LMU KLINIKUM
Medizinische Klinik und Poliklinik III
Campus Grosshadern
Campus Innenstadt

FINAL STUDY REPORT

Study Drugs:	Capecitabine plus Bevacizumab versus Capecitabine plus Irinotecan plus Bevacizumab
Study Condition:	Randomized Phase III Study
Study Title:	Sequential first-line therapy of metastatic colorectal cancer with capecitabine/FUFA, irinotecan and bevacizumab - Capecitabine/FUFA plus bevacizumab versus capecitabine/FUFA plus irinotecan plus bevacizumab as first-line therapy for metastatic colorectal cancer -
Protocol code:	ML22011 (AIO KRK0110)
EudraCT No.:	2009-013099-38
Study Initiation:	September 2010
First Patient In:	December 21st, 2010
Last Patient In:	April 06th, 2016
Last Patient Out:	April 15th, 2019
Database extract:	September 16th, 2020

Inhaltsverzeichnis

1. Name of Sponsor/Company

The legal funder (sponsor) of the trial is Klinikum Grosshadern, University of Munich, Marchioninistrasse 15, 81377 Munich, Germany. Prof. Dr. med. Volker Heinemann acts as Sponsor Delegated Person.

Roche Pharma AG supported the trial with study medication and a research grant and reviewed the manuscript before journal submission, but had no role in the design and conduct or collection, management, analysis, interpretation, and publication of the trial.

Prof. Dr. med. Volker Heinemann and Prof. Dr. med. Dominik Paul Modest had full access to all study data. Prof. Dr. med. Volker Heinemann had the final responsibility for the decision to submit for publication.

2. Name of Finished Product

Irinotecan is a semisynthetic analogue of the natural alkaloid camptothecin and is an antineoplastic agent that acts as a specific inhibitor of the enzyme DNA topoisomerase I. In most tissues, irinotecan is metabolised to SN-38 that is more active than irinotecan. The inhibition of DNA topisomerase I leads to single strand DNA lesions, thus inhibiting DNA replication and transcription. SN-38 is inactivated by the enzyme UGT1A1 by glucuronidation, so that patients with UGT1A1 polymorphism are likely to develop severe irinotecan-related toxicities such as diarrhoea and neutropenia.

FUFA (5-fluorouracil and folinic acid): 5-fluorouracil and folinic acid are authorized medicinal products for the treatment of metastatic colorectal cancer.

5-fluorouracil (5-FU) is a pyrimidine antagonist of the group of antimetabolites. Its mechanism of action is based on the inhibition of thymidylate synthase and incorporation of 5-FUmetabolites into RNA and DNA.

Folinic acid stabilises the complex between FdUMP and thymidilate synthase and thereby increases the inhibitory effect on DNA synthesis.

The present study compares two treatment regimens including strategies of escalation as well as of de- and re-escalation.

Treatment with Capecitabine/FUFA and bevacizumab (Arm A: Cape/FUFA + Bev) is compared to combination treatment with Capecitabine/FUFA and irinotecan and additional bevacizumab (Arm B: Cape/FUFA + Iri + Bev) until progression. In case of progression in Arm A, escalation to Cape/FUFA + Iri + Bev is allowed. In Arm B, de-escalation to Cape/FUFA + Bev in case of toxicity or stable course of disease and later re-escalation to Cape/FUFA + Iri + Bev is another option.

3. Name of Active Substance

Capecitabine is an orally administered non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU), rationally designed to generate the cytostatic 5-fluorouracil preferentially in tumor tissue through exploitation of high intratumoral concentrations of thymidine phosphorylase (TP). TP is found in significantly increased concentrations in a wide range of tumor types, including colorectal, breast and gastric cancers, compared to normal tissue.

Pharmacokinetic studies have shown almost complete absorption through the gastro-intestinal wall after oral administration. Direct intestinal exposure to 5-FU is thereby avoided.

Capecitabine is metabolized to 5-FU via a three-step enzymatic cascade, with the final conversion to 5-FU mediated by TP.

Bevacizumab is a humanized monoclonal antibody targeting the vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2) on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vasculation of tumors, normalizes remaining tumor vasculature, and inhibits the formation of new tumor vasculature, thereby inhibiting tumor growth. Thus the interruption of this pathway prevents the formation of new blood vessels and normalizes existing tumor blood vessels and vessel permeability allowing cytotoxic drug access into the tumor.

4. Individual Study Table: Referring to Part of the Dossier (Volume, Page)

N/A

5. Title of Study

Sequential first-line therapy of metastatic colorectal cancer with capecitabin/FUFA, irinotecan and bevacizumab - Capecitabin/FUFA plus Bevacizumab versus Capecitabin/FUFA plus Irinotecan plus Bevacizumab as initial therapy for metastatic colorectal cancer –

Sequenzielle Erstlinientherapie des metastasierten kolorektalen Karzinoms mit Capecitabin/FUFA, Irinotecan und Bevacizumab - Capecitabin/FUFA plus Bevacizumab versus Capecitabin/FUFA plus Irinotecan plus Bevacizumab als Erstlinientherapie beim metastasierten kolorektalen Karzinom –

EUDRA-CT: 2009-013099-38

6. Investigators

Principal Investigator and Representative of the Sponsor:

Prof. Volker Heinemann MD

Munich University Hospital, Grosshadern Campus

Department of Medicine III,

Marchioninistr. 15

81377 Munich, Germany

Telephone: +49 (0)89-4400-0

Fax: +49 (0)89-4400-72257

E-mail: Volker.Heinemann@med.uni-muenchen.de

Study coordinators:

Dr Dominik Modest (MD), Munich University Hospital, Grosshadern Campus, Medical Clinic III

Dr Clemens Gießen-Jung (MD), Munich University Hospital, Grosshadern Campus, Department of Medicine III

Tumour bank and Biobank:

Head of the Study-related Tumour and Biobank: Prof. Heinemann MD and Dr Dominik Modest (MD), Munich University Hospital, Grosshadern Campus, Medical Clinic III

Protocol committee:

Dr L. Fischer von Weikersthal (MD)
St. Marien Amberg Hospital
Specialised Practice for Haematology and Internal Oncology
Mariahilfbergweg 7
92224 Amberg, Germany

Prof. M. Geissler MD
Esslingen Hospital, Dept. for Gastroenterology, Haematology and Oncology
Hirschlandstr. 97
73730 Esslingen, Germany

Prof. F. Kullmann MD
Weiden Hospital
Söllnerstr. 16
92637 Weiden, Germany

Prof. W.-H. Schmiegel MD
Medical University Hospital
Miners' Guild Hospital
Dept. for Internal Medicine
In der Schornau 23-25
44892 Bochum

Dr A. Kretzschmar (MD)
HELIOS Hospital Berlin-Buch
Robert Rössle Hospital
Department of Hematology, Oncology and Tumour Immunology
Schwanebecker Chaussee 50
13125 Berlin, Germany

Project management, Monitoring and Data management

Dr B. Deuss (MD)
ClinAssess GmbH
Birkenbergstr. 82
51379 Leverkusen, Germany
Telephone: +49 (0)2171 36 336 -0
Fax: +49 (0)2171 36336 -55
E-mail: b.deuss@clinassess.de

Biometrics and statistics:

Swantje Held
ClinAssess GmbH
Birkenbergstr. 82
51379 Leverkusen, Germany
Telephone: +49 (0)2171 36 336 -0
Fax: +49 (0)2171 36336 -55
E-mail: s.held@clinassess.de

7. Study centre(s)

Heinemann (Munich), Potenberg (Berlin), Spes (Altötting), Fischer von Weikersthal (Amberg), Sieber (Gummersbach), Vehling-Kaiser (Landshut), Behrens (Halle/Saale), Wilke (Fürth), Bangerter (Augsburg), Pross (Berlin), Harder (Singen), Späth-Schwalbe (Berlin), Asperger (Halle/Saale), Teschendorf (Dortmund), Wagner (Deggendorf), Kullmann (Weiden), Römmele (Nürtingen), Denzlinger (Stuttgart), Lindig (Jena), Peveling gen Reddemann (Leverkusen), Bremer (Münster), Speidel (Hennigsdorf), Freier (Hildesheim), Heider (Leverkusen), Rubanov (Hameln), Freiberg-Richter (Dresden), Mayerle (Greifswald), Schulmann (Arnsberg), Winter (Düsseldorf), Wierecky (Hamburg), Aldaoud (Leipzig), Trojan (Frankfurt), Hünerlitüroglu (Neuss), Peuser (Leipzig), Hahn (Herne) Gassmann (Siegen), Vogel (Hannover), Lorentz (Worms), Uhlig (Naunhof), Papke (Neustadt in Sachsen), Decker (Ravensburg), Bernhard (Darmstadt), Schenk (Regensburg), Buschmann (Bonn), Stauch (Kronach), Schröder (Mülheim a. d. Ruhr), Whitlock (Balingen), Kanzler (Schweinfurt), Rauh (Witten), Hielscher (Chemnitz), Hennemann (Duisburg-Rheinhausen), Schuch (Hamburg), Simon (Ostfildern), Zirlik (Freiburg), Luttenberger (Memmingen), Greeve (Paderborn), März (Osnabrück), Koch (Datteln), Ewald (Kulmbach), Schmidt (München), Kojouharoff (Darmstadt), Mezger (Karlsruhe), Nischik (Greven), Egger (Lahr), Graf (Düsseldorf), Kunst (Nienburg), Schmiegel (Bochum), Baake (Pinneberg), Kiani (Bayreuth), Göhler (Dresden), Steffens (Stade), Schwaner (Berlin), Ettrich (Ulm), Liersch (Münster), Graeven (Mönchengladbach), Beck (Mönchengladbach), Schlichting (Rotenburg), Depenbusch (Gütersloh), Müller (Leer), Lüdde (Aachen), Killing (Wetzlar), Schulz (Frechen).

(Also see attachment: study centers)

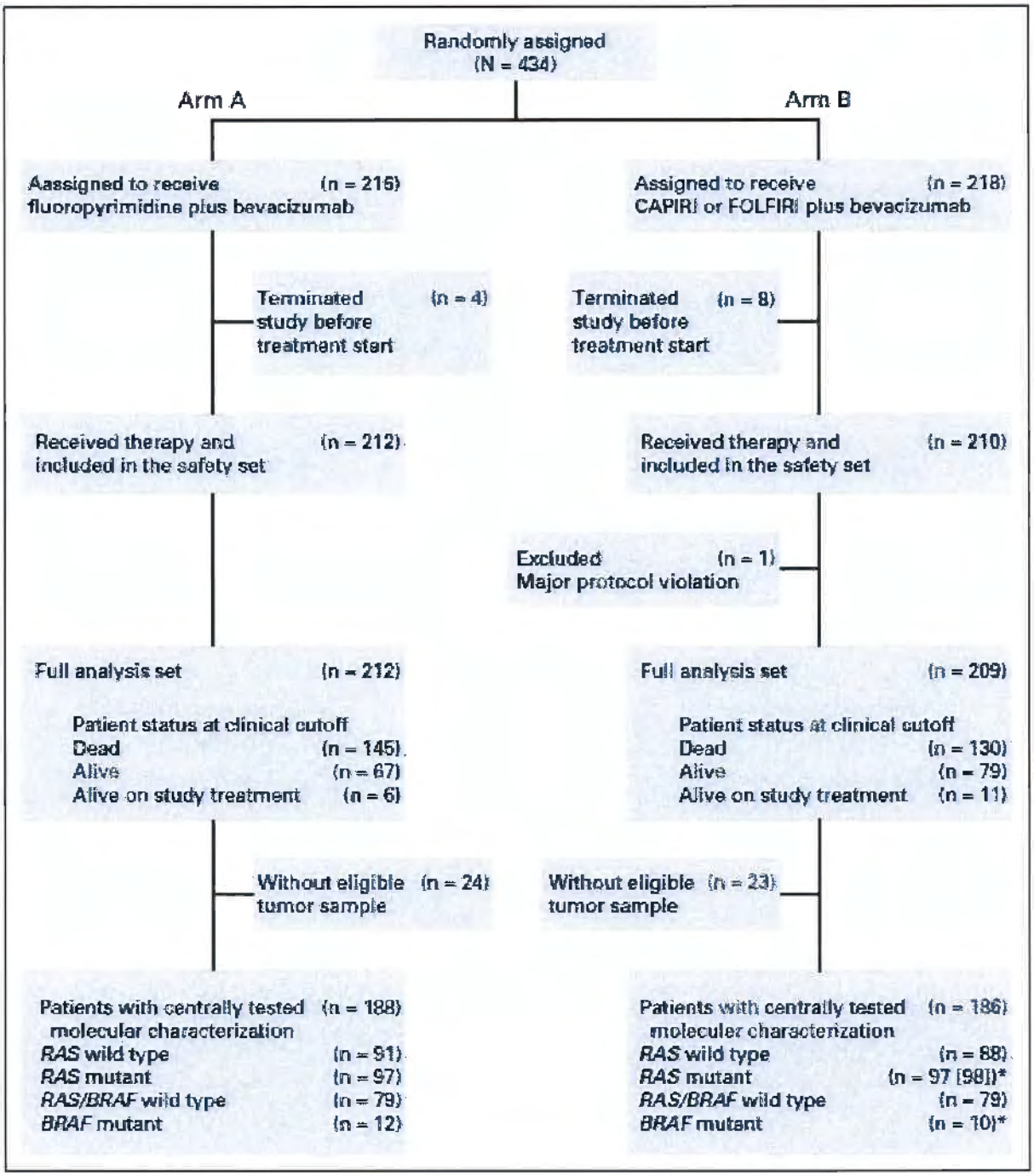
8. Publication (reference)

Modest DP, Fischer von Weikersthal L, Decker T, et al. Sequential Versus Combination Therapy of Metastatic Colorectal Cancer Using Fluoropyrimidines, Irinotecan, and Bevacizumab: A Randomized, Controlled Study-XELAVIRI (AIO KRK0110). J Clin Oncol. 2019;37(1):22-32.

