



HAL
open science

**Maintenance treatment with fluoropyrimidine plus
bevacizumab versus fluoropyrimidine alone after
induction chemotherapy for metastatic colorectal cancer:
The BEVAMAINT - PRODIGE 71 - (FFCD 1710)
phase III study**

Sylvain Manfredi, Anthony Turpin, David Malka, Emilie Barbier, Pierre
Laurent-Puig, Aziz Zaanani, Laeticia Dahan, Astrid Lièvre, Jean-Marc Phelip,
Pierre Michel, et al.

► **To cite this version:**

Sylvain Manfredi, Anthony Turpin, David Malka, Emilie Barbier, Pierre Laurent-Puig, et al.. Maintenance treatment with fluoropyrimidine plus bevacizumab versus fluoropyrimidine alone after induction chemotherapy for metastatic colorectal cancer: The BEVAMAINT - PRODIGE 71 - (FFCD 1710) phase III study. *Digestive and Liver Disease*, 2020, 52 (10), pp.1143-1147. 10.1016/j.dld.2020.06.034 . hal-04548048

HAL Id: hal-04548048

<https://hal.science/hal-04548048v1>

Submitted on 29 Nov 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Maintenance treatment with fluoropyrimidine plus bevacizumab versus fluoropyrimidine alone after induction chemotherapy for metastatic colorectal cancer: the BEVAMAIN - PRODIGE 71 - (FFCD 1710) phase III study.

Authors

Manfredi S, Turpin A, Malka D, Emilie B, Laurent-Puig P, Zaanan A, Dahan L, Lièvre A, Phelip J-M, Michel P, Hautefeuille V, Legoux J-L, Lepage C, Tougeron D, Aparicio T.

Background: Maintenance treatments with fluoropyrimidine alone or combined with bevacizumab after induction chemotherapy are two standard options in first-line metastatic colorectal cancer (mCRC). However, no trial has compared these two maintenance regimens.

Methods: BEVAMAIN is a multicenter, open-label, randomized phase III trial comparing fluoropyrimidine alone or plus bevacizumab as maintenance treatment after induction polychemotherapy in mCRC. The primary endpoint is the time-to-treatment failure (TTF), calculated from date of randomization to first radiological progression, death, start of a new chemotherapy regimen (different from induction or maintenance chemotherapy) or end of maintenance treatment without introduction of further chemotherapy. We expect a 2-month TTF improvement from 6 months in the monotherapy arm to 8 months in the combination arm (hazard ratio [HR], 0.75). Based on a two-sided α risk of 5% and a power of 80%, using Schoenfeld method, 379 events are required (planned enrolment, 400 patients). Patients with mCRC, whose disease is measurable according to RECIST 1.1 criteria and controlled (objective response or stable disease) – but remains unresectable – after 4 to 6 months of induction polychemotherapy (doublet or triplet chemotherapy with or without anti-EGFR or bevacizumab), and who have recovered from limiting adverse events of induction polychemotherapy are eligible for randomization. Randomization is stratified according to

center, response to induction chemotherapy (objective response vs stable disease), ECOG performance status (0-1 vs 2), maintenance fluoropyrimidine (5-fluorouracil vs capecitabine) and primary tumor status (resected vs not). Capecitabine or bolus and infusional 5-fluorouracil plus folinic acid (simplified LV5FU2 regimen) are both accepted for maintenance chemotherapy, at investigator's discretion. Clinical evaluation, tumor imaging, carcinoembryonic antigen and circulating tumor DNA dosages are planned at enrolment and every 9 weeks. The maintenance treatment will be discontinued in the event of unbearable toxicity, progression or patient refusal. After maintenance discontinuation, reintroduction of induction polychemotherapy is recommended; otherwise a second-line treatment is started. The enrolment has begun in January 2020.

