Bevacizumab as adjuvant treatment for colon cancer: Updated results from the S-AVANT phase III study by the GERCOR Group

T. André,[1] D. Vernerey,[2] S.A. Im,[3] G. Bodoky,[4] R. Buzzoni,[5] S. Reingold,[6] F. Rivera,[7] J. McKendrick,[8] W. Scheithauer,[9] G. Ravit,[10] G. Fountzilas,[11] W.P. Yong,[12] R. Isaacs,[13] P. Österlund,[14] J.T. Liang,[15] G.J. Creemers,[16] M. Rakez,[17] E. Van Cutsem,[18] D. Cunningham,[19] J. Tabernero,[20] A. de Gramont[17,21]

[1]Department of Medical Oncology, Saint-Antoine Hospital, Paris, France

[2]Methodology and Quality of Life Unit in Oncology, University Hospital of Besançon, INSERM UMR 1098, Besançon, France

[3]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

[4]Department of Medical Oncology, Combined Szent István and Szent László Hospitals, Budapest, Hungary

[5]Department of Medical Oncology, Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy

[6]Department of Medical Oncology, William Osler Health Centre Brampton Civic Hospital, Brampton, Canada

[7]Department of Medical Oncology, Hospital Universitario Marqués de Valdecilla, Santander, Spain

[8]Department of Medical Oncology, Eastern Health, Box Hill Hospital, Melbourne, Australia

[9]Department of Medical Oncology, Vienna General Hospital (AKH), Medizinische Universität Wien, Vienna, Austria

[10]Division of Oncology, Tel Aviv Sourasky Medical Center, Tel-Aviv University, Tel Aviv, Israel

[11]Department of Medical Oncology, Papageorgiou Hospital Aristotle University of Thessaloniki, Thessaloniki, Greece

[12]Department of Hematology-Oncology, National University of Singapore, Singapore, Singapore

[13] Department of Medical Oncology, Palmerston North & Crest Hospitals, Palmerston North, New Zealand

[14] Department of Oncology, Helsinki and Tampere University Hospitals, University of Helsinki, Helsinki/Tampere, Finland

[15] Department of Surgery, National Taiwan University Hospital, Taipei, Taiwan

[16] Department of Medical Oncology, Catharina Hospital, Eindhoven, The Netherlands

[17]Department of Internal Medicine, University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium

[18] Department of Medicine, The Institute of Cancer Research/Royal Marsden NHS Foundation Trust, Sutton, United Kingdom

[19] Department of Medical Oncology, Vall d'Hebron University Hospital and Institute of Oncology (VHIO), UVic, IOB-Quiron, CIBERONC, TTD Group, Barcelona, Spain

[20] Department of Medical Oncology, Franco-British Institute, Levallois-Perret, France

Corresponding author:

Prof Thierry André, Department of Medical Oncology, Saint-Antoine Hospital, 184 Rue du Faubourg Saint-Antoine, 75012 Paris, France; Tel: +33 01 71 97 03 87; Email: thierry.andre@aphp.fr

ORCID number: https://orcid.org/0000-0002-5103-7095

ABSTRACT

BACKGROUND: The AVANT study did not meet its primary endpoint of improving disease-free survival (DFS) with the addition of bevacizumab to oxaliplatin-based chemotherapy in stage III colon cancer (CC). We report here the long-term survival results (S-AVANT).

PATIENTS AND METHODS: Patients with curatively resected stage III CC were randomized to FOLFOX4, FOLFOX4-bevacizumab, or XELOX-bevacizumab.

RESULTS: 2867 patients were randomized: FOLFOX4: *n*=955, FOLFOX4-bevacizumab: *n*=960, XELOX-bevacizumab: *n*=952. With a median of 6.73 years follow up (interquartile range [IQR] 5.51-10.54), 672 patients died, of whom 198 (20.7%), 250 (26.0%), and 224 (23.5%) in FOLFOX4, FOLFOX4-bevacizumab, and XELOX-bevacizumab arm, respectively. 10-year OS were 74.6%, 67.2%, and 69.9%, (P = 0.003) and 5-year DFS were 73.2%, 68.5%, and 71.0% (P = 0.174), respectively. OS and DFS hazard ratios were 1.29 (95% CI 1.07-1.55; P = 0.008) and 1.16 (95% CI 0.99-1.37; P = 0.063) for FOLFOX4-bevacizumab versus FOLFOX4 and 1.15 (95% CI 0.95-1.39; P = 0.147) and 1.1 (95% CI 0.93-1.29; P = 0.269) for XELOX-bevacizumab versus FOLFOX4, respectively. CC-related deaths (*n*=542) occurred in 157 (79.3%) patients receiving FOLFOX4, 205 (82.0%) receiving FOLFOX4-bevacizumab, and 180 (80.4%) receiving XELOX-bevacizumab (P = 0.764), while non-CC-related deaths occurred in 41 (20.7%), 45 (18.0%), and 44 (19.6%) patients, respectively. Cardiovascular-related and sudden deaths during treatment or follow-up were reported in 13 (6.6%), 17 (6.8%), and 14 (6.3%) patients, in the FOLFOX4, FOLFOX4-bevacizuamb, and XELOX-bevacizumab arm, respectively (P = 0.789). Treatment arm, gender, age, histological differentiation, performance status, T/ N stages, and localization of primary tumor were independent prognostic factors of OS in stage III.