9. Studied period (years): date of first enrolment, date of last completed

The trial randomly assigned 434 patients from 82 centers in Germany between December 21, 2010, and April 6, 2016. Of these, 422 patients received therapy and formed the safety set. One patient was excluded because of a major protocol violation.

No study interruptions or premature endings / dropouts were reported (also see attached DSUR Reports)



10. Phase of development

Randomized, controlled phase III trial

11. Objectives

primary

- Evaluation of efficacy and tolerability of both treatment algorithms in patients with untreated metastatic colorectal cancer.

secondary

- Evaluation of study treatment with regard to ORR, PFS, OS and quality of life
- Evaluation of safety and toxicity

The primary end point was structured hierarchically—it was defined that if, and only if, noninferiority of TFS (sequential treatment v up-front triple-therapy) was demonstrated, a comparison of symptomatic toxicity would define the superior treatment arm. In both arms, TFS was calculated as the time from random assignment to failure of the Iri-containing regimen. In the sequential treatment arm, this presumed that the escalation Iri was performed and led to at least stabilization of the disease according to RECIST 1.1. In all other scenarios—that is, no escalation or no disease control with Iri—TFS was defined as having occurred at first progression. In the case of no event occurring during study therapy, the end point was defined as the start of a new treatment line (use of at least one new anticancer drug that was not part of the study), first progression after study therapy, or death, whichever came first.

Secondary end points of the trial included progression-free survival-1 (PFS-1; time from random assignment to disease progression, use of a new anticancer drug, or death from any cause), overall survival (OS; time from random assignment to death from any cause), overall response rate (according to RECIST 1.1), safety (type, frequency and association of adverse effects and study treatment according to NCI-CTCAE, Version 4.0), and tolerability. Evaluation of efficacy according to molecular subgroups was also a secondary end point.

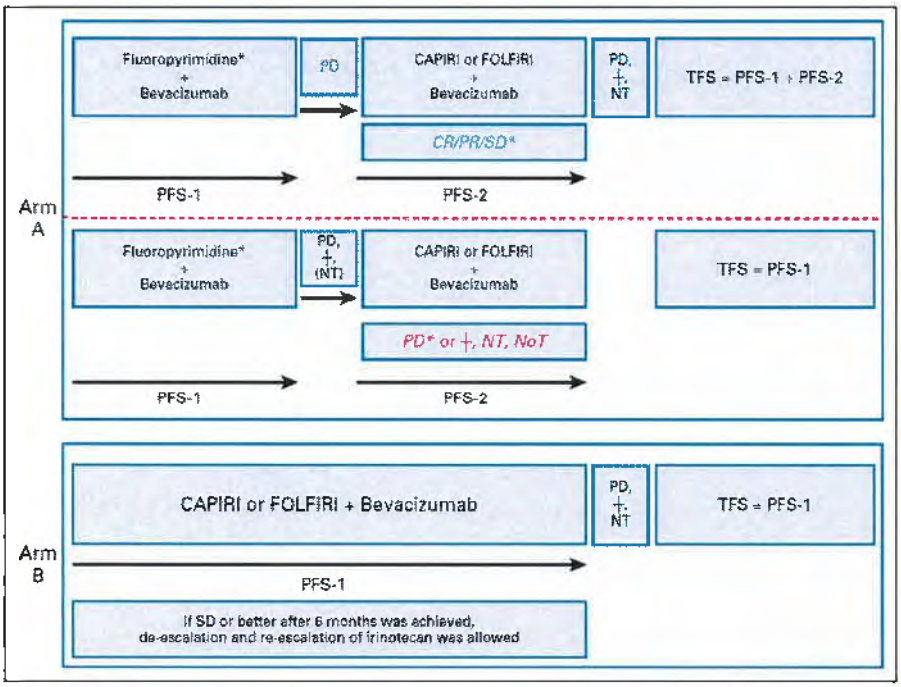


FIG 1. Definition of the primary end point in the sequential treatment arm A. CAPIRI, capecitabine in combination with irinotecan; CR, complete remission; FOLFIRI, fluorouracil and leucovorin in combination with irinotecan; NoT, no escalation treatment given; NT, new treatment (not study therapy); PD, progressive disease; PFS, progression-free survival; PR, partial remission; SD, stable disease (all evaluations according to RECIST 1.1); TFS, time to failure of the strategy. (*) Best response of per protocol escalation; (†) death.

12. Methodology (1)

Patients

Main inclusion criteria were age ≥ 18 years; Eastern Cooperative Oncology Group performance status of 0 to 1; stage IV, histologically confirmed colorectal cancer; adequate organ function and unresectable disease (or patient's wish not to undergo surgery), and one or moremeasurable tumor lesion on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Key exclusion criteria included prior chemotherapy for mCRC, adjuvant therapy within 6 months before trial enrolment, cardiac insufficiency greater than New York Heart Association grade II or cardiac ischemic event within 6 months before study start, and major bleeding event within 6 months before study start and untreated brain metastases. For complete inclusion and exclusion criteria see below.

Trial Design and Conduct

The trial was conducted in accordance with the protocol and in compliance with the Declaration of Helsinki and in accordance with GCP. The protocol was approved by the ethics committees of all centers (Data Supplement). All patients provided written informed consent before trial entry. A template of the latest version of the Informed Consent Form is attached in

the Appendix. A contract research organization (ClinAssess GmbH, Leverkusen, Germany) was responsible for randomization, data management, monitoring, and primary data analysis. Random assignment was organized centrally by fax in a 1:1 fashion using permuted blocks (size 4). Leukocytes (< 8,000/mL v ≥ 8,000/mL), alkaline phosphatase (< 300 U/L v ≥ 300 U/L), and prior adjuvant therapy (yes v no) served as stratification factors.

Treatment

The initial study protocol defined capecitabine as the FP backbone, including a CAPIRI regimen established in two randomized trials of the Arbeitsgemeinschaft Internistische Onkologie study group. On the basis of increasing evidence that CAPIRI and FOLFIRI were comparable in combination with Bev, as well as to ensure greater flexibility for patients and centers, an amendment in 2013 allowed regimens that were based on infusional FU and capecitabine. The choice of the respective FP for each patient was reported initially and not changed during the course of the study. For detailed information regarding dose and mechansim of action of the used study drugs see attached protocol (chapter 4). Patients in arm A started therapy with FP + Bev. Either capecitabine-based (oral capecitabine 1,250 mg/m^2 twice daily, days 1 to 14, plus infusional Bev 7.5 mg/kg body weight on day 1, repeated every 3 weeks) or FU-based (intravenous on day 1: racemic folinic acid with 400 mg/m^2, FU bolus of 400 mg/m^2, FU over 46 hours 2,400 mg/m^2 and 5mg/kg body weight of Bev, repeated every 2 weeks) regimens were administered. After first progression, treatment was continued with CAPIRI + Bev (oral capecitabine 800 mg/m2 twice daily, days 1 to 14, intravenous Iri 200mg/m^2 on day 1 plus Bev at a dose of 7.5 mg/kg body weight infused on day 1, repeated every 3 weeks) or biweekly FOLFIRI + Bev with Iri at a dose of 180 mg/m^2 in addition to the FU regimen described above. Patients in arm B received initial CAPIRI or FOLFIRI + Bev (FP + Iri + Bev) as described. In arm B, de-escalation of Iri (in the case of at least stable disease for > 6 months) and consecutive re-escalation to the full regimen - after progression while on de-escalated treatment - was allowed. Treatment was continued until disease progression, occurrence of unacceptable toxicity, complete response, or until a physician and/or patient decision that study therapy be stopped or changed (for any reason). Subsequent therapy was defined if a drug—not being part of the previous line of therapy—was used.

Assessments

Tumors were assessed by computed tomography (abdomen and chest) within 28 days before study start, and follow-ups were scheduled every 9 weeks until the end of treatment. After the study, assessments were carried out every 3 months until death or for a maximum of 5 years.

All adverse events (according to the National Cancer Institute Common Terminology Criteria for Adverse Events) were documented from enrolment to the final study visit. All recorded toxicities were classified as symptomatic versus nonsymptomatic according to the study protocol by sponsor representatives (D.P.M. and V.H.).

RAS and BRAF Mutation Detection

Tumor samples were evaluated centrally for KRAS, NRAS, and BRAF mutations using a pyrosequencing approach, as described in the Data Supplement and Appendix Table A1.

TABLE A1. Primer Sequences for Polymerase Chain Reaction and Pyrosequencing of *KRAS*, *NRAS*, and *BRAF* Mutations

Gene	Exon	Primer	Codon
KRAS	2		Codon 12, 13
		Forward	5′ NNNGGCCTGCTGAAAATGACTGAA 3′
		Reverse	5′ Biotin TTAGCTGTATCGTCAAGGCACTCT 3′
		Sequencing	5′ TGTGGTAGTTGGAGCT 3′
	3		Codon 59, 61
		Forward	5′ AATTGATGGAGAAACCTGTCTCTT 3′
		Reverse	5′ Biotin TCCTCATGTACTGGTCCCTCATT 3′
		Sequencing	5′ TCTCTTGGATATTCTCGAC 3′
	4		Codon 117
		Forward	5′ CTGAAGATGTACCTATGGTCCTAG 3′
		Reverse	5′ Biotin CTGAGCCTGTTTTGTGTCTACTG
		Sequencing	5′ ACCTATGGTCCTAGTAGGAA 3′
			Codon 146
		Forward	5′ GGCTCAGGACTTAGCAAGAAGTTA 3′
		Reverse	5′ Biotin AGTTATGATTTTGCAGAAAACAGA 3′
		Sequencing	5′ GAATTCCTTTTATTGAAAC 3′
NRAS	2		Codon 12, 13
		Forward	5′ CTTGCTGGTGTGAAATGACTGAG 3′
		Reverse	5′ Biotin GGATTGTCAGTGCGCTTTT 3′
		Sequencing	5′ TGGTGGTGGTTGGAG 3′
	3		Codon 59, 61
		Forward	5′ AAACCTGTTTGTTGGACATACTG 3′
		Reverse	5′ Biotin TATTGGTCTCTCATGGCACTGT 3′
		Sequencing	5′ TTGTTGGACATACTGGAT 3′
	4		Codon 117
		Forward	5′ Biotin ATGATGTACCTATGGTGCTAGTGG 3′
		Reverse	5′ CGTAACTCTTGGCCAGTTCG 3′
		Sequencing	5′ TCCTTGTTGGCAAATC 3′
			Codon 146
		Forward	5′ CGAACTGGCCAAGAGTTACG 3′
		Reverse	5′ Biotin TGAAAGCTGTACCATACCTGTCTG 3′
		Sequencing	5′ TCCATTCATTGAAACCT 3′
BRAF	15		Codon 600
		Forward	5′ TGAAGACCTCACAGTAAAAATAGG 3′
		Reverse	5′ Biotin TCCAGACAACTGTTCAAACTGAT 3′
		Sequencing	5′ GTAAAAATAGGTGATTTTGG 3′

Toxicity Score

The toxicity score was calculated as mean number of symptomatic adverse event reactions - at least National Cancer Institute Common Terminology Criteria for Adverse Events grade 2 - per treatment cycle, adjusted for 2- versus 3-weekly regimens, during the timeframe of TFS.

Statistical Analysis

Primary analysis of TFS was performed in the full analysis set population. The full analysis set included all patients who underwent random assignment, received study treatment, and had no major violation of inclusion or exclusion criteria. Treatment duration was defined as treatment with drugs that were part of the protocol - FP, Iri, and Bev. In arm A, this consisted of initial therapy plus the escalation regimen. The primary end point was to assess the noninferiority of TFS induced by sequential treatment (arm A) versus initial combination chemotherapy (arm B). On the basis of published data on FOLFIRI or CAPIRI + Bev, amedian TFS (PFS) of 10 months in the standard arm was expected. (2-6)From a clinical point of view, the difference in an early end point is generally considered meaningful if the relative benefit is greater than 20%, which corresponds to a hazard ratio (HR) of less than 0.8. (7, 8). Therefore, we aimed to exclude a relative disadvantage by sequential treatment of 20%, corresponding to a limit for noninferiority of 8 months (Δ = 2 months). Thus, noninferiority is shown at a significance level of 5% if the lower limit of the 90% CI (HR) is 0.8 or more.21 The initial design

required 506 events for TFS. In 2015, as a result of slow recruitment, which occurred in the context of competing studies and a subsequent trend for more intensive treatment concepts, (8-10) and after consultation with the leading ethical committee and a respective recommendation, the sponsor decided to accept a reduced power of 70%, which resulted in 378 events needed.