Rationale and aims

The prognosis of patients with unresectable metastatic colorectal cancer (mCRC) has significantly improved with the advent of several combinations of chemotherapy and biologics (anti-EGFR, antiangiogenics). The duration of first-line induction chemotherapy is questioned because of limiting toxicities during long periods with a potential negative impact on patients' quality of life (QoL). The aims of maintenance treatment are to control tumor progression, avoid toxicity and maintain QoL. Maintenance chemotherapy after induction chemotherapy has become a standard of care in patients with unresectable mCRC, and the body of evidence may be summarized as follows: i) induction chemotherapy should last 4 to 6 months (1-6) ; ii) patients whose disease is controlled (objective response or stable disease) – but remains unresectable – after induction chemotherapy are eligible for maintenance therapy; iii) fluoropyrimidine monotherapy is effective as maintenance treatment (1); iv) bevacizumab alone does not improve PFS compared to no treatment (4) **but is non inferior to continuation of induction chemotherapy** (5); v) combination of bevacizumab with fluoropyrimidine

improves progression-free survival (PFS) compared to bevacizumab alone or no treatment, but not overall survival (OS) (2, 3); vi) combination of bevacizumab with fluoropyrimidine is an accepted option for maintenance treatment (6), although no trial to date has compared maintenance therapy with bevacizumab plus fluoropyrimidine versus fluoropyrimidine alone. As first-line therapy for mCRC, the combination of bevacizumab with fluoropyrimidine has demonstrated a PFS improvement compared to fluoropyrimidine alone, at the expense of increased toxicity in several studies (7, 8). There are some reasons to add bevacizumab to fluoropyrimidine during maintenance treatment: i) continuation of bevacizumab beyond first progression in mCRC improves OS (9), ii) a tumor flare might happen after antiangiogenic discontinuation; and iii) bevacizumab combined to chemotherapy is not associated with impaired QoL compared to chemotherapy alone in mCRC patients, even in the elderly (10). On the other hand, maintenance treatment with fluoropyrimidine alone: i) spares patients the specific toxicity of anti-angiogenic drugs, including potentially life-threatening adverse events (e.g. arterial thromboembolic events, gastrointestinal perforations); ii) is less costly; iii) if capecitabine-based, is a full-oral, convenient, outpatient regimen, allowing supervision by specialized nurses.

Although maintenance treatment is mandatory after oxaliplatin-based induction chemotherapy as cumulative neurotoxicity becomes limiting usually before disease progression, maintenance strategy is also used after irinotecan-based induction chemotherapy or triplet chemotherapy (4, 11). **Data on optimum duration of induction therapy with anti-EGFR and data on maintenance therapy after induction therapy with anti-EGFR are scarce (5), we have choose to include the induction therapy with anti-EGFR with the same 4-6 months duration usually used in induction therapy without anti-EGFR.** Also, the impact of bevacizumab-based maintenance therapy after anti-EGFR-containing induction chemotherapy is not known. For these reasons, we designed the BEVAMAIN T trial, in which we enroll patients after

induction doublet or triplet chemotherapy with oxaliplatin and/or irinotecan, with or without anti-EGFR or anti-VEGF monoclonal antibody.

Study design

BEVAMAINT-PRODIGE 71-FFCD 1710 is a multicenter, open-label, randomized, phase III cooperative trial of PRODIGE French intergroup (FFCD, UNICANCER GI and GERCOR networks) comparing maintenance therapy with fluoropyrimidine and bevacizumab to fluoropyrimidine alone after first-line induction chemotherapy for unresectable mCRC. The trial has started in January 2020. The theoretical end of recruitment is June 2022. The primary endpoint analysis is planned in September 2023.