CONCLUSIONS: S-AVANT confirms the initial AVANT report. No benefit of the bevacizumab addition to FOLFOX4 adjuvant therapy in patients with stage III CC was observed in terms of DFS with a negative effect in OS, without increase in non-CC related deaths.

Clinical trial identification: NCT00112918.

Keywords: colon cancer, adjuvant, bevacizumab, FOLFOX, XELOX

Key message

The AVANT study did not improve disease-free survival (primary endpoint) with the addition of bevacizumab to oxaliplatin-based chemotherapy in stage III resected colon cancer. The current finding with a median follow-up of 6.73 years is consistent with the initial AVANT report showing a negative effect of bevacizumab on OS when given with adjuvant FOLFOX4 therapy in stage III colon cancer.

INTRODUCTION

Colorectal cancer (CRC) is the fourth most common cancer in the world and the second leading cause of death [1]. Close to 25% of patients with colon cancer (CC) are diagnosed with stage III disease in Western countries [2].

Adjuvant chemotherapy with fluoropyrimidines (5-fluorouracil and leucovorin [5-FU/LV] or capecitabine) and oxaliplatin (FOLFOX or XELOX) is the current standard of care for patients with stage III CC based on the findings from three large phase III trials, the Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer (MOSAIC), the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07, and the NO16968 [3-7].

Vascular endothelial growth factor (VEGF) inhibition with bevacizumab, a humanized anti-VEGF monoclonal antibody, has a direct anti-vascular effect in patients with metastatic CRC when given with chemotherapy that is reflected by improved overall survival (OS) [8]. The AVANT (Bevacizumab-Avastin® adjuVANT) phase III trial failed to demonstrate the superiority of bevacizumab added to oxaliplatin in combination with either 5-FU/LV (FOLFOX4) or capecitabine (XELOX) compared with FOLFOX4 in terms of disease-free survival (DFS) in patients who had undergone surgery with curative intent for stage III CC [9]. In line with the AVANT study results, the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-08 trial that also evaluated bevacizumab with adjuvant oxaliplatin-based chemotherapy showed no efficacy (DFS) of this treatment in US patients with stages II and III CC [10, 11]. The UK QUick And Simple And Reliable 2 (QUASAR 2) trial showed similar results when bevacizumab was added to adjuvant capecitabine [12].

Here we report the long-term survival follow-up updated survival results for the AVANT study of patients with stage III CC (the S-AVANT study).

METHODS AND PATIENTS

Patients

Complete eligibility criteria have been previously reported [9]. Briefly, eligible patients had histologically-confirmed stage III colon carcinoma according to the American Joint Cancer Committee/International Union Against Cancer (AJCC/UICC) staging system, were older than 18 years of age, and had their curative surgery performed 4 to 8 weeks before randomization.

The main exclusion criteria included: the presence of a remaining tumor, carcinoembryonic antigen >1.5 x the upper normal limit after surgery, prior anti-angiogenic treatment, major surgery, open biopsy or major traumatic injury <28 days before the study treatment, and abnormal hematologic, hepatic, or renal function. The S-AVANT protocol was approved by the Ethics Review Committee or Institutional Review Board at participating sites. All patients provided informed consent.

Trial design

AVANT was a prospective, multicenter, randomized, parallel, open-label, 3-arm phase III trial in patients operated for high-risk stage II and III CC. It was an event or time-driven trial only for stage III patients. The study continued until 36 months after the last patient was randomized. The 3-year DFS for stage III (the primary objective) data were mature for analysis in 2010 and were published in 2012 [9].

The S-AVANT study was designed for the final DFS and OS analysis with extended follow-up of patients randomized in the AVANT trial. The sponsor (ROCHE) followed-up on study and locked data on June 30, 2010 (a 3-year minimum follow-up period). At that time, median follow-up for the study population was 48 months. In 2012, the sponsor transferred the AVANT database to GERCOR for an additional update.