Survival-based outcomes were described by the Kaplan- Meier method, expressed as medians, and compared with log-rank test and Cox proportional hazards regression (expressed as HRs with CIs). Response rates were compared using Fisher's exact test, and odds ratios were indicated. Toxicity and treatment intensity were assessed in all patients (safety set) who received treatment within the study. Comparison of symptomatic toxicities per treatment cycle was conducted using a Wilcoxon rank sum test. Additional differences between study arms were described and evaluated using an inverse Kaplan-Meier method (follow-up) and Fisher's exact test (comparison of dichotomous variables between study arms). Two-sided significance level was set to .05, except for TFS. Analyses and graphics were performed/generated using SAS SAS/STAT, Version 9.4; SAS Institute, Cary, NC, and SPSS, Version 22, IBM, Armonk, NY).

13. Number of patients (planned and analysed)

Initially it was planned to enrol a total of 516 patients, because 506 events were needed to achieve a power of 80%. In 2015, as a result of slow recruitment, which occurred in the context of competing studies and a subsequent trend for more intensive treatment concepts, (8-10) and after consultation with the leading ethical committee and a respective recommendation, the sponsor decided to accept a reduced power of 70%, which resulted in 378 events (189 events per arm) needed. The trial randomly assigned 434 patients from 82 centers in Germany.

TABLE 1. Baseline Characteristics of the Full Analysis Set and the Population Evaluable for Molecular Characterization

Characteristic	Full Analysis Set		*RAS/BRAF* Evaluable Subgroup of Full Analysis Set	
	Fluoropyrimidine Plus Bevacizumab (n = 212)	CAPIRI or FOLFIRI Plus Bevacizumab (n = 209)	Fluoropyrimidine Plus Bevacizumab (n = 188)	CAPIRI or FOLFIRI Plus Bevacizumab (n = 186)
Sex				
Male	137 (64.6)	144 (68.9)	123 (65.4)	128 (68.8)
Female	75 (35.4)	65 (31.1)	65 (34.6)	58 (31.2)
Median age, years	71.0	69.0	72.0	69.0
Patients ≥ 70 years	93 (43.9)	117 (56.0)	78 (41.5)	102 (54.8)
ECOG performance status				
0	127 (59.9)	124 (59.3)	116 (61.7)	111 (59.7)
1	85 (40.1)	83 (38.7)	72 (38.3)	73 (39.2)
Unknown	0 (0.0)	2 (1.0)	0(0.0)	2 (1.1)
Laboratory values				
Leukocyte count ≥ 8,000/μL	98 (46.2)	94 (45.0)	88 (46.8)	83 (44.6)
Alkaline phosphatase ≥ 300 U/L	27 (12.7)	25 (12.0)	22 (11.7)	21 (11.3)
Onset of metastases				
Synchronous	151 (71.2)	145 (69.4)	135 (71.8)	129 (69.4)
Metachronous	57 (26.9)	59 (28.2)	51 (27.1)	53 (28.5)
Unknown	4 (1.9)	5 (2.4)	2 (1.1)	4 (2.2)
Site of primary tumor				
Left (splenic flexure-rectum)	140 (66.0)	138 (66.0)	122 (64.9)	123 (66.1)
Right (transverse colon-cecum)	68 (32.1)	64 (30.6)	62 (33.0)	57 (30.6)
Unknown	4 (1.9)	7 (3.3)	4 (2.1)	6 (3.2)
No. of metastatic sites (%)				
1	74 (34.9)	75 (35.9)	67 (35.6)	72 (38.7)
≥ 2	133 (62.7)	126 (60.3)	117 (62.2)	107 (57.5)
Unknown	5 (2.4)	8 (3.8)	4 (2.1)	7 (3.8)
No. of Metastatic sites (%)				
Liver	153 (72.2)	159 (76.1)	137 (72.9)	140 (75.3)
Liver only	48 (22.6)	55 (26.3)	44 (23.4)	52 (28.0)
Lung	108 (50.9)	86 (41.1)	98 (52.1)	75 (40.3)
Lymph nodes	76 (35.8)	82 (39.2)	64 (34.0)	70 (37.6)
Peritoneum	16 (7.5)	9 (4.3)	14 (7.4)	9 (4.8)
Other	55 (25.9)	48 (23.0)	47 (25.0)	42 (22.6)
Prior treatment				
Surgery of primary tumor	163 (76.9)	154 (73.7)	146 (77.7)	142 (76.3)
Adjuvant chemotherapy	49 (23.1)	48 (23.0)	43 (22.9)	45 (24.2)
Radiotherapy	36 (17.0)	32 (15.3)	33 (17.6)	29 (15.6)
Fluoropyrimidine used				
Capecitabine	151 (71.2)	136 (65.1)	133 (70.7)	123 (66.1)
Infusional fluorouracil	61 (28.8)	73 (34.9)	55 (29.3)	63 (33.9)

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: CAPIRI, capecitabine in combination with irinotecan; ECOG, Eastern Cooperative Oncology Group; FOLFIRI, fluorouracil and leucovorin in combination with irinotecan.

14. Diagnosis and criteria for inclusion and exclusion

All female and male patients can enter the study if they meet the following criteria:

- Written consent of the patient
- Histologically confirmed metastatic colorectal cancer
- Metastases are unresectable or the patient cannot or does not wish to undergo a surgical procedure.
- No prior chemotherapy of the metastatic disease

- Metastases measurable according to RECIST, Version 1.1 (CT of the chest/abdomen within the last 4 weeks before registration)
- Age ≥ 18 years
- ECOG performance status 0-1
- Life expectancy > 3 months
- Determination of the KRAS status (decentralised implementation, result not a requirement at the time of inclusion)
- The patient consents to the storage of tumour material for the purpose of molecular analyses, including determination of the genetic profile of the tumour
- Time interval since previous adjuvant chemotherapy > 6 months
- Time interval of ≥ 28 days since previous major surgical interventions, open biopsies or significant trauma; ≥ 7 days since port implantation or other minor surgical procedures; 2 days since placement of a CVC.
- Women of childbearing potential must use adequate contraceptive measures
- An existing pregnancy is ruled out
- Normal cardiac function confirmed by ECG and echocardiography (LVEF ≥ 55%)
- Patients not receiving anticoagulation must have an INR < 1.5 ULN and a PTT < 1.5 ULN. The use of therapeutically dosed anticoagulation is permitted as long as the INR and PTT values are within the therapeutic range and the patient has been on a stable dose of the anticoagulant for at least 2 weeks.
- Continuous medication with ASA up to a dose of 325 mg/day is permitted. The administration of clopidogrel up to the recommended dose of 75 mg/day or ticlopidine up to the recommended dose of 2x250 mg/day is permitted. In contrast, a combination of ASA with clopidogrel or ticlopidine is not permitted.
- Patients with < 2+ proteinuria on the urine stick analysis. For patients with ≥ 2+ proteinuria on the urine stick analysis at baseline, a 24-hour urine collection is to be carried out, whereby the proteinuria must be at ≤ 1 g/24 hours.
- Patients with a history of grade 3-4 thrombosis (NCI CTCAE, Version 4.0) are expected to receive prophylactic anticoagulation.
- Adequate organ function as defined below:

SYSTEM	LABORATORY VALUES
Haematology	
Neutrophils	≥1,500/µL
Haemoglobin	≥9 g/dL
Platelets	≥100,000/µL
Hepatic	
Albumin	≥2.5 g/dL
Serum bilirubin	≤1.5 mg/dL
AST and ALT	≤2.5 × ULN ≤5.0 × ULN in hepatic metastatic spread
Renal	
Serum creatinine	≤1.5 mg/dL - OR -
Calculated creatinine clearance[1]	≥50 mL/min (GFR: Cockroft and Gault)

[1] calculated using the Cockcroft and Gault method.

Patients meeting any of the following criteria will not be included in the study:

- Primarily resectable metastases and the patient's wish to undergo surgery.
- Grade III or IV heart failure (NYHA functional classification)

- Comorbidities or physical conditions that make the patient unsuitable for participating in the study or that would interfere with the safety of the study participant
- Myocardial infarction, unstable angina, cardiac angioplasty or coronary stenting within the previous 6 months
- History of arterial thromboembolism including stroke, transient ischemic attack or cerebrovascular disorders within the previous 6 months
- Severe bleeding within the previous 6 months (except for tumour bleeding prior to resection), coagulopathy or bleeding diathesis
- Abdominal or tracheooesophageal fistulas, gastrointestinal perforations within the past 6 months prior to admission to the study
- Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or > 100 mmHg diastolic) on antihypertensive therapy
- History of recurrent thromboembolic events (> 1 episode of deep vein thrombosis, peripheral embolism) during the previous 2 years
- Severe wound healing disorder or ulceration or bone fractures
- Pregnant or breastfeeding patients
- Any psychological, familial, sociological or geographical event that prevents compliance with the study protocol
- Additional cancer therapy (chemotherapy, radiation, biological therapy, immunotherapy or hormonal therapy) during the study
- Concomitant treatment with other investigational medicinal products or any other expressly prohibited medication during the study or participation in another clinical study subject to the German Medicinal Products Act
- Contraindications to treatment with irinotecan and/or FUFA
- Any known immediate or delayed hypersensitivity reaction or idiosyncrasy to medicinal products chemically related to capecitabine, 5-fluorouracil, folinic acid, irinotecan, or bevacizumab
- Acute or subacute ileus or chronic inflammatory bowel disease
- Known glucuronidation defect (Gilbert-Meulengracht syndrome)
- Untreated brain metastases
- Known malignant secondary neoplasm within the last 5 years (except for basal cell carcinoma of the skin or carcinoma of the uterine cervix in situ)
- Known alcohol or drug abuse
- Lack of or limited legal capacity

15. Test product, dose and mode of administration

During the conduct of the trial, all drugs are used within their respective lable and the centres are requested to buy the drugs themselves. (For batch numbers see Attachments: Certificate of Compliance)

The initial study protocol defined capecitabine as the FP backbone, including a CAPIRI regimen established in two randomized trials of the Arbeitsgemeinschaft Internistische Onkologie study group. On the basis of increasing evidence that CAPIRI and FOLFIRI were comparable in combination with Bev, as well as to ensure greater flexibility for patients and centers, an amendment in 2013 allowed regimens that were based on infusional FU and capecitabine. The choice of the respective FP for each patient was reported initially and not changed during the course of the study. Patients in arm A started therapy with FP 1 Bev. Either capecitabine-based (oral capecitabine 1,250 mg/m^2 twice daily, days 1 to 14, plus infusional Bev 7.5 mg/kg body weight on day 1, repeated every 3 weeks) or FU-based (intravenous on day 1: racemic folinic acid with 400 mg/m^2, FU bolus of 400 mg/m^2, FU over 46 hours 2,400 mg/m^2 and 5mg/kg body weight of Bev, repeated every 2 weeks) regimens were administered. After first progression, treatment was continued with CAPIRI + Bev (oral capecitabine 800 mg/m2 twice daily, days 1 to 14, intravenous Iri 200mg/m^2 on day 1 plus Bev at a dose of 7.5 mg/kg body weight infused on day 1, repeated every 3 weeks) or biweekly FOLFIRI + Bev with Iri at a dose of 180 mg/m^2

in addition to the FU regimen described above. Patients in arm B received initial CAPIRI or FOLFIRI + Bev (FP 1 Iri 1 Bev) as described. In arm B, de-escalation of Iri (in the case of at least stable disease for > 6 months) and consecutive re-escalation to the full regimen - after progression while on de-escalated treatment - was allowed.

16. Duration of treatment

Treatment was continued until disease progression, occurrence of unacceptable toxicity, complete response, or until a physician and/or patient decision that study therapy be stopped or changed (for any reason). Subsequent therapy was defined if a drug—not being part of the previous line of therapy—was used.

17. Reference therapy, dose and mode of administration

The local investiagtor will choose the fluoropyrimidine (capecitabine or infusional 5-FU/leucovorin) („investigators choice"). The choice is final and should not be changed during the conduct of the trial. In arm A treatment will start with either capecitabine plus bevacizumab or with 5-FU/leucovorin plus bevacizumab. Treatment in arm B will start with either CAPIRI plus bevacizumab or FOLFIRI plus bevacizumab.

During the conduct of the trial, all drugs are used within their respective lable and the centres are requested to buy the drugs themselves.

Arm A (experimental arm)

The experimental arm (arm A) of the trial can be performed with one of the following regimens (choice of investigator):

Capecitabine plus bevacizumab (three-week regimen)

capecitabine: 2 x 1250 mg/m2	day 1-14
bevacizumab: 7.5 mg/kg	day 1

5-FUFA plus bevacizumab (two-week regimen)

Folin acid 400 mg/m²	iv	120 min	day 1
5-FU 400 mg/m²		bolus	day 1
5-FU 2400 mg/m²	iv	in 46 h	day 1-2
Bevacizumab:		5.0 mg/kg	day 1

Treatment is continued until disease progression or unacceptable toxicity. In case of progression, treatment is escalated (to arm B regimens): to CAPIRI plus bevacizumab (if capecitabine was used) or FOLFIRI plus bevacizumab (if 5-FUFA was the initial backbone)

Arm B (standard arm)

Patients receive initial CAPIRI or FOLFIRI plus bevacizumab. In case of failure (progression, death, toxicity) study treatment will end.

