-Meier estimation for overall survival resulted in a median OS of 23.2 months, with a 95% CI from 22.2 to 24.1 months. With regard to treatment subgroups, patients receiving treatment in combination with irinotecan had a 2.6 months longer median overall survival compared to the subgroup treated in combination with oxaliplatin. The multivariate Cox proportional hazard model revealed that age, ECOG status, number of metastatic sites, alkaline phosphatase, and CEA level at baseline were relevant and independent prognostic factors for prognosis of progression-free survival. With regard to

prognosis of overall survival, additionally WBC at baseline was an independent prognostic parameter.

11.2 LIMITATIONS

Several limitations of this form of observational study should be taken into account when comparing our findings with those from randomised clinical trials. Although the documented data were subject to clinical review and inconsistency resolution by site queries was performed, no on-site verification of investigator-reported data against medical records took place. The investigators could choose their preferred chemotherapy combination partner (with different profile of potential side effects) and use individual methods and schedule of evaluating the outcome. We designed the study with minimal patient selection criteria in order to increase the likelihood that our population would be representative of the clinical practice setting in Germany. The analyses of demographic as well as anamnestic baseline data of the population in this trial were in concordance with available epidemiologic data for patients with colorectal cancer.[21] We therefore believe that this observational study provides valuable information regarding the use of bevacizumab under the conditions and specifications of the German healthcare system.

11.3 INTERPRETATION

In general, the efficacy end point data, as reported from several large pivotal studies on bevacizumab added to first-line chemotherapy in advanced colorectal cancer, were confirmed by the results from this observational study. The most reliable and mature parameter is progression-free survival, based on observed events in 2,461/3,029 patients (81%). Table 77 and Table 78 show the efficacy end point data of this trial in comparison to published results of phase III trials and other observational studies or registries with bevacizumab in patients with colorectal cancer.

Table 77 Major effectiveness endpoints in bevacizumab phase III trials in colorectal cancer and in this study

	AVF2107g	NO16966	E3200	this study
n (with bevacizumab)	n = 402	n = 699	n = 286*	n = 3,029
Response rate [%]	44.8%	46.5%	24.4%	52%
PFS, median [months]	10.6	9.4	7.3	10.3
OS, median [months]	20.3	21.2	12.9	23.2

* Treatment arm with FOLFOX4 + bevacizumab

Table 78 Major effectiveness endpoints in the bevacizumab observational studies and registries in colorectal cancer and in this study

	BRiTE	ARIES	ML18664	this study
n (with bevacizumab)	n = 1,953	n = 1,550	n = 1,777	n = 3,029
Response rate [%]	not available	53.4%	60%	52%
PFS, median [months]	10.0	10.2	10.2	10.3
OS, median [months]	25.1	23.3	24.8	23.2

Based on the 3,029 assessable patients in this observational study, the reported ORR was 52%, which is higher than previously reported in randomised trials [Hurwitz et al. 20041; Saltz et al. 20083]. The trial E3200 is not fully comparable to the study presented here, because the E3200 protocol was designed for patients receiving bevacizumab in second-line after pretreatment with irinotecan. One possible explanation for the higher response observed in the present study in comparison to the studies AVF2107g and NO16966 could be that the investigator-reported response assessments were not independently reviewed and confirmed (e.g. according to RECIST guidelines). Moreover, “best response” according to the definition of this study did not require verification at a second, subsequent examination. However, the overall response rate of 52% is in concordance with response rates of other published observational studies [Kozloff et al. 2009[22]; Hofheinz et al. 2014[19]].

