SYNOPSIS

Title	A randomized trial investigating the role of FOLFOX-4 or XELOX (3 versus 6 months) regimen duration and bevacizumab as adjuvant therapy for patients with stage II/III colon cancer
Sponsor	Fondazione GISCAD per la Ricerca sui Tumori
Clinical Phase	III
Objectives	
Primary	To assess whether a 3-month (6 cycles) FOLFOX-4 treatment or 12-week (4 cycles) XELOX treatment is at least not inferior to a 6-month (12 cycles) FOLFOX-4 treatment or 24-week (8 cycles) XELOX treatment in terms of RFS in patients with radically resected stage II/III colon cancer To assess whether the combination of BEV and FOLFOX-4 is superior to FOLFOX-4 alone in terms of RFS in patients with radically resected high-risk stage III (T4, N+, M0, or *any* T, N2, M0) colon cancer
Secondary	To assess whether a 3-month (6 cycles) FOLFOX-4 treatment or 12-week (4 cycles) XELOX treatment is at least not inferior to a 6-month (12 cycles) FOLFOX-4 treatment or 24-week (8 cycles) XELOX treatment in terms of OS in patients with radically resected stage II/III colon cancer To assess whether the combination of BEV and FOLFOX-4 is superior to FOLFOX-4 alone in terms of OS in patients with radically resected high-risk stage III (T4, N+, M0, or any T, N2, M0) colon cancer To evaluate the safety profiles of the treatment groups
Study design	This project consists of two independent, following specific eligibility criteria and different randomisation schemes studies, later on called **DURATION study** and **BEV study**. Once randomised in the duration study, patients fulfilling eligibility criteria for BEV study may also be randomized to receive BEV or no BEV, in addition to FOLFOX-4 chemotherapy only**.** As both are open label studies, there will be no blinding of treatment assignment.
DURATION study	Open-label, randomised, phase III, multicentre, study designed to optimize FOLFOX-4/XELOX treatment duration, evaluating the efficacy and safety of a 3-month FOLFOX-4 treatment or 12 week XELOX treatment vs. a 6-month FOLFOX-4 treatment or 24 week XELOX treatment as adjuvant chemotherapy in patients with radically resected stage II/III colon cancer. The study regimen includes: **Arm A**: (3-month FOLFOX-4): OXA, and 5-FU/LV or (12-week XELOX): OXA and CAPE **Arm B**: (6-month FOLFOX-4): OXA, and 5-FU/LV or (24-week XELOX): OXA and CAPE FOLFOX-4 chemotherapy will be administered either for 3 months for a total of 6 planned cycles (Arm A) or for 6 months for a total of 12 cycles (Arm B). XELOX chemotherapy will be administered either for 12 weeks for a total of 4 planned cycles (Arm A) or for 24 weeks for a total of 8 cycles (Arm B). A randomisation ratio of 1 "3-month FOLFOX-4 or 12-week XELOX" : 1 "6-month FOLFOX-4 or 24-week XELOX" will be applied.
BEV study	In the subgroup of patients with high-risk stage III (T4, N+, M0, or any T, N2,

	M0) colon carcinoma which the FOLFOX-4 treatment has been already chosen , a 2x2 factorial design can be applied, assessing the benefit of the addition of BEV to the FOLFOX-4 regimen. Therefore in these patients, a second randomization may be done (plus or minus BEV), generating the following 4 arms (A and B are identical to the A and B arms in the DURATION study): **Arm A**: 3-month FOLFOX-4 **Arm B**: 6-month FOLFOX-4 **Arm C**: FOLFOX-4 for 3 months +BEV for 6 months **Arm D**: FOLFOX-4 for 6 months + BEV for 6 months In arm C and D, BEV will be given for 6 months for a total of 12 cycles independently from the duration of chemotherapy. A randomisation ratio of 1 BEV: 1 follow-up will be applied. In case of a confirmed recurrence/appearance of new colon cancer patients will be followed for survival until the end of study follow-up period. Follow-up will be continued until the achievement of the required number of events (see also Length of study). During the course of the trial, an independent Data and Safety Monitoring Board (DSMB) will advise the Steering Committee on efficacy and safety aspects of the study.
Number of patients	2860-4100 (depending on case-mix of patients) in the DURATION study. 430-620 (depending on case-mix of patients) in the BEV study
Target population	Patients who have undergone surgery for colon cancer, defined as a tumor location ≥12 cm from the anal verge by endoscopy and/or above the peritoneal reflection at surgery, without gross or microscopic evidence of residual disease after surgery with curative intent.
Inclusion criteria	– Histologically confirmed AJCC/UICC high-risk stage II or stage III colon cancer . High-risk stage III patients (T4, N+, M0, or any T, N2, M0) may also be further randomized in the BEV study (plus or minus BEV) – Stage II patients have to be considered at high-risk if they fulfill ≥1 of the following criteria: ▪ T4 tumours, ▪ grade ≥3, ▪ clinical presentation with bowel obstruction or perforation, ▪ histological signs of vascular or lymphatic or perineural invasion, ▪ <12 nodes examined – Age ≥18 years – Curative surgery no less than 3 (4 in the BEV study) and no more than 10 weeks prior to randomization – ECOG performance Status (ECOG-PS) ≤1 – Signed written informed consent obtained prior to any study specific procedures
Exclusion criteria	– Macroscopic or microscopic evidence of residual tumor (R1 or R2 resections). Patients should never have had any evidence of metastatic disease (including presence of tumor cells in the ascites). The isolated finding of cytokeratin positive cells in the bone marrow is not considered evidence of metastatic