Patient eligibility criteria

Inclusion criteria are: histologically confirmed CRC with synchronous or metachronous unresectable metastases; measurable disease before the induction treatment according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1); unresectable disease according to local multidisciplinary team meeting after induction chemotherapy; ECOG performance status ≤ 2 ; disease control (complete response, partial response or stable disease) after 4-6 months of first-line induction chemotherapy with doublet (fluoropyrimidine + irinotecan or oxaliplatin) or triplet (fluoropyrimidine + irinotecan + oxaliplatin) +/- targeted therapy (cetuximab, panitumumab, bevacizumab); hepatic arterial infusion (HAI) oxaliplatin is allowed; life expectancy > 3 months; age ≥ 18 years; patient at least 4 weeks from any major surgery; total bilirubin $< 25 \mu\text{mol/L}$; aminotransferases < 3 times the upper limit of normal values (ULN) (< 5 ULN in case of liver metastasis); prothrombin rate $> 60\%$; alkaline phosphatases < 2.5 ULN (< 5 ULN in case of liver metastasis); neutrophils $> 1500/\text{mm}^3$; platelets $> 100\,000/\text{mm}^3$; hemoglobin ≥ 9 g/dL; creatinine clearance > 30 ml/min (MDRD) (for

creatinine clearance comprised between 30 and 50 ml/min dose adjustment is recommended for capecitabine); proteinuria $\leq 2+$ (dipstick urinalysis) (if $> 2+$, proteinuria must be $\leq 1\text{g}/24\text{h}$); recovery from limiting toxicity from induction chemotherapy; negative urinary or serum pregnancy test for pre-menopausal female patients; male and female patients of childbearing potential agree to use a highly effective contraceptive method; affiliation to a health insurance system; and written informed consent.

Non-inclusion criteria are: curative-intent (R0/R1) resection of metastases after induction chemotherapy; known brain or leptomeningeal metastases; other concomitant or previous malignancy (except adequately treated in situ carcinoma with complete remission for > 5 years); history of hand-foot syndrome of grade > 1 during previous fluoropyrimidine-based chemotherapy; myocardial infarction < 6 months; severe coronary disease or severe cardiac dysfunction; uncontrolled hypertension (defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg), history of hypertensive crisis or hypertensive encephalopathy; pregnancy or breast-feeding; treatment with sorivudine or analogs (brivudine), phenytoin or analogs; partial or complete dihydropyrimidine deshydrogenase deficiency (uracilemia ≥ 16 ng/mL); peptic ulcer not healed after treatment; intestinal perforation or intestinal fistula not resolved; previous or active gastrointestinal bleeding; thromboembolic event and/or history of thromboembolic event; any contraindication to bevacizumab or fluoropyrimidine; severe hepatic insufficiency (Child-Pugh B or C); and any condition that, according to investigator's opinion, may preclude patient's follow-up.

Randomization

Patients will be randomized after induction chemotherapy in a 1:1 ratio using the minimization technique. Randomization will be stratified based on: center, response (complete or partial response vs stabilization), performance status (0-1 vs 2), primary tumor

status (resected vs no) and maintenance fluoropyrimidine (simplified LV5FU2 regimen vs capecitabine day (D)1 to D14 vs continuous treatment with half-dose capecitabine). The tumor evaluation performed after induction chemotherapy will be used as baseline.

Study treatments

In the experimental arm, fluoropyrimidine plus bevacizumab (Arm B), three options are allowed (Figure 1):

- Option B1: Capecitabine 1250 mg/m² twice daily (i.e. 2500 mg/m²/d) D1 to D14 plus bevacizumab 7.5 mg/kg i.v. at D1, every 3 weeks. For frail patients, capecitabine dose could be reduced to 1000 mg/m² twice daily (2000 mg/m²/d);
- Option B2: Capecitabine 625 mg/m² twice daily (i.e. 1250 mg/m²/d) D1 to D21 plus bevacizumab 7.5 mg/kg i.v. at D1, every 3 weeks;
- Option B3: simplified LV5FU2 (L-folinic acid 200 mg/m² or DL-folinic acid 400 mg/m² i.v. during 2h, followed by 5-FU i.v. bolus 400 mg/m² then 2400 mg/m² during 46h at D1 plus + D1 bevacizumab 5 mg/kg i.v. at D1, every 2 weeks.

In the control arm (Arm A), the same three options (A1, A2, A3) are allowed, without bevacizumab. In both arms, treatment is administered until radiological or clinical progression, patient's refusal, unacceptable toxicity or investigator's decision. If progression occurs during maintenance therapy, induction chemotherapy can be reintroduced at the investigator's discretion. All toxicities requiring dose adjustments will be evaluated according to the NCI-CTC v4.0 scale and managed as usually recommended for 5FU, capecitabine and bevacizumab.