The median PFS of 10.3 months is consistent with that reported in previous randomised clinical trials (range of 7.3–10.6 months [Hurwitz et al. 20041; Saltz et al. 20083; Giantonio et al. 20077; Schmoll et al. 2012[23]; Hecht et al. 2009[24]]) and observational cohorts (range of 9.5–11 months [Kubala et al. 2010;[25] Van Cutsem et al. 2009;[26] Kozloff et al. 2009[22]; Bendell et al. 2012[27]]). PFS by chemotherapy regimen appeared to be higher with irinotecan-based treatment regimens compared to oxaliplatin-based regimens, a similar trend was also observed for the population of the BRiTE observational study.[22] PFS findings in other subgroups were in line with expectations and comparable to previous randomised trials [Tebutt et al. 2010].[28]

The median OS of 23.2 months confirms the results of the observational studies (Table 78), and is slightly higher compared to the results of the phase III trials in first-line treatment [Hurwitz et al. 20041; Saltz et al. 20083]. This observation is probably due to the broader access to highly active new agents used in the second-line and further-line treatments for colorectal cancer since the time period of the earlier trials. As for PFS, the evaluation of OS by chemotherapy regimen showed that the median OS in patients receiving irinotecan-based chemotherapy regimen (24.8 months) was longer compared to patients receiving oxaliplatin-based regimens (22.2 months). Similarly, slight numerical although not clinically relevant differences were noted in the ARIES study, between FOLFOX plus bevacizumab (23.7 months) and FOLFIRI plus bevacizumab (25.5 months) and in the randomised phase II AIO 0604 study between oxaliplatin-based (24.4

months) and irinotecan-based (25.5 months) treatment both combined with capecitabine and bevacizumab [Bendell et al. 2012[27]; Schmiegel et al. 20139]. Interestingly, the effectiveness results in this study were comparable to the ARIES observational study, although the population in this study was in median older (median age 67 vs 62 years, 19% ≥ 75 years vs 15%), and slightly more often of poorer general condition at baseline (ECOG ≥ 2: 11% vs 7%).

The previously published AVEX trial in patients ≥70 years of age and not suitable for treatment with chemotherapy doublets (n = 280) reported a clinically significant benefit in terms of PFS and OS by adding bevacizumab to low doses of capecitabine (1,000 mg/m² twice daily) [Cunningham et al. 2013[29]]. Within the larger sample size of this study, we were also able to demonstrate that bevacizumab is effective as routine therapy in a large cohort of elderly patients. As would be expected, younger patients tend to have a higher response and disease control rate (<70 years: ORR 54%, median PFS 10.4 months, median OS 24.3 months) than older patients (≥70 years: ORR 48%, median PFS 9.0 months, median OS 21.6 months). The results observed in this study for the subgroup of patients ≥ 70 years are well aligned with those of the AVEX trial in terms of PFS and OS (bevacizumab plus capecitabine: PFS 9.1 months, OS 20.7 months). This reinforces the need to treat older patients in the same way as their younger counterparts, but with treatment tailored according to the baseline performance status and disease stage.

Also of interest is the observation that the prognostic score according to Köhne was highly predictive for the PFS and OS. Patients in the high-risk Köhne subgroup had significantly worse survival outcomes (p<0.0001) and also appeared to have an inferior ORR compared with those in the low- and intermediate-risk groups. These findings are in line with other studies investigating the effects of baseline performance status measures on outcomes in patients with mCRC [Diaz et al. 2005;[30] Sanoff et al. 2008;[31] Sargent et al. 2009][32]. Furthermore, with the ECOG performance status at baseline, number of metastatic sites, and alkaline phosphatase levels at baseline, three parameters of the Köhne score were revealed as being independent prognostic factors for PFS and OS by multivariate Cox proportional hazard analysis. This provides further support for using the Köhne score as a tool for predicting the disease course when applying regimens containing bevacizumab in clinical practice as well as in active clinical trials.

We were also able to determine that the KRAS status (which was available in 57% of the patients) was not predictive for response or survival outcomes in this setting. The ORR was similar in patients with either wild-type or mutant tumours and there appeared to be little impact of the KRAS mutant status on either PFS or OS in this patient population. This is in line with several previous trials investigating the influence of the KRAS mutation status on the efficacy of bevacizumab in combination with various chemotherapy regimens, which also showed minimal differences in terms of efficacy [Hurwitz et al. 2009;[33] Reinacher-Schick et al. 2010;[34] Selcukbiricik et al. 2013][35].