Treatment plan

Patients were randomized (stratified by geographic region and stage of disease) in a 1:1:1 ratio to receive one of the three treatment options: FOLFOX4 for 24 weeks followed by a 24-week observation (arm A), FOLFOX4-bevacizumab for 24 weeks followed by bevacizumab monotherapy for a further 24 weeks (arm B), or XELOX-bevacizumab for 24 weeks followed by bevacizumab monotherapy for a further 24 weeks (arm C). FOLFOX4 and XELOX were administered as previously described [9]. Bevacizumab 5 mg/kg was administered over 30 to 90 minutes as an intravenous infusion on day 1 prior to oxaliplatin 5 mg/kg every 2 weeks (FOLFOX4) or oxaliplatin 7.5 mg/kg every 3 weeks (XELOX). Bevacizumab monotherapy was administered at 7.5 mg/kg every 3 weeks. If capecitabine or 5-FU was discontinued due to toxicity, the patient could continue bevacizumab, but not on oxaliplatin.

Endpoints

The primary endpoint of S-AVANT was OS of the stage III population randomized in the AVANT study. Secondary endpoints were updated DFS, prognostic factors, subgroup analysis, and late comorbidities.

OS was defined as the time between randomization and death. Patients who were still alive at the clinical cutoff date were censored at the date at which they were last confirmed to be alive. DFS was defined as time from randomization to the first relapse, second primary cancer, or death from any cause. Event-free patients at the clinical cutoff date were censored at the last date at which they were known to be disease-free. Recurrences and new occurrences were based on the investigator's tumor evaluations scheduled every 6 months after randomization up to 4 years. The centers open in S-AVANT were requested to actualize the 8 and 10 years' follow-up data.

Statistical analysis

The final OS analysis included all stage III randomized patients in the AVANT trial including those lost to follow-up in the centers not participating in the S-AVANT study. Median value (interquartile range), mean (standard deviation), and frequency (percentage) were provided for description of continuous and categorical variables, respectively. Categorical variables were compared using a chi-square test (or Fisher's exact test, if appropriate). Median value (interquartile range) for continuous variables was compared using Kruskal Wallis test. OS and DFS were estimated using the Kaplan-Meier method and described using median or rate at specific time points with 95% confidence intervals (CI). Cause of death (CC-related, non-CC-related, cardiovascular-related, and sudden deaths) were described and compared among arms. Follow-up duration was calculated using a reverse Kaplan-Meier estimation [13].

Cox proportional hazard models were performed to estimate hazard ratios (HRs) and 95% CIs for factors associated with OS and DFS. The association of baseline parameters with OS and DFS were first assessed using univariate Cox analyses and then parameters with *P* values of less than 0.05 were entered into the final multivariable Cox regression model with stratification for treatment arm, after consideration of collinearity among variables of the correlation matrix. The assumption of proportionality was checked by plotting log-minus-log survival curves and cumulative martingale process plots. Subgroup analyses for treatment arms associations (FOLFOX4-bevacizumab versus FOLFOX4 and XELOX-bevacizumab versus FOLFOX4) with OS and DFS were performed and summarized with forest plots. The interaction term in each subgroup was obtained by considering subgroup, treatment arm, and interaction in the Cox model. The interaction was considered significant if $P < 0.1$. A sensitivity landmark analysis of the treatment effect in patients alive at 4 years without any recurrence event was performed. All analyses were performed using SAS version 9.4 (SAS Institute, Cary NC, USA) and R software version 2.15.2 (R Development Core Team, Vienna, Austria; http://www.r-project.org). *P* values were uncorrected for multiple tests**.** Considering that this study is an updated analysis of survival results from the AVANT clinical trial with

long-term follow-up and that no statistical hypothesis were formulated for this analysis, *P* values are shown for exploratory purpose. All tests were two-sided.

RESULTS

Patient characteristics

From December 2004 to June, 2007, 3451 CC patients were randomised at 330 centres in 34 countries (the ITT population, Figure 1). Overall, 2867 (83.0%) patients had stage III; 955 in arm A (FOLFOX4), 960 in arm B (FOLFOX4-bevacizumab), and 952 in arm C (XELOX-bevacizumab). Patient characteristics were well balanced between groups (Table 1). The median follow-up for the whole population was 6.73 years (IQR: 5.51-10.54) with no difference among the treatment arms (Table 1). Of 2322 stage III patients still alive after the AVANT study database lock, 976 (42.0%) had an updated median follow-up of 11.0 years.

Survival

OS events were observed in 198 (20.7%), 250 (26.0%), and 224 (23.5%) patients in the FOLFOX4, FOLFOX4-bevacizumab, and XELOX-bevacizumab arm, respectively. The 3, 5, and 10-year OS rates are reported in Table 2. For patients receiving FOLFOX4, FOLFOX4-bevacizumab, and XELOX-bevacizumab the 10-year OS rates were 74.6% (95% CI 70.9-77.9), 67.2% (95% CI 63.1-70.9), and 69.9% (95% CI 65.8-73.6), respectively (Table 2). The OS HR was 1.29 (95% CI 1.07-1.55; $P = 0.008$) for FOLFOX4-bevacizumab versus FOLFOX4 and 1.15 (95% CI 0.95-1.39; $P = 0.148$) for XELOX-bevacizumab versus FOLFOX4 (global log-rank $P = 0.029$; Figure 2).