Trial objectives and endpoints

The main objective of the BEVAMAIN phase III trial is to compare efficacy of maintenance therapy with bevacizumab plus fluoropyrimidine versus fluoropyrimidine alone after induction chemotherapy. The primary endpoint is the time-to-treatment failure (TTF), calculated from the date of randomization (after the end of induction chemotherapy) to first radiological or clinical progression (according to RECIST 1.1) with or without further chemotherapy, death or end of maintenance treatment without further chemotherapy for any reason. Patients alive with no radiological progression and still under maintenance treatment will be censored at the date of last news. The secondary endpoints are progression-free survival (PFS1), defined as the time between randomization and the first radiological/clinical progression or death (whatever occurs first); PFS2, defined as the time between the end of maintenance treatment and radiological progression or death whatever the cause. Patients alive and without progression will be censored at the date of the last news. PFS1 and PFS2 will be calculated according to investigator's assessment and independent centralized review (RECIST V1.1); overall survival (OS); toxicity according to NCI-CTC v4.0; and quality of life according to QLQ-C30 questionnaire.

Monitoring of the patients

The inclusion workup, conducted within the 14 days before randomization (except for the morphological examinations which may be performed during the 3 weeks before randomization), includes clinical examination (weight, height and body surface area, blood pressure, pulse, temperature, ECOG performance status); complete blood cell count, coagulation tests, liver enzymes, albumin, creatinine, serum electrolytes, CA 19-9, CEA, dipstick urinalysis, pregnancy test if women of childbearing, and dihydropyrimidine deshydrogenase testing; tumor *RAS*, *BRAF* and mismatch repair status; electrocardiogram; thoraco-abdominal-pelvic computed tomography (CT) scan (or abdominal magnetic

resonance imaging + thoracic CT scan without injection if injected CT-scan contraindicated); and QLQ-C30 quality-of-life questionnaire. For patients participating in the ancillary optional biological study of circulating tumor DNA, two cell-free DNA tubes of blood are taken, one before the first treatment course and the other just before the third capecitabine cycle or the fourth simplified LV5FU2 cycle.

During the maintenance treatment, patients will be evaluated for safety before each cycle. Evaluations every 9 weeks include clinical examination, biological tests, quality of life questionnaires and the same morphological exams performed at the initial evaluation.

Follow-up after discontinuation of the treatment includes clinical examination and biological tests within 30 days after treatment stop. After radiological progression, patients are followed according to the local practice until death but at least every 3 months. Complementary examinations are left at the investigator's decision. The subsequent treatments received will be registered. The date of tumor progression after reintroduction of induction therapy or second-line therapy and the date of death will be recorded.

Calculation of sample size and statistical methods

The statistical hypotheses are: H0: The median TTF is not different between the two arms; H1: a difference of 2 months in the median TTF is expected in favor of arm B (fluoropyrimidine plus bevacizumab) with a median TTF of 8 months, compared to 6 months in arm A (fluoropyrimidine alone; hazard ratio=0.75). Based on a two-sided α risk of 5% and a power of 80%, using Schoenfeld method, 379 events are required. With a follow-up of 36 months, a recruitment rate of 12 patients per month and taking into account 5% of patients lost to follow-up, 400 patients have to be enrolled (200 patients/arm). All randomized patients, whatever their eligibility and whatever treatment they have received, will be analyzed in the treatment arm allocated at randomization in an intention-to-treat (ITT)

population. The safety population (SP) is defined as ITT patients who have received at least one dose of treatment and will be used to evaluate toxicity.