	disease – Previous anti-angiogenic treatment for any malignancy; cytotoxic chemotherapy, radiotherapy or immunotherapy for colon cancer – Other malignancies within the last 5 years (other than curatively treated basal cell carcinoma of the skin and/or in situ carcinoma of the cervix) – Lactating women – Fertile women (<2 years after last menstruation) and men of childbearing potential not willing to use effective means of contraception – History of clinically relevant psychiatric disability , precluding informed consent – Clinically relevant cardiovascular disease – Patients with known allergy to Chinese hamster ovary cell proteins or other recombinant human or humanized antibodies or to any excipients of BEV formulation, or to any other components of the study drugs (***only for the BEV study***) – History or presence of other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or patient at high risk from treatment complications – Evidence of bleeding diathesis or coagulopathy – Current or recent (within 10 days prior to study treatment start) use of full-dose oral or parenteral anticoagulants or thrombolytic agent for therapeutic purposes – Severe renal impairment (only for the capecitabine use) – Chronic, daily treatment with high-dose aspirin (>325 mg/day) or clopidogrel (>75 mg/day) – Current or recent (within the 28 days prior to randomization) treatment with another investigational drug or participation in another investigational study
Length of study	This is an event driven study. The study will continue until approximately 1270 and 390 events have occurred in patients enrolled in the DURATION study and BEV study, respectively. In order to achieve this targeted number of events in the DURATION study, it will be necessary to randomise 2860-4100 patients, based on the observed case-mix of the patients. It is expected that approximately 60% of the enrolled patients will be treated with FOLFOX-4 treatment and that high-risk (T4, N+, M0, or any T, N2, M0) stage III patients will be about 25% of the total sample, therefore about 430-620 patients should be considered for the inclusion in the BEV study, assuring the required number of patients. The total enrollment period is expected to be of about 4 years for both studies and the statistical analyses are expected to be approximately 7 years after the beginning of randomisation.
Treatment regimens	The treatments will consist of: – 3 or 6 months of FOLFOX-4 (12 or 24 weeks of XELOX) in the DURATION study – FOLFOX-4 (3 or 6 months) plus or minus a fixed 6-month period of BEV treatment in the BEV study. FOLFOX-4 treatment **Day 1**: OXA, 85 mg/m^2 administered as intravenous infusion over 2 hours in

	250 mL dextrose 5% or sterile water for injection concurrently (via a Y-connector) with LV, 100 mg/m^2 administered as intravenous infusion over 2 hours, in 250 mL dextrose 5%, or sterile water for injection followed by 5-FU, 400 mg/m^2 administered as a bolus injection (intravenous push administered by hand in approximately 2 minutes), followed by 5-FU, 600 mg/m^2 administered as a intravenous infusion over 22 hours. **Day 2**: LV, 100 mg/m^2 administered as intravenous infusion over 2 hours, in 250 mL dextrose 5%, followed by 5-FU, 400 mg/m^2 administered as a bolus injection (intravenous push administered by hand), followed by 5-FU, 600 mg/m^2 administered as a intravenous infusion over 22 hours. XELOX treatment DAY 1: - OXA 130 mg/m^2 administered as intravenous infusion over 2 hours in 250 mL dextrose 5% - CAPE 1000 mg/m^2 administrated per os twice daily DAY 2-14 - CAPE 1000 mg/m^2 os twice daily CAPE will be administered and labelled according to local practice. Patients should be advised to take CAPE tablets twice daily, morning and evening, with water within 30 minutes after a meal. Cycles are to be repeated every 21 days for atotal of either 4 cycles in Arm A or 8 cycles in Arm B. Bevacizumab will be administered at the dose of 5 mg/kg as an intravenous infusion over 30 (±10) – 90 (±15) minutes prior to OXA on day 1 only of a two week cycle of FOLFOX-4 treatment. BEV will be administered initially over 90 (±15) minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60 (±10) minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes.
Assessment	
Efficacy	*Primary:* relapse free survival, defined as recurrence of colon cancer and all treatment related deaths or a death from other reasons. Second primary colorectal cancer and other primary cancer will be ignored, and loss to follow-up will be censored. *Secondary:* Overall survival
Safety	– Toxicity, graded according to the NCI-CTAE version 3.0 – Frequency and nature of adverse events (AEs) as well as serious adverse events (SAEs) – Total cumulative dose, received versus planned dose – Incidence and timing of dose reductions and/or modifications of time – Premature withdrawals During the course of the trial, an independent Data and Safety Monitoring Board (DSMB) will advise the Steering Committee on efficacy and safety aspects of the study.
Patient assignment	The DURATION study and the BEV study are independent, following specific eligibility criteria and different randomisation schemes. Once randomised in the