DFS events were observed in 282 (29.5%), 326 (34%), and 305 (32%) patients in the FOLFOX4, FOLFOX4-bevacizumab, and XELOX-bevacizumab arm, respectively. The 3, 5, and 10-year DFS rates are reported in Table 2. For patients receiving FOLFOX4, FOLFOX4-bevacizumab, and XELOX-bevacizumab, the 5-year DFS rates were 73.2% (95% CI 70.2-

75.9), 68.5% (95% CI 65.4-71.4), and 71% (95% CI 67.9-73.8), respectively (Table 2). The DFS HR was 1.16 (95% CI 0.99-1.37; $P = 0.063$) for the FOLFOX4-bevacizumab arm versus FOLFOX4 arm and 1.10 (95% CI 0.93-1.29; $P = 0.269$) for the XELOX-bevacizumab arm versus FOLFOX4 arm (global log-rank $P = 0.174$; Figure 2). Of 1973 (68.8%) patients alive and relapse-free at 4 years, 33 (4.9%) and 47 (6.9%) treated with FOLFOX4, 35 (5.5%) and 45 (7.0%) with FOLFOX4-bevacizumab, and 33 (5.1%) and 52 (8.0%) with XELOX-bevacizumab experienced OS and DFS event, respectively (Table 2).

Adjusted analysis and prognostic factors

Univariate analysis of prognostic factors for OS and DFS is reported in Supplementary Table S1 (available at *Annals of Oncology* online).

In multivariate analysis, treatment arm, gender, age (<70 versus ≥70), differentiation (well/moderately versus poorly), ECOG PS (0 versus 1), T stage (T1-3 versus T4), N stage (N1 versus N2), and primary tumor localization (right versus left colon) were independent prognostic factors for OS (Table 3). The same factors, but differentiation and primary tumor localization remained as independent prognostic factors for DFS (Table 3).

Similar associations of treatment arm and outcome were found in multivariate analysis after adjusting for other prognostic factors. Forest plots for main OS and DFS prognostic factors are shown in Figures 3.

A statistically significant differential effect on OS for the addition of bevacizumab to FOLFOX4 (FOLFOX4-bevacizumab versus FOLFOX4) was observed among T/N classification subgroup (interaction P value of 0.035) with a detrimental effect observed in T1-T3N1 patients. A similar observation was made for DFS (Figure 3).

In patients at low-risk of recurrence (T1-T3N1), OS HR was 1.68 (95% CI 1.23-2.30; *P* = 0.001) for FOLFOX4-bevacizuamb versus FOLFOX4 and 1.33 (95% CI 0.96-1.85; *P* = 0.085) for XELOX-bevacizumab versus FOLFOX4 (log-rank *P* = 0.005; Figure 4).

In patients at high-risk (T4 or N2), OS HR was 1.08 (95% CI 0.86-1.37; *P* = 0.508) for FOLFOX4-bevacizumab versus FOLFOX4 and 1.05 (95% CI 0.83-1.33; *P* = 0.689) for XELOX-bevacizumab versus FOLFOX4 (log-rank *P* = 0.784; Figure 5).

Comparisons of OS and DFS in stage III CC patients according to subgroups of T1-3, N1, T4, and N2 disease are presented in Supplementary Figures S1, S2, S3, and S4, respectively (available at *Annals of Oncology* online).

Safety and causes of death

Early safety data for high-risk stage II and III CC patients have been previously reported [9].

With a total 672 deaths for stage III cases included, CC-related deaths occurred in 542 patients (80.7%) with no difference between arms; FOLFOX4: 157/198 (79.3%), FOLFOX4-bevacizumab: 205/250 (82.0%), XELOX-bevacizumab: 180/224 (80.4%; *P* = 0.764). Non-colon cancer-related deaths occurred in 130 patients with stage III, in whom those related to cardiovascular diseases and sudden deaths were reported in 13 out of 41 non-colon cancer related deaths (31.7%), 17/45 (37.8%), and 14/44 (31.8%) in the FOLFOX4, FOLFOX4-bevacizumab, and XELOX-bevacizumab arms, respectively (*P* = 0.789). In a sensitivity analysis, a competing risks approach was applied to consider other cause of death than cardiovascular. We estimated cumulative incidence functions from competing risks data and compared the sub-distribution for each cause across arms [14]. The analysis confirmed that there are no differences in cardiovascular death among arms (Supplementary Figures S5, available at *Annals of Oncology* online).