All the baseline characteristics will be described in the overall population and by treatment arm. The quantitative variables will be described by the usual statistics as means (with standard deviation), medians (with interval interquartiles) and minimum-maximum. The qualitative variables will be described using patient numbers and percentages. Comparisons between the two arms will be done using Student t test, Wilcoxon's test (depending on the quantitative variable distribution), Chi² test or Fisher Exact test for qualitative variables. For survival analyses (TTF, OS, PFS1, PFS2), the Kaplan-Meier method will be used to estimate medians, and curves will be plotted. The medians and the rates at different times will be described with their 95% confidence intervals. The two arms will be compared using the log-rank test. Hazard ratios will be calculated using Cox models. The median follow-up time will be calculated using the "reverse Kaplan-Meier" method. Adverse events (toxicity events) will be described for each treatment arm, by number of patients within each SOCs (System Organ Classes). The worst severity grade observed for each SOC in a given patient will be retained. Adverse events will also be described by grouping the maximum grade 1-2 versus 3-4-5.

Quality of life will be evaluated using the EORTC QLQ-C30 questionnaires. The time until definitive deterioration of the global health score, defined as the time between the date of randomization and the date of death or date of first deterioration by more than five points on the global health scale in comparison with the better score during the follow-up, will be calculated. Patients alive without deterioration will be censored at date of last news.

Pre-planned analyses of the primary and secondary endpoints for major clinical baseline data (gender, age, sidedness, resection or not of primary tumor, response or stabilization after induction chemotherapy, type of induction chemotherapy, CEA level, leucocyte count, platelet count, performance status, *BRAF* and *RAS* status) will be also performed.

Administrative and ethical considerations

The trial sponsor is the FFCD (Fédération Francophone de Cancérologie Digestive). The trial is registered under the EudraCT number 2019-001875-35. This trial was authorized by the French national health authority, the Agence Nationale de Sécurité du Médicament (ANSM), on September 13, 2019. The trial is registered on the clinicaltrials.gov website with the number NCT04188145. This trial received approval from an Institutional Review Board (IRB), Comité de Protection des Personnes SUD OUEST ET OUTRE MER on November 6, 2019.

This trial will be conducted in accordance with current French law, with the ethical principles of the Helsinki Declaration of 1964 and its subsequent revisions, with Good Clinical Practice of the International Conference on Harmonization (ICH–E6, 17/07/96), with European directive 2001/20/EC on the conduct of clinical trials, with the Huriet Act as amended (20/12/88) on the protection of persons participating in biomedical research, and with the provisions laid down by the CNIL, the French data protection agency (Act no. 94-548 of 01/07/94 completing Act no. 78-17 of 06/01/78) and the European Regulation 2016/679 of 27 April 2016. In accordance with the recommendations of the French cancer action plan (measure 5.1), this document was submitted to the Patient Advisory Board for Clinical Research of the French League Against Cancer.

Ancillary studies

Blood and tumor samples will be collected in all patients who consent to translational research projects in order to identify predictive markers of treatment efficacy, including the sequential assessment of ctDNA. Increased ctDNA may predict tumor progression earlier than morphologic or clinical examination. To date, there are no data on the dynamic evolution of

ctDNA in patients during maintenance treatment. Therefore, ctDNA represents a marker of tumor burden which is easily detectable and relevant to analyze in the BEVAMAINT trial.

Formalin-fixed, paraffin-embedded tumor blocks will be used to analyze potential molecular markers.

Conflict of interest

TA: Honoraria: Roche, Servier, Amgen, Bioven, Sanofi, Ipsen ; Travel : Roche, Bayer

JLL: Personal Fees: Novartis, Keocyt, Pfizer, Servier. Grant: Sanofi. Non-Financial support: Ipsen, Novartis, Merck Serono, Servier, Keocyt.