No major unexpected findings were identified with respect to the safety of the drug. In general routine practice, adverse events of specific interest occurred with the expected frequencies: gastrointestinal perforation in 1%, arterial thrombotic events in 3% and one (multiple) case of reversible posterior leukoencephalopathy. Bevacizumab-related hypertension (all grades) was

recorded in 16% of the patients, severe cases of CTC grade 3-4 were reported for 2.3%. A differentiation between patients on antihypertensive medication at baseline or de novo hypertension was not applied. Our results are within the range of the published data of other large observational trials: the reported frequency for new or worsened hypertension in the ARIES trial was 8.2% [Bendell et al. 2012][27]; in the BRiTE study 22% were reported with de novo hypertension requiring medication, and further 22% of patients, who were on antihypertensive medication at baseline, with worsening hypertension under treatment with bevacizumab [Kozloff et al. 2009].[22]

Importantly, the rates of patients with an ADR (19%) or SADR (6%) with possible causality to bevacizumab were within the expected ranges compared to e.g. the results of the observational trial ARIES[27] (SADR 9.9% with causality to bevacizumab), or the phase III trial AVEX[29] (SADR 14%, with causality to any substance), although the latter study focused on older patients with probably less tolerance to more intensive treatment regimens. Nevertheless the rate of ADRs was generally lower than those reported in earlier clinical trials of bevacizumab-based chemotherapy regimens [Hurwitz et al. 2004;1 Kabbinavar et al. 2005;2 Saltz et al. 2008;3 Tebbutt et al. 2010;[28] Giantonio et al. 2007]7, non-randomised studies/patient registries [Van Cutsem et al. 2009[26]; Kozloff et al. 2009][22] and a similar non-interventional study previously conducted in Germany [Stein et al. 2015][20]. This may reflect the growing routine of physicians, when administering these novel regimens. No new safety signals were detected, either for the individual chemotherapy regimens combined with bevacizumab or in terms of ADRs of specific interest in association with bevacizumab treatment.

11.4 GENERALISABILITY

The efficacy and safety experience, as reported from the international pivotal clinical trials, seem to translate into the routine practice treatment of an unselected patient population in Germany.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSION

In conclusion, this large observational, non-interventional study in Germany shows that the use of bevacizumab in combination with standard chemotherapy is a safe treatment option and offers potentially higher efficacy compared to standard chemotherapy alone for patients with mCRC. The safety profile and reliable antitumour effectiveness of bevacizumab plus chemotherapy was confirmed in this trial. Efficacy as well as safety results were comparable to those of other trials, especially to other large observational studies [Kozloff et al. 2009[22]; Bendell et al. 2012[27]]. The findings were particularly reinforcing for the effectiveness in elderly patients and individuals with

poor prognostic parameters. The median age of 67 years in this study's population being higher than in similar controlled trials while maintaining efficacy, age per se does not seem to be a limiting factor for a bevacizumab-based treatment approach.

The study also confirmed data published concerning the KRAS status, which was not predictive for survival in this therapeutical setting. However, this evidence is limited by the fact that in 43% of the patients no information for this parameter was available.

The frequency of (serious) adverse drug reactions with causal relationship to bevacizumab was within the expected ranges reported from previous randomised clinical trials, as well as observational studies. Thus no new safety signals were observed; neither with regard to adverse drug reactions specifically associated with bevacizumab, nor to not in the IB labelled adverse drug reactions.

14. REFERENCES

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APPENDICES

See stand-alone documents listed in Annex 1.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	1	08 April 2016	ML21520_additional_figures.pdf
2	2	08 April 2016	ML21520_statistical_report.pdf
3	3	08 April 2016	ML21520_list_of_participating_centres.pdf

ANNEX 2. ADDITIONAL INFORMATION

None.