DISCUSSION

The long-term follow-up results of the S-AVANT study confirm the lack of DFS benefit for the addition of bevacizumab to either FOLFOX4 (HR = 1.16) or XELOX (HR = 1.11) in patients with resected stage III CC. Data update with a longer follow-up show detrimental effect on OS with bevacizumab and oxaliplatin-based adjuvant chemotherapy (FOLFOX4 [HR = 1.29] or XELOX [HR = 1.15]), without increase in non-CC related deaths. The negative effect of bevacizumab and oxaliplatin-based chemotherapy on OS (FOLFOX4 versus FOLFOX4-bevacizumab) support that administration of bevacizumab should be avoided completely in patients with stage III CC in the adjuvant setting. The detrimental effect of bevacizumab in our study occurred early since the death rate was similar for patients without relapse after 4 years.

Several hypotheses could explain the failure of bevacizumab in the adjuvant setting. Arrested angiogenesis is a component of cell dormancy [15] and experimental models have shown that dormant tumor cells can be protected from chemotherapy [16]. In our subgroup analysis (FOLFOX4 versus FOLFOX4-bevacizumab), bevacizumab had a significant detrimental effect on DFS and OS in the T1-T3N1 low-risk subgroup, but not in the T4 or N2 high-risk subgroup. One hypothesis is a different effect of bevacizumab on tumor dormant micrometastases between low-risk and high-risk stage III CC.

The two other studies, with a shorter follow-up period than S-AVANT, showed a non-significant deleterious effect of bevacizumab in the adjuvant setting of CC or CRC. In QUASAR 2 (high-risk stage II and stage III CRC), after a median follow-up of 4.92 years, the median OS was 89.4% in the capecitabine arm and 87.5% in the capecitabine plus bevacizumab arm (HR = 1.11) [12]. In NSABP C08, after 5-year median follow-up, the median OS for patients with stage III CC was 78.7% in the mFOLFOX6 arm and 77.6% in the mFOLFOX6 plus bevacizumab arm (HR = 1.00) [4, 5, 10, 11].

No new or unexpected safety signals were observed in the current study that could explain the death rates with bevacizumab in our findings. The long-term safety of bevacizumab in combination with FOLFOX4 or XELOX did not demonstrate increased cardiovascular disease-related or sudden death rates.

Bevacizumab is not the only drug to show the efficacy in metastatic CRC, but not in the early-stages of disease. Irinotecan and cetuximab, which are both approved for metastatic disease, failed to show benefit in adjuvant trials [17-20]. The disappointing results from the recent trials of these molecularly targeted agents against stage II and/or III CC highlight a need to identify new potential strategies for adjuvant treatment of CC. Given that adjuvant trials are long, expensive and large, it would be valuable to have access to preclinical models predictive of early-stage disease. The negative outcome of recent adjuvant trials in CC despite the regimen activity in the metastatic setting, raises the question of the driving signals triggering the launch of adjuvant trials in patients with CC and of the need of alternative developmental approaches in adjuvant therapy [21].

In conclusion, the S-AVANT study confirms that bevacizumab does not prolong DFS when added to adjuvant chemotherapy in patients with stage III CC and shows a statistically significant negative effect on OS with bevacizumab plus FOLFOX4-based adjuvant therapy, without increase in non-colon cancer-related deaths. Therefore, bevacizumab should not be used in adjuvant treatment of patients with curatively resected stage III CC.

ACKNOWLEDGEMENTS

The authors thank Magdalena Benetkiewicz (PhD, GERCOR) for providing editorial assistance.

FUNDING

This updated analysis was supported by F. Hoffmann-La Roche AG. No grant number applicable. Study sponsors (ROCHE for AVANT and GERCOR for S-AVANT) were involved in study design, data interpretation, and the decision to submit the report for publication in conjunction with the authors. Employees of the GERCOR collected and managed the data and undertook data analysis. The principal investigator (AdG) had full access to all study data and had final responsibility for the decision to submit for publication.

DISCLOSURES

TA has declared consulting/advisory role and/or honoraria from: Amgen, BMS, Chugai, HalioDx, MSD Oncology, Yakult, AstraZeneca, Pierre Fabre, Roche/Ventana, Sanofi, Servier and travel/accommodations/expenses from: Roche/Genentech, MSD Oncology, and BMS. DV has declared consulting/advisory role and/or honoraria from: HalioDx, Janssen-Cilag, OSE Immunotherapeutics, Prestizia, Celgene. GMB has declared consulting/advisory role and/or honoraria from: Bayer, Ipsen, Janssen, Lilly, Novartis, Pfizer, Roche; has declared travel/accommodations/expenses from: Janssen, Lilly, Novartis, Pfizer, Roche. FR has declared consulting/advisory role and/or honoraria from: Amgen, Merck Serono, Roche, Sanofi, Bayer, Lilly, Celgene, MSD, Tecnofarma; has declared research funding/funding from: Amgen, Merck Serono, Roche, Sanofi, Bayer, Lilly, Celgene, MSD; has declared Speaker Bureau/Expert testimony for: Amgen Roche Sanofi Bayer Lilly Celgene. RG has declared consulting/advisory role and/or honoraria from: Bayer, MSD, Novartis, BMS, Lilly,