Treatment is continued until progression or unacceptable toxicity. After treatment of at least 6 months, de-escalations (pausing of irinotecan) are allowed and treatment should be continued with the fluoropyrimidine plus bevacizumab. If toxicities require earlier de-escalation of irinotecan, patient maybe re-exposed to the full irinotecan-based regimen in case of disease progression (at the discretion of the investigator) The time of definite progression to the full regimen (CAPIRI/FOLFIRI plus bevacizumab) will be evaluated as PFS-1.

CAPIRI + bevacizumab (three week regimen)

capecitabine:	2 x 800 mg/m2	day 1-14,

irinotecan:	200 mg/m2	day 1
bevacizumab:	7.5 mg/kg	day 1
FOLFIRI + bevacizumab (two week regimen)		
irinotecan 180 mg/m² iv, 30 - 90 min		day 1
floinic acid 400 mg/m² iv, 120 min		day 1
5-FU 400 mg/m²	bolus	day 1
5-FU 2400 mg/m²	iv 46 h	days 1-2
bevacizumab:	5.0 mg/kg	days 1

18. Criteria for evaluation: Efficacy, Safety

Tumors were assessed by computed tomography (abdomen and chest) within 28 days before study start, and follow-ups were scheduled every 9 weeks until the end of treatment. After the study, assessments were carried out every 3 months until death or for a maximum of 5 years.

All adverse events (according to the National Cancer Institute Common Terminology Criteria for Adverse Events) were documented from enrolment to the final study visit. All recorded toxicities were classified as symptomatic versus nonsymptomatic according to the study protocol by sponsor representatives (D.P.M. and V.H.).

19. Statistical methods

The primary analysis of TFS is performed in the full analysis set (FAS) population, corresponding to an intent-to-treat analysis. The FAS includes all patients that underwent randomisation, received study treatment and had no major violation of in-/exclusion criteria. In arm A (initial fluoropyrimidine plus bevacizumab), TFS is defined as time from randomisation to second progression (failure of the irinotecan-containing regimen after escalation). If no escalation is possible/done at first progression or if no response or stable disease can be observed during the irinotecan-containing escalation, TFS is defined as having occurred at time of first progression. In case of no event occurring during study therapy, the endpoint is defined as start of a new treatment-line (at least one anticancer drug that was not part of the study protocol), first progression after study therapy or death, whichever came first. In this regard a PFS-2 was estimated as time from escalation to second-progression (if not occurring as best response), death or use of a new drug. In arm B time to failure of strategy was calculated as time from randomisation to first progression to the full irinotecan-containing regimen (including a re-escalation of irinotecan in case of de-escalated therapy after at least six months disease control, see above), use of at least one new anticancer drug or death.

Demographic and prognostic baseline measures will be analyzed for heterogeneity between the two treatment arms. Clinical and laboratory toxicity graded according NCI CTC (version 4.0) will be collected for all patients. Quality of life will be measured using the EORTC QLC-C30 questionnaire. Categorical data comparisons between treatment arms will be performed applying Fisher's exact test, chi-square test and Mantel-Haenszel test, as appropriate. Event-related data (TFS, PFS, OS) will be reported according to the life-table method (Kaplan and Meier) and compared using the logrank test. In case of non-conformity with proportional hazard assumptions the generalized Wilcoxon signed-rank test may be used as modified by Peto et al. and Prentice et al. [14, 15, 16].

Univariate estimation for prognostic factors will be performed as described above. In case of need for multivariate analysis appropriate regression models e.g. logistic regression model, Cox proportional hazard model will be adopted.

The primary objective of the study is to examine two hierarchically ordered hypotheses on the comparative efficacy and toxicity. The primary efficacy endpoint is the time to failure of strategy (TFS). The objective is to show non-inferiority of the experimental arm. The primary toxicity analysis is performed confirmatively if (and only if) non-inferiority with respect to TFS was shown. This hierarchically ordered approach precludes an inflation of the overall type I error in case of more than one study hypothesis. The primary safety endpoint is a toxicity score defined as the mean number of NCI CTC grade 2 - 4 findings per cycle during the whole TFS period. Only symptomatic toxicities will be taken into account, and not any events that are manifested as laboratory abnormality or change only. With respect to toxicity the objective is to show superiority of the experimental arm.

The primary endpoint was to test non-inferiority of TFS induced by sequential treatment (arm A) versus initial combination chemotherapy (arm B). A 90% confidence-interval margin for non-inferiority was set to a hazard ratio for time to failure of strategy of 0·8. With a power of 80%, the initial design required 516 events for time to failure of strategy. In 2015, it appeared that due to slow recruitment, a completion of recruitment in a reasonable time-frame was not realistic. After consultation with the leading ethical committee and a respective recommendation, the sponsor decided to accept a reduced power of 70%, resulting in 378 events needed.

The primary endpoints will be analyzed confirmatively with a global level of significance $p \leq 0.05$ (one-sided). All other parameters will be estimated in a descriptive analysis with report of means, medians, ranges and confidence intervals. All additional p-values will be estimated exploratorily without adjustment of the level of significance, using two-sided test procedures.

20. Summary – Conclusions (1)

Efficacy

The primary analysis of TFS was based on 380 (90.3%) of 421 events. Median TFS in the initial FP 1 Bev group (arm A) was 9.6 months (90% CI, 8.6 to 10.6 months) and 9.9 months (90% CI, 8.8 to 10.6 months) in the initial FP 1 Iri1Bev group (arm B). HR for TFS was 0.86 with a 90% CI of 0.73 to 1.02, which exceeded the noninferiority margin of 0.8. Adjusted—by stratification factors—analysis for TFS was as follows: HR, 0.88; 90% CI, 0.72 to 1.08. Subgroups indicated benefit from the upfront combination therapy in patients with RAS/BRAF wild-type tumors (HR, 0.61; 90% CI, 0.46 to 0.82; P = .005), but not in patients with RAS mutant tumors (HR, 1.09; 90% CI, 0.81 to 1.46; P = .58; Fig 3A, Fig 3C, and Table 2). An exploratory Cox proportional hazards regression model analysis of TFS for interaction of RAS mutational status and study arm was significant (P = .03). Median OS was not significantly different (HR, 0.84; 95% CI, 0.66 to 1.06; P = .14) between study arms, and findings in subgroups were consistent with observations in TFS. Objective response rates, PFS-1, and molecular subgroups are summarized in Table 2, and treatment duration and efficacy of the sequential treatment arm are indicated in Appendix Table A4.

TABLE 2. Efficacy in the Full Analysis Set and in Molecular Defined Populations According to Treatment Group

Population	Best Response: Overall Response, %	Best Response: Odds Ratio (95% CI)*	Progression-Free Survival-1: Time, Months (95% CI)	Progression-Free Survival-1: Hazard Ratio (95% CI)†	Time to Failure of Strategy: Time, Months (90% CI)	Time to Failure of Strategy: Hazard Ratio (90% CI)†	Overall Survival: Time, Months (95%CI)	Overall Survival: Hazard Ratio (95% CI)†
Full analysis set								
Fluoropyrimidine plus bevacizumab (n = 212)	36.8	0.50 (0.34 to 0.74)	8.0 (6.9 to 9.9)	0.70 (0.57 to 0.85)	9.6 (8.6 to 10.6)	0.86 (0.73 to 1.02)	21.9 (20.2 to 25.0)	0.84 (0.66 to 1.06)
CAPIRI or FOLFIRI plus bevacizumab (n = 209)	53.6	*P* = .005	9.9 (8.7 to 10.9)	*P* < .001	9.9 (8.8 to 10.6)	*P* = .16	23.5 (20.9 to 27.9)	*P* = .14
Molecular characterized group								
Fluoropyrimidine plus bevacizumab (n = 188)	37.2	0.51 (0.34 to 0.77)	8.0 (6.6 to 8.9)	0.69 (0.56 to 0.86)	9.6 (8.5 to 10.3)	0.85 (0.71 to 1.02)	21.4 (20.1 to 25.0)	0.77 (0.60 to 0.99)
CAPIRI or FOLFIRI plus bevacizumab (n = 186)	53.8	*P* = .001	10.2 (8.8 to 11.1)	*P* < .001	10.2 (9.0 to 10.9)	*P* = .14	26.5 (22.4 to 28.7)	*P* = .04
KRAS wild-type group								
Fluoropyrimidine plus bevacizumab (n = 91)	41.8	0.46 (0.25 to 0.82)	8.0 (6.5 to 9.9)	0.54 (0.39 to 0.74)	8.8 (7.6 to 10.6)	0.66 (0.50 to 0.86)	23.5 (17.5 to 28.6)	0.67 (0.44 to 0.94)
CAPIRI or FOLFIRI plus bevacizumab (n = 98)	61.4	*P* = .009	11.8 (9.4 to 13.2)	*P* < .001	11.8 (10.1 to 13.0)	*P* = .01	28.5 (23.3 to 36.0,	*P* = .02
RAS mutant group								
Fluoropyrimidine plus bevacizumab (n = 91)	36.0	0.57 (0.32 to 1.02)	8.1 (6.0 to 10.2)	0.87 (0.65 to 1.17)	10.0 (8.5 to 11.5)	1.09 (0.81 to 1.46)	21.3 (19.6 to 23.0)	0.92 (0.65 to 1.29)
CAPIRI or FOLFIRI plus bevacizumab (n = 97)	46.4	*P* = .09	9.5 (8.2 to 10.8)	*P* = .34	9.4 (8.0 to 10.7)	*P* = .58	25.2 (16.1 to 28.6)	*P* = .62
RAS/BRAF wild-type group								
Fluoropyrimidine plus bevacizumab (n = 79)	44.3	0.41 (0.22 to 0.79)	8.4 (6.5 to 9.9)	0.49 (0.35 to 0.69)	9.1 (7.8 to 10.9)	0.61 (0.46 to 0.82)	25.2 (20.8 to 29.8)	0.56 (0.38 to 0.81)
CAPIRI or FOLFIRI plus bevacizumab (n = 79)	65.8	*P* = .01	12.6 (10.3 to 14.6)	*P* < .001	12.6 (10.4 to 14.3)	*P* = .005	32.2 (26.1 to 46.4)	*P* = .01
BRAF mutant group								
Fluoropyrimidine plus bevacizumab (n = 12)	25.0	0.78 (0.12 to 5.10)	6.9 (4.2 to 10.2)	1.43 (0.59 to 3.47)	6.9 (4.2 to 10.2)	1.62 (0.76 to 3.47)	12.4 (10.2 to 20.2)	1.50 (0.60 to 3.76)
CAPIRI or FOLFIRI plus bevacizumab (n = 10)	30.0	*P* = .79	4.5 (3.1 to 8.4)	*P* = .43	4.5 (3.1 to 8.4)	*P* = .29	7.8 (4.7 to 13.5)	*P* = .38

Abbreviations: CAPIRI, capecitabine in combination with irinotecan; FOLFIRI, fluorouracil and leucovorin in combination with irinotecan.
*P value calculated by Fisher's exact test.
†P values were calculated using log-rank tests.

TABLE A4. Treatment Duration, Efficacy, and Onset of Adverse Events in the Sequential Treatment Arm

Efficacy in Arm A (initial FP + Bev; n = 212)	Patients With Escalation (n = 80)	Patients Without Escalation (n = 132)
Treatment duration with FP + Bev		
Median time, months (range)	6.9 (1.0-21.5)	5.2 (0.0-27.5)*
PFS-1		
Median time, months (95% CI)	6.9 (6.3 to 8.1)	8.6 (7.5 to 10.0)
Adverse events grade 3-5 during PFS-1, %	70.0	75.8
Treatment duration with FP + Iri + Bev		
Median time, months (range)	2.8 (0.0-15.3)	—
PFS-2		
Median time, months (95% CI)	8.2 (6.6 to 8.8)†	—
Adverse events grade 3-5 after Iri escalation, %	72.5	—
TFS		
Median time, months (95% CI)	10.8 (8.7 to 14.3)	8.6 (7.5 to 10.0)

Abbreviations: Bev, bevacizumab; FP, fluoropyrimidine; Iri, irinotecan; PFS, progression-free survival; TFS, time to failure of the strategy.
*On the basis of 130 patients, data missing from two patients.
†Estimated in 39 patients with at least disease control (stable disease or response according to RECIST 1.1).

Toxicity and Safety

The toxicity score of symptomatic grade 2 to 5 events per treatment cycle significantly favored arm A versus arm B (arithmetic mean, 0.6; standard deviation, 0.7 v arithmetic mean, 0.7; standard deviation, 0.7; P = .03). Adverse events—related or unrelated to study—of grade 3 or more were reported in 80.7% of patients in arm A and 77.1% of patients in arm B. Details are listed in Table 3. In this table the most frequent hematological and gastrointestinal Adverse Events are listed as well as the most common Adverse Events that are to be expected in regard to the used medication. A complete listing of all Serious Adverse Events is attached in the Appendix.