JMP - Honoraria: travel and hospitality : Merck, Roche, Amgen, Bayer, Sanofi, Servier ; Grant: Roche, Merck

AL: honoraria for lectures/ consulting/advisory relationship from AAA, Amgen, Bayer, BMS, Celgene, HaliuDx, Incyte, Ipsen, Lilly, Merck, Novartis, Pierre Fabre, Roche, Sandoz and Servier; travel support from AAA, Bayer, Ipsen, Merck, Novartis, Pfizer, Roche and Servier; research funding from Novartis, Integragen, Incyte

VH : honoraria for lectures / consulting / advisory relationship from AAA, Amgen, Ipsen, Merck, Novartis and Servier; Travel support from AAA, Amgen, Bayer, Ipsen, Novartis, Pfizer

AT has served in a consulting/advisory role and or received honoraria for Amgen, Merck, Servier, Mylan and has received travel, accommodations, and expenses from Astra-Zeneca, Pfizer, Sanofi

DT has served in a consulting/advisory role and or received honoraria for MSD, BMS, Amgen, Merck, Servier, Roche, Astra-Zeneca, and has received travel, accommodations, and expenses from Sanofi, Roche, Servier, MSD

AZ Funding: Amgen, Roche / Advisory board: Baxter, Merck Serono, MSD, Servier, Sanofi, Lilly / Honoraria: Baxter, Roche, Merck Serono, MSD, Amgen, Servier, Sanofi, Lilly / Travel: Amgen, Merck, Roche, Servier

PLP : Personal Fees: Servier, Sanofi, Merck Serono, MSD, Astrazeneca, Amgen, Biocartis, Roche, BMS

SM : travel and hospitality: Sirtex Medical Europe GmbH, NOVARTIS PHARMA SAS, MSD France, JANSSEN-CILAG, Lilly France SAS, AMGEN SAS, ROCHE SAS, IPSEN PHARMA, ASTRAZENECA. Funding: Lilly France SAS.

DM: Honoraria: Roche, Amgen, Bayer AG, Merck Serono, Servier, Sanofi

PM: Consulting or Advisory Role: Roche and Sanofi .

LD: personal grants for Clinical research for Ipsen, Lilly, MSD and Sanofi ; for Payment for lectures and consultancy for Amgen, Baxalta, Celgene, Lilly, Merck, Sanofi and Roche ; travel grants from Celgene, Ipsen and Sanofi.

Financial support

This trial was supported by the French National Cancer Institute (INCa: PHRC-K 2018 program) and sponsored by the University Hospital of Dijon.

References

1. Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer--a GERCOR study. *J Clin Oncol* 2006; 24: 394-400.
2. Hegewisch-Becker S, Graeven U, Lerchenmuller CA, et al. Maintenance strategies after first-line oxaliplatin plus fluoropyrimidine plus bevacizumab for patients with metastatic colorectal cancer (AIO 0207): a randomised, non-inferiority, open-label, phase 3 trial. *Lancet Oncol* 2015; 16: 1355-69.
3. Simkens LH, van Tinteren H, May A, et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. *Lancet* 2015; 385: 1843-52.
4. Aparicio T, Ghiringhelli F, Boige V, et al. Final results of PRODIGE 9, a randomized phase III comparing no treatment to bevacizumab maintenance during chemotherapy-free intervals in metastatic colorectal cancer. *J Clin Oncol* 2018; 36: 674-681.
5. Díaz-Rubio E, Gómez-España A, Massutí B, et al. Spanish Cooperative Group for the Treatment of Digestive Tumors. First-line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: the phase III MACRO TTD study. *Oncologist*. 2012;17(1):15-25.
6. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016; 27: 1386-422.
7. Kabbinavar FF, Schulz J, McCleod M, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. *J Clin Oncol* 2005; 23: 3697-3705.
8. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013; 14: 1077-1085.
9. Bennouna J, Sastre J, Arnold D et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol* 2013; 14: 29-37.
10. Aparicio T, Bouché O, Francois E, et al. Geriatric analysis from PRODIGE 20 randomized phase II trial evaluating bevacizumab + chemotherapy versus chemotherapy alone in older patients with untreated metastatic colorectal cancer. *Eur J Cancer* 2018; 97: 16-24.
11. Koeberle D, Betticher DC, von Moos R, et al. Bevacizumab continuation versus no continuation after first-line chemotherapy plus bevacizumab in patients with metastatic colorectal cancer: a randomized phase III non-inferiority trial (SAKK 41/06). *Ann Oncol* 2015; 26: 709-714.

Fig 1: study design