Medison, Janssen, Takeda, Roche, Merck; has declared travel/accommodations/expenses from: BMS, Roche, Merck, GAD Medical; has declared research grant/funding (institution) from: Novartis. PÖ has declared consulting/advisory role and/or honoraria from: Amgen, Bayer, Celgene, Lilly, Merck, Nordic Drugs, Roche, Sanofi, Baxalta/Servier, Eisai; has declared travel/accommodations/expenses from: Amgen, Celgene, Merck, Nordic Drugs, Roche; has declared research grant/funding (institution) from: Amgen, Lilly, Merck, Nordic Drugs, Roche, Sanofi, Baxalta/Servier; has declared Speaker Bureau/Expert testimony for: Celgene, Nordic Drugs, Baxalta/Servier, Eisai; has declared travel/accommodations/expenses from: Amgen, Celgene, Merck, Nordic Drugs, Roche, AbbVie, AstraZeneca, Pierre Fabre. EVC has declared consulting/advisory role and/or honoraria from: Amgen, Bayer, BMS, Celgene, Lilly, Novartis, Servier, Roche, MSD, Ipsen, Sanofi, Boehringer; has declared research grant/funding (self) from: Amgen, Bayer, Celgene, Lilly, Novartis, Servier, Roche, Merck, MSD, Ipsen, Sanofi, Boehringer; has declared travel/accommodations/expenses from: Roche.

DC has declared research grant/funding (institution) from: Amgen, AstraZeneca, Bayer, Celgene, Medimmune, Merck Serono, Merrimack, Sanofi, Novartis, Roche. JT has declared consulting/advisory role and/or honoraria from: Array Biopharma, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Chugai, Genentech, Inc., Genmab A/S, Halozyme, Imugene Limited, Inflection Biosciences Limited, Ipsen, Kura Oncology, Lilly, MSD, Menarini, Merck Serono, Merrimack, Merus, Molecular Partn, American Society of Clinical Oncology – ASCO, American Association for Cancer Research – AACR, European Organization for Research and Treatment of Cancer – EORTC, Cancer Core Europe (CCE), Worldwide Innovative Networking (WIN) Consortium in Personalized C; has declared research grant/funding (institution) from: Agendia BV, Amgen SA, Debiopharm International SA, Janssen-Cilag SA, Mologen AGm Novartis Farmacéutica SA, Pharma Mar, Roche Farma SA,

Laboratorios Servier SL, Symphogen A/S; has declared scientific advisory role for: Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Genentech, Lilly, MSD, Merck Serono, Novartis, Pfizer, F. Hoffmann-La Roche, Sanofi, Symphogen, Taiho and Takeda. ADG has declared consulting/advisory role and/or honoraria from: Yakult, Chugai Pharma. All other authors have declared no conflicts of interest.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.

2. Chen VW, Hsieh MC, Charlton ME et al. Analysis of stage and clinical/prognostic factors for colon and rectal cancer from SEER registries: AJCC and collaborative stage data collection system. Cancer 2014; 120 Suppl 23: 3793-3806.

3. Andre T, Boni C, Mounedji-Boudiaf L et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004; 350: 2343-2351.

4. Kuebler JP, Wieand HS, O'Connell MJ et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol 2007; 25: 2198-2204.

5. Yothers G, O'Connell MJ, Allegra CJ et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. J Clin Oncol 2011; 29: 3768-3774.

6. Haller DG, Tabernero J, Maroun J et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol 2011; 29: 1465-1471.

7. Schmoll HJ, Tabernero J, Maroun J et al. Capecitabine Plus Oxaliplatin Compared With Fluorouracil/Folinic Acid As Adjuvant Therapy for Stage III Colon Cancer: Final Results of the NO16968 Randomized Controlled Phase III Trial. J Clin Oncol 2015; 33: 3733-3740.

8. Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350: 2335-2342.

9. de Gramont A, Van Cutsem E, Schmoll HJ et al. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. Lancet Oncol 2012; 13: 1225-1233.

10. Allegra CJ, Yothers G, O'Connell MJ et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. J Clin Oncol 2011; 29: 11-16.

11. Allegra CJ, Yothers G, O'Connell MJ et al. Bevacizumab in stage II-III colon cancer: 5-year update of the National Surgical Adjuvant Breast and Bowel Project C-08 trial. J Clin Oncol 2013; 31: 359-364.