TABLE 3. Grade 1 to 4 Adverse Events and Events of Special Interest

	Grade									
	FP + Bev (n = 212)					FP + Iri + Bev (n = 210)				
Event	1	2	3	4	≥ 2*	1	2	3	4	≥ 2*
Any adverse event	0.5	16.5	66.0	13.2	97.2	3.3	16.7	60.5	14.8	93.8
Symptomatic toxicity grade ≥ 2 per treatment cycle	Mean, 0.6; standard deviation, 0.7					Mean, 0.7; standard deviation, 0.7				
Leucocytopenia	20.8	9.4	4.2	0.9	14.6	31.9	15.2	6.7	—	21.9
Neutropenia	45.3	7.1	4.2	11.3	22.6	44.8	18.6	7.1	9.0	34.8
Febrile neutropenia	—	—	—	0.9	0.9	—	—	1.0	0.5	1.4
Thrombocytopenia	32.5	2.8	1.9	0.5	5.2	24.3	0.5	1.0	1.4	2.8
Anemia (hemoglobin)	63.7	22.6	2.8	1.4	26.9	63.3	22.9	3.3	—	26.2
Infection	18.4	21.2	8.0	0.5	29.7	18.1	20.0	7.1	0.5	27.6
Fever	6.6	3.8	0.5	—	4.2	9.0	3.3	3.8	0.5	7.6
Nausea	22.2	10.8	3.8	—	14.5	21.0	22.9	4.3	—	27.1
Vomiting	9.4	4.7	1.9	—	6.6	11.4	9.0	2.9	0.5	12.4
Diarrhea	20.3	17.9	10.4	0.9	30.2	23.3	19.0	11.9	1.9	32.9
Mucositis/stomatitis	15.6	9.9	3.3	—	13.2	13.8	7.6	1.9	—	9.5
Hand-foot syndrome	9.9	19.3	16.0	—	35.4	15.2	6.7	4.8	—	11.4
Pain	22.2	30.2	5.7	—	35.8	27.6	21.0	6.2	—	27.1
Alopecia	12.3	12.3	—	—	12.3	19.0	21.0	—	—	21.0
Hypertension	13.7	16.9	30.7	0.5	50.0	9.0	21.0	30.5	1.4	52.9
Thromboembolic event	0.9	3.8	10.4	1.9	16.0	1.0	4.3	6.2	1.9	12.9
Bleeding/hemorrhage	13.7	3.3	2.4	—	5.7	14.3	3.8	1.0	—	4.8
Fistula	—	—	—	—	—	—	0.5	—	—	0.5
GI perforation	—	—	—	—	—	—	—	—	0.5	0.5
Proteinuria	2.4	1.4	—	—	1.4	1.4	2.4	—	—	2.4

NOTE. Data are given as percent unless otherwise noted. Adverse event terms were predefined in the case report forms. Hematologic laboratory values were reported and calculated on the basis of the laboratory assessments, all other adverse events were reported and coded by Medical Dictionary for Regulatory Activities version 13.1 preferred terms. All terms are included regardless of whether there are considered related to study treatment or not.

Abbreviations: Bev, bevacizumab; FP, fluoropyrimidine; Iri, irinotecan.

*Includes seven deaths (adverse events of grade 5): three in arm A (one unclear death, two diarrhea) and four in arm B (one cardiac failure plus thromboembolic event, one intestinal ischemia, one neutropenic sepsis, and one sepsis). Of these seven events, four were deemed to be related to the study therapy (one diarrhea, cardiac failure plus thromboembolic event, intestinal ischemia, and neutropenic sepsis).

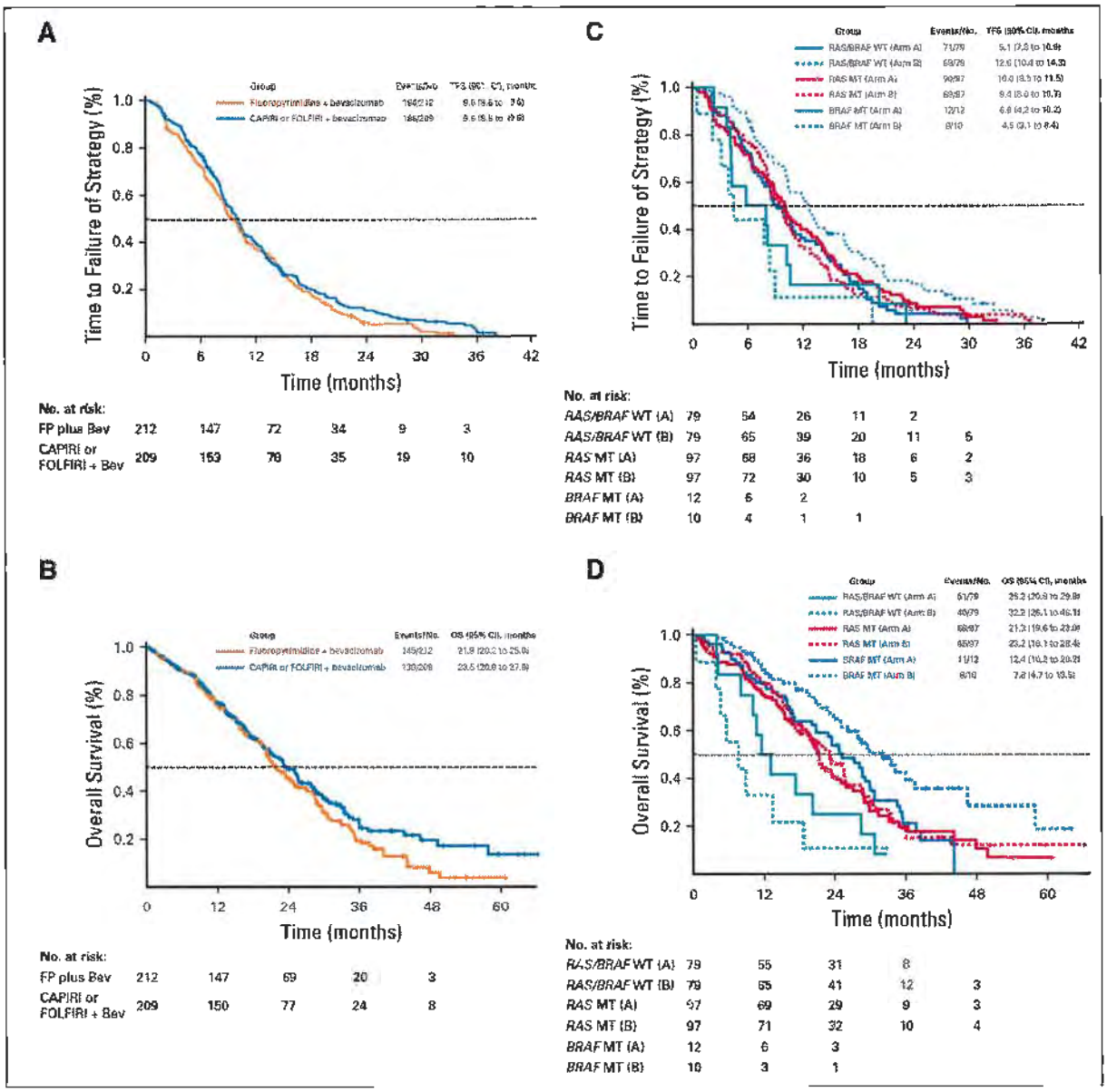


FIG 3. Kaplan-Meier estimates of the full analysis set and the molecular subgroups. (A and B) Kaplan-Meier estimates of time to failure of strategy and overall survival in the full analysis set and (C and D) time to failure of strategy and overall survival in molecular subgroups (*RAS/BRAF* wild type [WT]/*RAS* mutant [MT]/*BRAF* MT, including one patient with an *RAS* plus *BRAF* MT tumor). All analyses were according to treatment group. Arm A: initial fluoropyrimidine (FP) plus bevacizumab (Bev); arm B: initial fluorouracil, leucovorin, or capecitabine in combination with irinotecan (Iri) plus Bev. CAPIRI, capecitabine in combination with irinotecan; FOLFIRI, fluorouracil and leucovorin in combination with irinotecan.

In conclusion, noninferiority of sequential therapy starting with FP + BEV versus initial FP + Iri + Bev could not be demonstrated nor ruled out. The limited feasibility of the sequential escalation of treatment as well as the inferior efficacy of the sequential strategy in patients with RAS/ BRAF wild-type tumors explain this outcome. Whereas initial combination chemotherapy plus Bev was clearly superior in patients with RAS/BRAF wild-type tumors, initial treatment with FP + Bev could be an acceptable approach in patients with RAS mutant tumors. These data suggest that RAS/BRAF mutation status may also be an important parameter in the optimal selection of Bev-based therapy.

21. Date of report

January, 27th 2021

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Protocol Changes

Protocol	Approval ethic committee	Approval PEI
Version 1.0 28.05.2010	23.09.2010	27.09.2010
Amendment 1 06.07.2010	03.08.2011	02.08.2011
Amendment 2 08.02.2013	21.03.2013	18.03.2013
Amendment 3 09.06.2015	02.07.2015	30.03.2015

Signatures

Title of Study:

Sequential first-line therapy of metastatic colorectal cancer with capecitabine/FUFA, irinotecan and bevacizumab

- Capecitabine/FUFA plus bevacizumab versus capecitabine/FUFA plus irinotecan plus bevacizumab as first-line therapy for metastatic colorectal cancer -

EUDRA-CT: 2009-013099-38

Munich, 17-Jun-2021
Place, date

Principal investigator & sponsor's representative
Prof. Dr. med. V. Heinemann

Munich, 30-JUN-2021
Place, date

Study Coordinator
PD Dr. med. Clemens Gießen-Jung

Attachements:

Study Centers

Titel	Nachname	Klinik	Straße	PLZ Ort
Prof. Dr. med.	**Heinemann**	Klinikum der Universität München-Klinikum Großhadern	Marchioninistraße 15	81377 München
OA Dr. med.	**Potenberg**	Evangelisches Waldkrankenhaus Spandau		13589 Berlin
OA Dr. med.	**Florschütz**	Städtisches Klinikum Dessau Akadem. Lehrkrankenhaus der Martin-Luther-Universität Halle-Wittenberg	Auenweg 38	06847 Dessau-Roßlau
Dr. med.	**Kempf**	Klinikum Landshut GmbH	Robert-Koch-Str.1	84034 Landshut
OA Dr. med	**Spes**	Kreisklinik Altötting-Burghausen	Vinzenz-von-Paul-Str. 10	84503 Altötting
Dr. med.	**Fischer von Weikersthal**	Schwerpunktpraxis für Hämatologie und Internistische Onkologie Gesundheitszentrum St. Marien GmbH	Mariahilfbergweg 7	92224 Amberg
CA Dr. med.	**Sieber**	Kreiskrankenhaus Gummersbach GmbH Tumorzentrum Oberberg	Wilhelm-Breckow-Allee 20	51643 Gummersbach
Dr. med.	**Schulze**	Schwerpunktpraxis für Hämatologie und Onkologie	Görlitzer Str. 10 a	02763 Zittau
Dr. med.	**Vehling-Kaiser**	Praxis	Achdorfer Weg 5	84036 Landshut
Dr. med.	**Behrens**	Praxis	Kleine Marktstraße 3	06108 Halle / Saale
Dr. med.	**Dietze**	Gemeinschaftspraxis Mainka/Dietze	Buchforststr. 14	51103 Köln
Dr. med.	**Wilke**	Gemeinschaftspraxis Dres. Wilke/Wagner	Jakob-Henle-Str. 1	90766 Fürth
	Groschek	Onkologische Gemeinschaftspraxis Würselen **(Angelagerter Behandlungsstandort Stollberg)**	Mauerfeldchen 72	52146 Würselen
Dr. med.	**Michl**	Fachärztin für Innere Medizin	Soliner Str. 65b	81479 München
Dr. med.	**Severin**	Praxis	Sachsenring 69	50677 Köln
Prof. Dr. med.	**Bangerter**	Gemeinschaftspraxis	Halderstraße 29	86150 Augsburg
Dr. med.	**Basovski**	Praxis	Ziegelhausstr. 50	88400 Biberach an der Riß
Dr. med.	**Zimber**	Internistische Gemeinschaftspraxis - Praxisklinik Drs. Zimber, Brendel, Hoesl, Maintz	Weiltinger Str. 11	90449 Nürnberg
Prof. Dr. med.	**Pross**	DRK Kliniken Berlin I Köpenick	Salvador- Allende- Straße 2-8	12559 Berlin
CA PD Dr. med.	**Harder**	Hegau-Bodensee-Klinikum Singen	Virchowstr. 10	78224 Singen
CA Prof. Dr.	**Späth-Schwalbe**	Vivantes Klinikum Spandau	Neue Bergstraße 6	13585 Berlin
Dr. med.	**Asperger**	Krankenhaus St. Elisabeth und St. Barbara	Mauerstraße 5	06110 Halle (Saale)
CA Dr. med.	**Teschendorf**	St.- Josefs-Hospital Dortmund-Hörde	Wilhelm.Schmidt-Str. 4	44263 Dortmund
Prof. Dr. med.	**Wagner**	DONAUISAR Klinikum Deggendorf	Perlasberger Strasse 41	94469 Deggendorf
CA Prof. Dr.	**Kullmann**	Kliniken Nordoberpfalz AG Klinikum Weiden	Söllnerstraße 16	92637 Weiden