	DURATION study, patients fulfilling eligibility criteria for BEV study may also undergo a further randomisation to receive BEV or no BEV, in addition to FOLFOX-4 chemotherapy. As both are open label studies, there will be no blinding of treatment assignment. In the DURATION study, allocation to treatment will be centrally done with 1:1 ratio using a block design randomization procedure stratified by center and AJCC/UICC stage [high-risk stage II vs. stage III], while in the BEV study, a randomisation ratio of 1 BEV : 1 follow-up will be applied, using a block design randomization procedure stratified by center and duration of FOLFOX-4 treatment (3-months vs. 6 months). Access to random system will be allowed by phone or via web.
Statistical methods	DURATION study Since this is a non-inferiority trial, efficacy analyses will be performed on per-protocol (PP) population. PP population is defined as all randomised patients, who won't have major violations of eligibility criteria as well as of study conduct, and who will receive at least one dose of FOLFOX-4 or XELOX**.** Major violations in the eligibility criteria and study conduct will be evaluated on a case by case basis in a pre-analysis meeting in order to define the population to be analysed. Primary efficacy analysis will be performed on RFS, using a two-tailed 95% confidence interval (CI) for the Hazard Ratio (HR). All RFS curves will be drawn with the Kaplan-Meier method. As secondary analysis, OS will be analysed in the same way of the primary parameter. BEV study Primary analysis of the BEV study will be performed on an intention to treat basis, therefore all randomised patients satisfying eligibility criteria will be included in the efficacy analysis. Major violations in the eligibility criteria and study conducti will be evaluate on a case by case basis in a pre-analysis meeting in order to define the population to be analysed. The comparison of RFS between the combinations FOLFOX-4 + BEV vs. FOLFOX-4 alone will be performed using a two-sided log-rank test. All RFS curves will be drawn with the Kaplan-Meier method. Absolute benefits at specific time points will be calculated with the Kaplan-Meier estimate of RFS in the control group at the time point (control RFS) and hazard ratio with the expression: absolute benefit=exp(hazard ratio*log[control RFS])–control RFS. Differences in median will be calculated in medians in a similar way, but with use of the expression: difference in medians=(control median/hazard ratio)–control median. The impact of potential confounders will be explored in a Cox proportional hazard model. Hazard ratios and 95%CI will be estimated from both procedures. As secondary analysis, OS will be analysed as for the primary parameter RFS.
Sample size considerations	DURATION study A 95% CI for HR will be used to assess the following statistical hypotheses: H_0: HR > 1.20 (null hypothesis)

	H_A: HR ≤ 1.20 (alternative, research hypothesis) Based on available evidence, no difference in efficacy are expected between FOLFOX-4 and XELOX treatment. The 3-month FOLFOX-4 (or 12-week XELOX) experimental arm will be considered not inferior if the superior margin of the 95% CI of the HR is ≤1.20. Assuming a true value of HR of 1.00, 1270 events are required in order to have a 90% probability of correctly rejecting the null hypothesis H_0. With a uniform accrual of 4 years, a follow-up of 3 years, and assuming that RFS at 3 years in the control arm ranges from 70% to 80%, the total number of required patients is 2860-4100. BEV study Assuming a randomisation ratio of 1 BEV : 1 f-up, 390 events are required in order to achieve a power of 0.80 of detecting an hazard ratio of 0.75 in favour of the experimental treatment with a Type I error of 0.05, two-sided, using the Mantel-Cox version of the log-rank test. Based on these assumptions, with a uniform accrual of 4 years, and a follow-up of 3 years, a RFS at 3 years in the control arm ranging from 45% to 55%, the total number of required patients is 580-680, as reported in the table below. Since it is expected approximately 60% of the enrolled patients will be treated with FOLFOX-4 treatment and that high-risk stage III patients will be about 25% of the total sample, the number of patients enrolled in the DURATION study will assure the required sample size of the BEV study.