12. Kerr RS, Love S, Segelov E et al. Adjuvant capecitabine plus bevacizumab versus capecitabine alone in patients with colorectal cancer (QUASAR 2): an open-label, randomised phase 3 trial. Lancet Oncol 2016; 17: 1543-1557.

13. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996; 17: 343-346.

14. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing Risk. J Am Stat Assoc 1999; 94: 496-509.

15. Almog N. Molecular mechanisms underlying tumor dormancy. Cancer Lett 2010; 294: 139-146.

16. Naumov GN, Townson JL, MacDonald IC et al. Ineffectiveness of doxorubicin treatment on solitary dormant mammary carcinoma cells or late-developing metastases. Breast Cancer Res Treat 2003; 82: 199-206.

17. Saltz LB, Niedzwiecki D, Hollis D et al. Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803. J Clin Oncol 2007; 25: 3456-3461.

18. Van Cutsem E, Labianca R, Bodoky G et al. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. J Clin Oncol 2009; 27: 3117-3125.

19. Alberts SR, Sargent DJ, Nair S et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. JAMA 2012; 307: 1383-1393.

20. Taieb J, Tabernero J, Mini E et al. Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomised phase 3 trial. Lancet Oncol 2014; 15: 862-873.

21. de Gramont A, Chibaudel B, Bonnetain F et al. Clinical Reasons for Initiation of Adjuvant Phase III Trials on Colon Cancer. Curr Colorectal Cancer Rep 2013; 9: 292-301.

Figure Legends

Figure 1. Flow-chart

Abbreviations: ITT, intent-to-treat; bev, bevacizumab

Figure 2. Overall survival (A) and disease-free survival (B) according to treatment arm in stage III patients

Abbreviations: y, years; bev, bevacizumab

Figure 3. Forest-plots for OS and DFS between FOLFOX4 versus FOLFOX4-bevacizumab (A and B) and FOLFOX4 versus XELOX-bevacizumab (C and D)

Abbreviations: HR, hazard ratio; LCI, 95% lower confidence interval; UCI, 95% upper confidence interval; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; PS, performance status

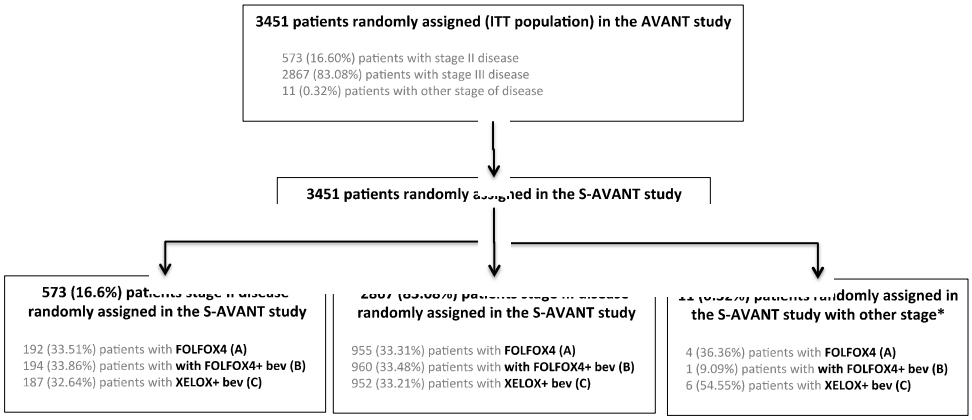
**P*-value for the interaction test between subgroup and treatment arm

Figure 4. Overall survival (A) and disease-free survival (B) according to treatment arm in stage III patients with T1-T3N1

Abbreviations: y, years; bev, bevacizumab

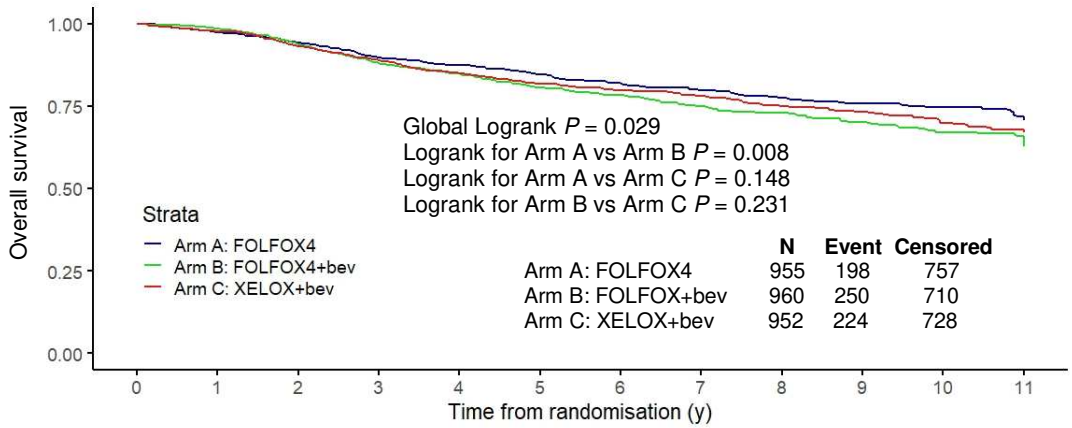
Figure 5. Overall survival (A) and disease-free survival (B) according to treatment arm in stage III patients with T4 or N2