Dr. med.	**Römmele**	medius-Kliniken gGmbH, Klinik Nürtingen	Auf dem Säer 1	72622 Nürtingen
Prof. Dr. med.	**Denzlinger**	Marienhospital Stuttgart	Böheimstr. 37	70199 Stuttgart
OA Dr. med.	**Lindig**	Universitätsklinikum Jena Klinik für Innere Medizin II	Erlanger Allee 101	07740 Jena
Dr. med.	**Peveling genannt Reddemann**	Praxis des MVZ Med 360° Leverkusen	Am Gesundheitspark 2 +11	51375 Leverkusen
CA Dr. med.	**Kremers**	Hämatoonkologische Praxis im Caritas-Krankenhaus Lebach	Heeresstraße 49	66822 Lebach
Dr. med.	**Bremer**	St.-Franziskus-Hospital	Hohenzollernring 72	48145 Münster
Dr. med.	**Speidel**	Praxis Ärzteforum Hennigsdorf	Marwitzer Str. 91	16761 Hennigsdorf
Dr. med.	**Franz-Werner**	Onkologische Schwerpunktpraxis Dres. Franz-Werner/Feustel Speyer	Hilgardstr. 26	67346 Speyer
PD Dr. med.	**Schmittel**	Praxis MVZ Ärzteforum Seestraße	Seestr.64	13347 Berlin
OA Dr. med.	**Möller-Fassbender**	Lukas-Krankenhaus GmbH	Hindenburgstraße 56	32257 Bünde
Dr. med.	**Freier**	Gemeinschaftspraxis	Goslarsche Landstraße 19	31135 Hildesheim
Dr.med.	**Heider**	Klinikum Leverkusen gGmbH Akadem. Lehrkrankenhaus der Universität zu Köln	Am Gesundheitspark 11	51375 Leverkusen
Dr.med.	**Rubanov**	Praxis	Lohstraße 4	31785 Hameln
Dr. med.	**Freiberg-Richter**	Gemeinschaftspraxis	Arnoldstr. 18	01307 Dresden
CA Prof. Dr.	**Kleber**	Ostalb-Klinikum Aalen Akadem. Lehrkrankenhaus der Uni. Ulm	Im Kälblesrain 1	73430 Aalen
Prof. Dr. med.	**Lerch**	Universitätsklinikum Greifswald	Ferdinand-Sauerbruch-Straße	17475 Greifswald
Dr. med.	**Schulmann**	MVZ am Klinikum Arnsberg GmbH	Springufer 7	59755 Arnsberg
Prof. Dr. med.	**Hoffmann**	St. Marien- und St. Annastiftskrankenhaus	Salzburger Str. 15	67067 Ludwigshafen
Dr. med.	**Lück**	Wissenschaftskontor Nord GmbH & o. KG	Trelleborger Str. 10B	18107 Rostock-Lütten-Klien
Dr. med. (H)	**Winter**	Kaiserswerther Diakonie Florence-Nightingale-Krankenhaus	Kreuzbergstr. 79	40489 Düsseldorf
Dr. med.	**Wierecky**	Überörtliche Gemeinschaftspraxis für Innere Medizin	Hohe Weide 17b	20259 Hamburg
Dr. med.	**Aldaoud**	Gemeinschaftspraxis Hämatologie / Onkologie	Strümpelstrasse 41	04289 Leipzig
Dr. med.	**Hoffmeister**	Universitätsklinikum Leipzig AöR	Liebigstraße 20	04103 Leipzig
Prof. Dr. med.	**Trojan**	Klinikum der Wolfgang Goethe-Universität Frankfurt am Main	Theodor-Stern-Kai 7	60590 Frankfurt
Dr. med.	Tschechne	Praxis	Iltener Straße 46	31275 Lehrte
	Wierer	Städt. Klinikum Neuss, Luksakrankenhaus GmbH	Preussenstraße 84	41464 Neuss
Dr. med.	**Peuser**	Onkologische Praxis am Diakonissenhaus	Georg-Schwarz-Str. 53	04179 Leipzig
Dr. med.	**Hahn**	Dokusan Gesellschaft für medizinische Studien mbH & Co. KG	Wiescherstr. 20	44623 Herne

CA Dr.	**Geer**	Diakonie-Klinikum Schwäbisch Hall gGmbH	Diakoniestraße 10	74523 Schwäbisch Hall
Dr. med.	**Moeller**	Gemeinschaftspraxis Dr. Spohn, Dr. Möller	Mauerstr. 5	06110 Halle
CA Dr. med.	**König**	Katholisches Klinikum Ruhrgebiet Nord GmbH Marien-Hospital	Hervester Straße 57	45768 Marl
Prof. Dr. med.	**Gassmann**	St. Marienkrankenhaus Siegen gGmbH	Kampenstr. 51	57072 Siegen
Prof. Dr. med.	**Vogel**	Medizinische Hochschule Hannover	Carl-Neubergstr. 1	30625 Hannover
Dr. med.	**Triebkorn**	Asklepois Klinik Weißenfels	Naumburger Str. 76	06667 Weißenfels
Dr. med.	**Lorentz**	Internistische Gemeinschaftspraxis	Wilhelm-Leuschner-Str. 11-13	67547 Worms
OÄ Dr. med.	**Hering-Schubert**	St. Georg Klinikum Eisenach	Mühlhäuser Str. 94	99817 Eisenach
Dr. med.	**Uhlig**	Praxis	Schulstr. 1	04683 Naunhof
Dr. med.	**Papke**	Internistische Praxis	Rosa-Luxemburg-Straße 6	01844 Neustadt in Sachsen
Dr. med.	**Krummenerl**	Martha Maria Krankenhaus Halle-Dölau gGmbH	Röntgenstr. 1	06120 Halle / Saale
Dr. med.	**Kohl**	Ammerland Klinik GmbH, Westerstede Lehrkrankenhaus der Uni. Göttingen	Lange Str. 38	26655 Westerstede
Dr. med.	**Metz**	Hämatologisch - Onkologische Schwerpunktpraxis Göttingen	Nikolausberger Weg 36	37073 Göttingen
Prof. Dr. med.	**Decker**	Studienzentrum Onkologie Ravensburg	Elisabethenstraße 19	88212 Ravensburg
Dr. med.	**Pohl**	Städtisches Klinikum Solingen	Gotenstr. 1	42653 Solingen
Prof. Dr. med.	**Bernhard**	Klinikum Darmstadt GmbH	Grafenstr. 9	64283 Darmstadt
Dr. med.	**Schenk**	Krankenhaus Barmherzige Brüder Regensburg Akadem. Lehrk. der Uni. Regensburg	Prüfeninger Straße 86	93049 Regensburg
Dr.med.	**Buschmann**	Praxiskooperation Bonn-Euskirchen	Europaring 42	53123 Bonn
Dr. med.	**Stauch**	Praxis Dr. Stauch	Niederbronner Str. 2	96317 Kronach
Dr. med.	**Hennesser**	Vinzenz Pallotti Hospital GmbH Bensberg	Vinzenz-Pallotti-Straße 20 - 24	51429 Bergisch Gladbach
Dr. med.	**Kubin**	Klinikum Traunstein	Cuno-Niggl-Straße 3	83278 Traunstein
Dr. med.	**Puchtler**	RoMed Klinikum Rosenheim	Pettenkoferstr. 10	83022 Rosenheim
PD Dr. med.	**Schröder**	Praxis Onko-Log Mülheim GbR	Kettwigerstr. 62	45468 Mülheim an der Ruhr
Dr. med.	**Whitlock**	Zollernalb Klinikum gGmbH Balingen	Tübinger Str. 30	72336 Balingen
Prof. Dr. med.	**Wendtner**	Klinikum Schwabing	Kölner Platz 1	80804 München
Dr. med.	**Jacobs**	Medizinische Statistik Saarbrücken, GbR	Am Ludwigsberg 78	63113 Saarbrücken
Prof. Dr. med.	**Kanzler**	Leopoldina Krankenhaus der Stadt Schweinfurt	Gustav-Adolf-Str. 8	97422 Schweinfurt
Dr. med.	**Rauh**	Fachinternistische Gemeinschaftspraxis Dres. Luhrenberg, Höhmann-Riese, Rauh, Knittel, Schweickert	Ardeystr. 105	58452 Witten
Dr. med.	**Hielscher**	Klinikum Chemnitz	Flemmingstr. 2	09116 Chemnitz
Dr. med.	**Balleisen**	Johanniter-Krankenhaus Rheinhausen GmbH	Kreuzacker 1-7	47228 Duisburg-Rheinhausen
PD Dr. med.	**Schuch**	Hämatologisch-Onkologische Praxis Altona (HOPA)	Mörkenstr. 47	22767 Hamburg

Dr. med.	**Simon**	medius Kliniken gGmbH, medius Klinik Ostfildern-Ruit	Hedelfinger Str. 166	73760 Ostfildern
PD Dr. med.	**Zirlik**	Universitätsklinikum Freiburg	Hugstetter 55	79106 Freiburg
Dr. med.	**Luttenberger**	Klinikum Memmingen	Bismarckstr. 23	87700 Memmingen
Dr. med.	**Zander**	Uniklinik Köln	Kerpenerstr. 62	50937 Köln
Prof. Dr. med.	**Greeve**	St. Vincenz-Krankenhaus GmbH Paderborn	Am Busdorf 2	33098 Paderborn
Dr. med.	**Sargin**	St.-Marienhospital Lünen	Altstadtstr. 23	44534 Lünen
Prof. Dr. med.	**Ruhnke**	Paracelsus Klinik, Zentrum f. Tumordiagnostik u.- therapie	Am Natruper Holz 69	49076 Osnabrück
Dr. med.	**Suttmann**	Klinikum Dritter Orden München-Nymphenburg	Menziger Str. 44	80638 München
Dr. med.	**Koch**	St. Vinzenz Krankenhaus	Rottstr. 11	45711 Datteln
Dr. med.	**Schulz**	Onkologische Praxis	Mühlenstraße 41	55543 Bad Kreuznach
Dr. med.	**Ruffert**	Eps-Early Phase Solutions GmbH	Goethe-Str. 3b	07743 Jena
Dr. med.	**Ewald**	Klinikum Kulmbach	Albert-Schweitzer-Str. 10	95326 Kulmbach
Dr. med.	**Schmidt**	Gemeinschaftspraxis	Bäckerstraße 4	81241 München
Dr. med.	**Kojouharoff**	Onkologisches Studienzentrum Darmstadt	Landgraf-Georg-Str. 100	64283 Darmstadt
Prof. Dr. med.	**Meyer zum Büschenfelde**	Vincentius-Diakonissen-Kliniken gAG	Südendstr. 32	76137 Karlsruhe
Dr. med.	**Nischik**	Maria-Josef-Hospital	Lindenstr. 29	48268 Greven
Dr. med.	Hellwig	Maria-Josef-Hospital	Lindenstr. 29	48268 Greven
Dr. med.	**Abenhardt**	MVZ MOPS Elisenhof	Prielmayerstr. 1	80335 München
Dr. med.	**Egger**	Ortenau Klinikum Lahr-Ettenheim	Klostenstr. 19	77933 Lahr
PD Dr. med.	**Graf**	Universitätsklinikum Düsseldorf	Moorenstr. 5	40225 Düsseldorf
Dr. med.	**Kunst**	Onkologische Praxis Nienburg	Ziegelkampstr. 35	31582 Nienburg
Prof. Dr. med.	**Schmiegel**	Medizinische Universitätsklinik Knappschaftskrankenhaus	In der Schornau 23-25	44892 Bochum
Dr. med.	**Fronhoffs**	Zentrum für ambulante Hämatologie und Onkologie	Humperdinckstr. 10-14	53721 Siegburg
Dr. med.	**Baake**	Onkologische Praxis Pinneberg	Fahltskamp 74	25421 Pinneberg
Dr. med.	**Grunewald**	AMEOS Klinikum Aschersleben Kreisklinik Aschersleben-Straßfurt gGmbH	Eislebener Str. 7a	06449 Aschersleben
Prof. Dr. med.	**Kiani**	Klinikum Bayreuth GmbH	Preuschwitzer Str. 101	95445 Bayreuth
Dr. med.	**Tessen**	Gemeinschaftspraxis	Kösliner Str. 14	38642 Goslar
Dr. med.	**Göhler**	Onkozentrum in Dresden	Leipziger Str. 118	01127 Dresden
PD Dr. med.	**Al-Batran**	Krankenhaus Nordwest GmbH	Steinbacher Hohl 2-26	60488 Frankfurt/Main
Dr. med.	**Meiler**	MVZ Klinik Dr. Hancken GmbH	Harsefelder Str. 8	21680 Stade
Dr. med.	**Schwaner**	Onkologische Schwerpunktpraxis Kurfürstendamm	Kurfürstendamm 65	10707 Berlin
Dr. med.	**Ettrich**	Universitätsklinikum Ulm Zentrum für Innere Med.	Albert-Einstein-Allee	89081Ulm
Dr. med.	**Liersch**	Gemeinschaftspraxis	Steinfurter Str. 60b	48149 Münster
Prof. Dr. med.	**Graeven**	Kliniken Maria Hilf GmbH - Krankenhaus St. Franziskus	Viersenerstr. 450,	41063 Mönchengladbach
Dr. med.	**Beck**	GMS mbH	Wildstr. 11	41239 Mönchengladbach

PD Dr. med.	**Seipelt**	Onkologische Schwerpunktpraxis	Kronbergerstr. 36b	65812 Bad Soden
Dr. med.	**Schlichting**	Diakoniekrankenhaus gGmbH	Elise-Averdieck-Str. 17	27356 Rotenburg
Dr. med.	**Depenbusch**	Onkodok GmbH	Brunnenstr. 14	33332 Gütersloh
Prof. Dr. med.	**Hegewisch-Becker**	MVZ für Innere Medizin in Hamburg -Eppendorf	Eppendorfer Landstr. 42	20249 Hamburg
Dr. med.	**Müller**	Praxis	Annenstr. 11	26789 Leer
Dr. med.	**Winkelmann**	Paul Gerhardt Diakonie Krankenhaus und Pflege GmbH, Ev. Krankenhaus Paul Gerhardt Stift	Paul -Gerhard-Str. 42-45	06886 Lutherstadt-Wittenberg
PD Dr. med.	**Lüdde**	Universitätsklinikum Aachen	Pauwelsstrasse 30	52074 Aachen
Dr. med.	**Killing**	Klinikum Wetzlar-Braunfels	Forsthausstr. 1-3	35578 Wetzlar
Dr. med.	**Schulz**	Pich Frechen	Kölner Str. 9	50226 Frechen
Prof. Dr. med.	**Maschmeyer**	Klinikum Ernst von Bergmann	Charlottenstr. 72	14467 Potsdam
Dr. med.	**Krammer-Steiner**	Klinikum Südstadt Rostock	Südring 81	18059 Rostock
PD Dr. med.	**Flaßhove**	Krankenhaus Düren gGmbH	Roonstr. 30	52351 Düren

Certificate of Compliance Bevacizumab:

Certificate of Compliance
for Investigational Medicinal Products

Certificate of Release

Study / Project Name:	**Bevacizumab** / Temozolomid / Irinotecanhydrochlorid 3 H2O		
Study No:	**ML22011**		
EudraCT No.:	2009-013099-38		
Dosage form / content:	vials	GP Order no:	1000253499
Strength / Potency:	400 mg / 16 ml	Batch No.:	H0019B01
Quantity of packages:	251 boxes x 1 vial		
Date of issue:	11-May-2011		
Customer name and address:		Roche Pharma AG, Grenzach-Wyhlen, Germany	
Distributor name and address:		GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany	

Packaging by:

Packager name, Department / Address:	GP Grenzach Produktions GmbH , Grenzach-Wyhlen, Germany
Certificate of Packaging:	corresponds

Certified Components:

Ro-No.:	487-6646/F02	Batch No.:	H0019B01
Analysis No.:		27090355	
Manufacturer name or marketing authorization holder, Department / Address:		Roche Diagnostic GmbH, Sandhofer Straße, Mannheim, Germany	
Certificate of Manufacturing:		corresponds	

Use-by:	November 2012
Storage conditions:	Store at 2°-8°C. Protect from light. Do not freeze. Do not shake.
Use Restrictions:	Material for Germany

Approval of Competent Authorities:

Reference / Amendment No.:	1102/01
Issued by:	Paul-Ehrlich-Institut, Langen
Date of issue:	24.09.2010

Comments:	SAP no.: 19115138 CfC no.: 01187915

I hereby certify that this batch complies with the requirements of Art. 13.3 of Directive 2001/20/EC.
The batch has been released for use in clinical studies in the EU by the Qualified Person of the Quality Control and Assurance Department of Roche Pharma AG, Grenzach, Germany
(Manufacturing License No.: DE_BW_01_MIA_2010_0074/DE_BW_01_Roche).

Date of approval: 12. MAI. 2011

Approved by:

Roche Pharma AG
Dr. Jörg Simon Müller
Qualified Person
D-79639 Grenzach-Wyhlen

Record Reference No: 11100420 document-ref: spt027098/V1.0 Page 1 of 1

Certificate of Compliance
for Investigational Medicinal Products

Revised Version

Certificate of Release

Study / Project Name:	**Bevacizumab** / Capacetabine / Irinotecanhydrochlorid 3 H2O		
Study No:	**ML22011**		
EudraCT No.:	2009-013099-38	GP Order No:	1000037301
Dosage form / content:	vials		
Strength / Potency:	400 mg / 16 ml	Batch No.:	H0003B01
Quantity of packages:	50 boxes x 1 vial		
Date of issue:	14-Jun-2011		
Customer name and address:		Roche Pharma AG, Grenzach-Wyhlen, Germany	
Distributor name and address:		GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany	

Packaging by:	
Packager name, Department / Address:	GP Grenzach Produktions GmbH , Grenzach-Wyhlen, Germany
Certificate of Packaging:	corresponds

Certified Components:			
Ro-No.:	487-6646/F02	Batch No.:	H0003B01
Analysis No.:		27074985	
Manufacturer name or marketing authorization holder, Department / Address:		Roche Diagnostic GmbH, Sandhofer Straße, Mannheim, Germany	
Certificate of Manufacturing:		corresponds	

Use-by:	January 2011
Storage conditions:	Store at 2°-8°C. Protect from light. Do not freeze. Do not shake.
Use Restrictions:	Material for Germany

Approval of Competent Authorities:	
Reference / Amendment No.:	1102/01
Issued by:	Paul-Ehrlich-Institut, Langen
Date of issue:	24.09.2010

Comments:	SAP No: 19115138

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Date of approval: (Revised Version)
14. JUNI 2011

Approved by:

Roche Pharma AG
Dr. Ulrich Huth
Qualified Person
79639 Grenzach-Wyhlen

Roche

Certificate of Compliance
for Investigational Medicinal Products

Certificate of Release

Study / Project Name:	**Bevacizumab** / Temozolomid / Irinotecanhydrochlorid 3 H2O		
Study No:	**ML22011**		
EudraCT No.:	2009-013099-38	GP Order No.:	1000037301
Dosage form / content:	vials	Packaging Order No.:	1000037301
Strength / Potency:	400 mg / 16 ml	Batch No.:	H0003B01
Quantity of packages:	50 boxes x 1 vial		
Date of issue:	15-Dec-2010		
Customer name and address:		Roche Pharma AG, Grenzach-Wyhlen, Germany	
Distributor name and address:		GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany	

Packaging by:

Packager name, Department / Address:	GP Grenzach Produktions GmbH , Grenzach-Wyhlen, Germany
Certificate of Packaging:	corresponds

Certified Components:

Ro-No.:	487-6646/F02	Batch No.:	H0003B01
Analysis No.:		27074985	
Manufacturer name or marketing authorization holder, Department / Address:		Roche Diagnostic GmbH, Sandhofer Straße, Mannheim, Germany	
Certificate of Manufacturing:		corresponds	

Use-by:	January 2011
Storage conditions:	Store at 2°-8°C. Protect from light. Do not freeze. Do not shake.
Use Restrictions:	Material for Germany

Approval of Competent Authorities:

Reference / Amendment No.:	1102/01
Issued by:	Paul-Ehrlich-Institut, Langen
Date of issue:	24.09.2010

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Date of approval:

Approved by:

Roche Pharma AG

Invalid
Replaced by: 10025601
Reason: Capecitabine instead of
Projectname: Temozolomid
Date 14.06.2011 Signature
PTQP Release, Roche Grenzach

Certificate of Compliance
for Investigational Medicinal Products

Revised Version

Certificate of Release

Study / Project Name:	**Bevacizumab / Capacetabine / Irinotecanhydrochlorid 3 H2O**		
Study No:	**ML22011**		
EudraCT No.:	2009-013099-38	GP Order No:	1000037299
Dosage form / content:	vials		
Strength / Potency:	100 mg / 4 ml	Batch No.:	H0003B01
Quantity of packages:	50 boxes x 1 vial		
Date of issue:	14-Jun-2011		
Customer name and address:		Roche Pharma AG, Grenzach-Wyhlen, Germany	
Distributor name and address:		GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany	

Packaging by:	
Packager name, Department / Address:	GP Grenzach Produktions GmbH , Grenzach-Wyhlen, Germany
Certificate of Packaging:	corresponds

Certified Components:			
Ro-No.:	487-6646/F01	Batch No.:	H0003B01
Analysis No.:		27075761	
Manufacturer name or marketing authorization holder, Department / Address:		Roche Diagnostic GmbH, Sandhofer Straße, Mannheim, Germany	
Certificate of Manufacturing:		corresponds	

Use-by:	January 2011
Storage conditions:	Store at 2°-8°C. Protect from light. Do not freeze. Do not shake.
Use Restrictions:	Material for Germany

Approval of Competent Authorities:	
Reference / Amendment No.:	1102/01
Issued by:	Paul-Ehrlich-Institut, Langen
Date of issue:	24.09.2010

Comments:	SAP No: 19115141

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Date of approval: (Revised Version)

14 JUNI 2011

Approved by:

Roche Pharma AG
Dr. Ulrich Huth
Qualified Person
79639 Grenzach-Wyhlen

Certificate of Compliance
for Investigational Medicinal Products
Certificate of Release

Study / Project Name:	**Bevacizumab** / Temozolomid / Irinotecanhydrochlorid 3 H2O		
Study No:	**ML22011**		
EudraCT No.:	2009-013099-38	GP Order No.:	1000037299
Dosage form / content:	vials	Packaging Order No.:	1000037299
Strength / Potency:	100 mg / 4 ml	Batch No.:	H0003B01
Quantity of packages:	50 boxes x 1 vial		
Date of issue:	15-Dec-2010		
Customer name and address:		Roche Pharma AG, Grenzach-Wyhlen, Germany	
Distributor name and address:		GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany	

Packaging by:

Packager name, Department / Address:	GP Grenzach Produktions GmbH , Grenzach-Wyhlen, Germany
Certificate of Packaging:	corresponds

Certified Components:

Ro-No.:	487-6646/F01	Batch No.:	H0003B01
Analysis No.:		27075761	
Manufacturer name or marketing authorization holder, Department / Address:		Roche Diagnostic GmbH, Sandhofer Straße, Mannheim, Germany	
Certificate of Manufacturing:		corresponds	

Use-by:	January 2011
Storage conditions:	Store at 2°-8°C. Protect from light. Do not freeze. Do not shake.
Use Restrictions:	Material for Germany

Approval of Competent Authorities:

Reference / Amendment No.:	1102/01
Issued by:	Paul-Ehrlich-Institut, Langen
Date of issue:	24.09.2010

I hereby certify that this batch complies with the requirements of Art. 13.3 of Directive 2001/20/EC. The batch has been released for use in clinical studies in the EU by the Qualified Person of the Quality Control and Assurance Department of Roche Pharma AG, Grenzach, Germany (Manufacturing License No.: DE_BW_01_MIA_2010_0074/DE_BW_01_Roche).

Date of approval:

Approved by: O. Danielewski

Dr. Oliver Danielewski

Invalid
Replaced by: 10025601
Reason: Capecitabine instead of Temozolomid
Project name:
Date: 14.06.2011 Signature
PTQP Release, Roche Grenzach

Certificate of Compliance
for Investigational Medicinal Products

Revised Version

Certificate of Release

Study / Project Name:	**Bevacizumab** / Capecitabine / Irinotecanhydrochlorid 3 H2O		
Study No:	**ML22011**		
EudraCT No.:	2009-013099-38	GP Order No:	1000038459
Dosage form / content:	vials		
Strength / Potency:	400 mg / 16 ml	Batch No.:	H0015B03
Quantity of packages:	186 boxes x 1 vial		
Date of issue:	14-Jun-2011		
Customer name and address:		Roche Pharma AG, Grenzach-Wyhlen, Germany	
Distributor name and address:		GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany	

Packaging by:	
Packager name, Department / Address:	GP Grenzach Produktions GmbH , Grenzach-Wyhlen, Germany
Certificate of Packaging:	corresponds

Certified Components:			
Ro-No.:	487-6646/F02	Batch No.:	H0015B03
Analysis No.:		27085659	
Manufacturer name or marketing authorization holder, Department / Address:		Roche Diagnostic GmbH, Sandhofer Straße, Mannheim, Germany	
Certificate of Manufacturing:		corresponds	

Use-by:	May 2012
Storage conditions:	Store at 2°-8°C. Protect from light. Do not freeze. Do not shake.
Use Restrictions:	Material for Germany

Approval of Competent Authorities:	
Reference / Amendment No.:	1102/01
Issued by:	Paul-Ehrlich-Institut, Langen
Date of issue:	40445

Comments:	SAP No: 19115138

I hereby certify that this batch complies with the requirements of Art. 13.3 of Directive 2001/20/EC. The batch has been released for use in clinical studies in the EU by the Qualified Person of the Quality Control and Assurance Department of Roche Pharma AG, Grenzach, Germany (Manufacturing License No.: DE_BW_01_MIA_2011_0058/DE_BW_01_Roche Pharma).

Date of approval: (revised version)

14 JUNI 2011

Approved by:

Roche Pharma AG
Dr. Ulrich Huth
Qualified Person
79639 Grenzach-Wyhlen

Certificate of Compliance
for Investigational Medicinal Products

Certificate of Release

Study / Project Name:	**Bevacizumab** / Temozolomid / Irinotecanhydrochlorid 3 H2O		
Study No:	**ML22011**		
EudraCT No.:	2009-013099-38	GP Order No.:	1000038459
Dosage form / content:	vials	Packaging Order No.:	1000038459
Strength / Potency:	400 mg / 16 ml	Batch No.:	H0015B03
Quantity of packages:	186 boxes x 1 vial		
Date of issue:	15-Dec-2010		
Customer name and address:		Roche Pharma AG, Grenzach-Wyhlen, Germany	
Distributor name and address:		GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany	

Packaging by:

Packager name, Department / Address:	GP Grenzach Produktions GmbH , Grenzach-Wyhlen, Germany
Certificate of Packaging:	corresponds

Certified Components:

Ro-No.:	487-6646/F02	Batch No.:	H0015B03
Analysis No.:		27085659	
Manufacturer name or marketing authorization holder, Department / Address:		Roche Diagnostic GmbH, Sandhofer Straße, Mannheim, Germany	
Certificate of Manufacturing:		corresponds	

Use-by:	May 2012
Storage conditions:	Store at 2°-8°C. Protect from light. Do not freeze. Do not shake.
Use Restrictions:	Material for Germany

Approval of Competent Authorities:

Reference / Amendment No.:	1102/01
Issued by:	Paul-Ehrlich-Institut, Langen
Date of issue:	24.09.2010

I hereby certify that this batch complies with the requirements of Art. 13.3 of Directive 2001/20/EC. The batch has been released for use in clinical studies in the EU by the Qualified Person of the Quality Control and Assurance Department of Roche Pharma AG, Grenzach, Germany (Manufacturing License No.: DE_BW_01_MIA_2010_0074/DE_BW_01_Roche).

Date of approval:

Approved by:

Invalid
Replaced by: 1104434
Reason: Projectname changed to Capecitabine instead of Temozolomide
Date 14.06.2011 Signature
PTQP Release, Roche Grenzach

Certificate of Compliance
for Investigational Medicinal Products

Revised Version

Certificate of Release

Study / Project Name:	**Bevacizumab / Capacetabine / Irinotecanhydrochlorid 3 H2O**		
Study No:	**ML22011**		
EudraCT No.:	2009-013099-38	GP Order No:	1000038458
Dosage form / content:	vials		
Strength / Potency:	100 mg / 4 ml	Batch No.:	H0103B01
Quantity of packages:	186 boxes x 1 vial		
Date of issue:	14-Jun-2011		
Customer name and address:		Roche Pharma AG, Grenzach-Wyhlen, Germany	
Distributor name and address:		GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany	

Packaging by:			
Packager name, Department / Address:		GP Grenzach Produktions GmbH , Grenzach-Wyhlen, Germany	
Certificate of Packaging:		corresponds	
Certified Components:			
Ro-No.:	487-6646/F01	Batch No.:	H0103B01
Analysis No.:		27084208	
Manufacturer name or marketing authorization holder, Department / Address:		Roche Diagnostic GmbH, Sandhofer Straße, Mannheim, Germany	
Certificate of Manufacturing:		corresponds	
Use-by:		February 2012	
Storage conditions:		Store at 2°-8°C. Protect from light. Do not freeze. Do not shake.	
Use Restrictions:		Material for Germany	
Approval of Competent Authorities:			
Reference / Amendment No.:		1102/01	
Issued by:		Paul-Ehrlich-Institut, Langen	
Date of issue:		40445	
Comments:		SAP No: 1911514	

I hereby certify that this batch complies with the requirements of Art. 13.3 of Directive 2001/20/EC. The batch has been released for use in clinical studies in the EU by the Qualified Person of the Quality Control and Assurance Department of Roche Pharma AG, Grenzach, Germany (Manufacturing License No.: DE_BW_01_MIA_2011_0058/DE_BW_01_Roche Pharma).

Date of approval: 14 JUNI 2011
(Revised Version)

Approved by:

Roche Pharma AG
Dr. Ulrich Huth
Qualified Person
79639 Grenzach-Wyhlen

Certificate of Compliance
for Investigational Medicinal Products

Certificate of Release

Study / Project Name:	**Bevacizumab** / Temozolomid / Irinotecanhydrochlorid 3 H2O		
Study No:	**ML22011**		
EudraCT No.:	2009-013099-38	GP Order No.:	1000038458
Dosage form / content:	vials	Packaging Order No.:	1000038458
Strength / Potency:	100 mg / 4 ml	Batch No.:	H0103B01
Quantity of packages:	186 boxes x 1 vial		
Date of issue:	15-Dec-2010		
Customer name and address:		Roche Pharma AG, Grenzach-Wyhlen, Germany	
Distributor name and address:		GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany	

Packaging by:

Packager name, Department / Address:	GP Grenzach Produktions GmbH , Grenzach-Wyhlen, Germany
Certificate of Packaging:	corresponds

Certified Components:

Ro-No.:	487-6646/F01	Batch No.:	H0103B01
Analysis No.:		27084208	
Manufacturer name or marketing authorization holder, Department / Address:		Roche Diagnostic GmbH, Sandhofer Straße, Mannheim, Germany	
Certificate of Manufacturing:		corresponds	

Use-by:	February 2012
Storage conditions:	Store at 2°-8°C. Protect from light. Do not freeze. Do not shake.
Use Restrictions:	Material for Germany

Approval of Competent Authorities:

Reference / Amendment No.:	1102/01
Issued by:	Paul-Ehrlich-Institut, Langen
Date of issue:	24.09.2010

I hereby certify that this batch complies with the requirements of Art. 13.3 of Directive 2001/20/EC. The batch has been released for use in clinical studies in the EU by the Qualified Person of the Quality Control and Assurance Department of Roche Pharma AG, Grenzach, Germany (Manufacturing License No.: DE_BW_01_MIA_2010_0074/DE_BW_01_Roche).

Date of approval:

Approved by: O. Danielewski

Roche Pharma AG

Certificate of Compliance
for Investigational Medicinal Products

Certificate of Release

Study / Project Name:	**Bevacizumab / Temozolomid / Irinotecanhydrochlorid 3 H2O**		
Study No:	**ML22011**		
EudraCT No.:	2009-013099-38	GP Order No:	1000253515
Dosage form / content:	vials		
Strength / Potency:	400 mg / 16 ml	Batch No.:	H0105B01
Quantity of packages:	251 boxes x 1 vial		
Date of issue:	11-May-2011		
Customer name and address:		Roche Pharma AG, Grenzach-Wyhlen, Germany	
Distributor name and address:		GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany	

Packaging by:

Packager name, Department / Address:	GP Grenzach Produktions GmbH , Grenzach-Wyhlen, Germany
Certificate of Packaging:	corresponds

Certified Components:

Ro-No.:	487-8646/F01	Batch No.:	H0105B01
Analysis No.:		27085512	
Manufacturer name or marketing authorization holder, Department / Address:		**Roche Diagnostic GmbH, Sandhofer Straße, Mannheim, Germany**	
Certificate of Manufacturing:		corresponds	

Use-by:	May 2012
Storage conditions:	Store at 2°-8°C. Protect from light. Do not freeze. Do not shake.
Use Restrictions:	Material for Germany

Approval of Competent Authorities:

Reference / Amendment No.:	1102/01
Issued by:	Paul-Ehrlich-Institut, Langen
Date of issue:	24.09.2010
Comments:	SAP 19115141

Invalid
Replaced by: 11100411
Reason: false strength
Date: 12.05.2011 | Signature: S4
PTQP Release, Roche Grenzach

I hereby certify that this batch complies with the requirements of Art. 13.3 of Directive 2001/20/EC.
The batch has been released for use in clinical studies in the EU by the Qualified Person of the Quality Control and Assurance Department of Roche Pharma AG, Grenzach, Germany
(Manufacturing License No.: DE_BW_01_MIA_2010_0074/DE_BW_01_Roche).

Date of approval: 12. MAI. 2011

Approved by:

Roche Pharma AG
Dr. Jörg Simon Müller
Qualified Person
D-79639 Grenzach-Wyhlen

Certificate of Compliance
for Investigational Medicinal Products

Certificate of Release

Revised Version

Study / Project Name:	**Bevacizumab / Capacetabine / Irinotecanhydrochlorid 3 H2O**		
Study No:	**ML22011**		
EudraCT No.:	2009-013099-38	Process Order No:	1000253515
Dosage form / content:	vials	SAP Material No / SAP Batch ID:	1000253515
Strength / Potency:	100 mg / 4 ml	Batch No.:	H0105B01
Quantity of packages:	251 boxes x 1 vial		
Date of issue:	09-Jun-2011		
Customer name and address:		Roche Pharma AG, Grenzach-Wyhlen, Germany	
Distributor name and address:		GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany	

Packaging by:	
Packager name, Department / Address:	GP Grenzach Produktions GmbH , Grenzach-Wyhlen, Germany
Certificate of Packaging:	corresponds

Certified Components:			
Ro-No.:	487-6646/F01	Batch No.:	H0105B01
Analysis No.:		27085512	
Manufacturer name or marketing authorization holder, Department / Address:		Roche Diagnostic GmbH, Sandhofer Straße, Mannheim, Germany	
Certificate of Manufacturing:		corresponds	

Use-by:	May 2012
Storage conditions:	Store at 2°-8°C. Protect from light. Do not freeze. Do not shake.
Use Restrictions:	Material for Germany

Approval of Competent Authorities:	
Reference / Amendment No.:	1102/01
Issued by:	Paul-Ehrlich-Institut, Langen
Date of issue:	24.09.2010

Comments:	SAP19115141

I hereby certify that this batch complies with the requirements of Art. 13.3 of Directive 2001/20/EC. The batch has been released for use in clinical studies in the EU by the Qualified Person of the Quality Control and Assurance Department of Roche Pharma AG, Grenzach, Germany (Manufacturing License No.: DE_BW_01_MIA_2011_0058/DE_BW_01_Roche Pharma).

Date of approval (revised version): 14 JUNI 2011

Approved by:

Roche Pharma AG
Dr. Ulrich Huth
Qualified Person
79639 Grenzach-Wyhlen

Certificate of Compliance
for Investigational Medicinal Products

Roche

Certificate of Release

Study / Project Name:	**Bevacizumab** / Capacetabine / Irinotecanhydrochlorid 3 H2O		
Study No:	**ML22011**		
EudraCT No.:	2009-013099-38	Process Order No:	100300717
Dosage form / content:	vials	SAP Material No / SAP Batch ID:	100300717
Strength / Potency:	400 mg / 16 ml	Batch No.:	H0127B02
Quantity of packages:	300 boxes x 1 vial		
Date of issue:	06-Dec-2011		
Customer name and address:		Roche Pharma AG, Grenzach-Wyhlen, Germany	
Distributor name and address:		GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany	

Packaging by:

Packager name, Department / Address:	GP Grenzach Produktions GmbH , Grenzach-Wyhlen, Germany
Certificate of Packaging:	corresponds

Certified Components:

Ro-No.:	487-6846/F02	Batch No.:	H0127B02
Analysis No.:		27093267	
Manufacturer name or marketing authorization holder, Department / Address:		Roche Diagnostic GmbH, Sandhofer Straße, Mannheim, Germany	
Certificate of Manufacturing:		corresponds	

Use-by:	April 2013
Storage conditions:	Store at 2°-8°C. Protect from light. Do not freeze. Do not shake.
Use Restrictions:	**Material for Germany**

Approval of Competent Authorities:

Reference / Amendment No.:	1102/01
Issued by:	Paul-Ehrlich-Institut, Langen
Date of issue:	24.09.2010

Comments:	SAP No.: 19115138

I hereby certify that this batch complies with the requirements of Art. 13.3 of Directive 2001/20/EC. The batch has been released for use in clinical studies in the EU by the Qualified Person of the Quality Control and Assurance Department of Roche Pharma AG, Grenzach, Germany (Manufacturing License No.: DE_BW_01_MIA_2011_0058/DE_BW_01_Roche Pharma).

Date of approval: 06. DEZ. 2011

Approved by:

Roche Pharma AG
Dr. Oliver Dąbielewski
Qualified Person
D-79639 Grenzach-Wyhlen

Record Reference No: 11176790 document-ref: spt027098/V1.0 Page 1 of 1

Certificate of Compliance
for Investigational Medicinal Products

Certificate of Release

Study / Project Name:	**Bevacizumab / Capecitabine / Irinotecanhydrochlorid 3 H2O**		
Study No:	**ML22011**		
EudraCT No.:	2009-013099-38	GP Order No:	1000435155
Dosage form / content:	vials		
Strength / Potency:	400 mg / 16 ml	Batch No.:	B7100B12
Quantity of packages:	120 boxes x 1 vial		
Date of issue:	12-Mar-2013		
Customer name and address:		Roche Pharma AG, Grenzach-Wyhlen, Germany	
Distributor name and address:		GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany	

Packaging by:	
Packager name, Department / Address:	GP Grenzach Produktions GmbH , Grenzach-Wyhlen, Germany
Certificate of Packaging:	corresponds

Certified Components:			
Ro-No.:	487-6646/F02	Batch No.:	B7100B12
Analysis No.:		07457513	
Manufacturer name or marketing authorization holder, Department / Address:		Roche Diagnostic GmbH, Sandhofer Straße, Mannheim, Germany	
Certificate of Manufacturing:		corresponds	

Use-by:	April 2014
Storage conditions:	Store at 2°-8°C. Protect from light. Do not freeze. Do not shake.
Use Restrictions:	**Material for Germany**

Comments:	SAP No.: 19115138 CfC No.: 01265276

I hereby certify that this batch complies with the requirements of Art. 13.3 of Directive 2001/20/EC. The batch has been released for use in clinical studies in the EU by the Qualified Person of the Quality Control and Assurance Department of Roche Pharma AG, Grenzach, Germany (Manufacturing License No.: DE_BW_01_MIA_2011_0058/DE_BW_01_Roche Pharma).

Date of approval: 15 MRZ 2013

Approved by:

Roche Pharma AG
Dr. Oliver Dandlewski
Qualified Person
D-79639 Grenzach-Wyhlen