Abbreviations: y, years; bev, bevacizumab



*2 patients with stage I, 7 patients with stage IV, 1 patient with stage unknown, 1 patient with stage II but low risk

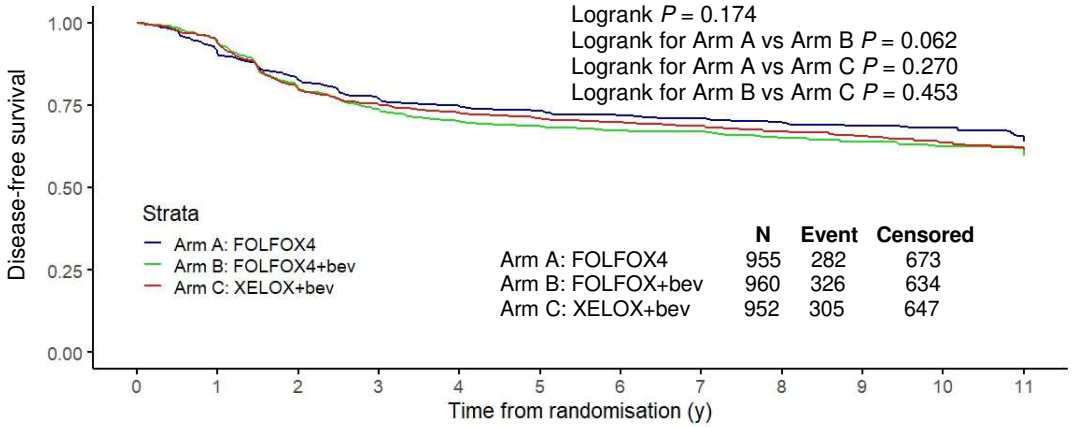
A



Number at risk

Arm A: FOLFOX4	955	906	868	822	792	716	528	324	273	252	211	141
Arm B: FOLFOX4+bev	960	929	875	816	775	695	499	313	261	238	192	132
Arm C: XELOX+bev	952	912	866	815	763	697	519	306	262	238	192	139

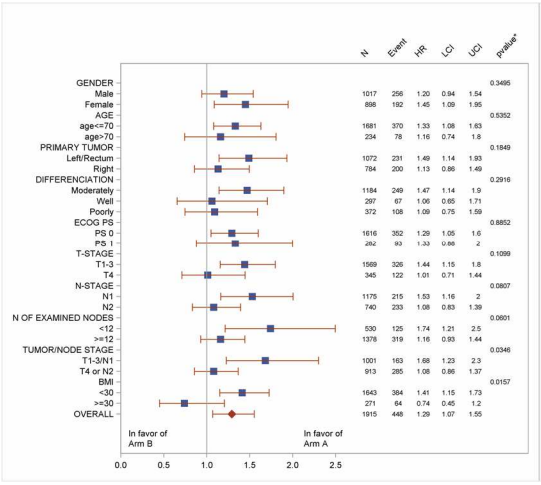
B



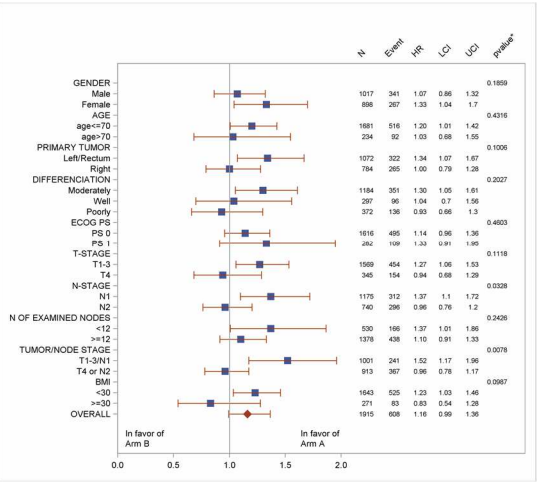
Number at risk

Arm A: FOLFOX4	955	843	761	706	680	624	467	289	244	228	193	129
Arm B: FOLFOX4+bev	960	885	751	685	642	592	428	273	222	206	170	117
Arm C: XELOX+bev	952	876	743	689	651	602	443	258	223	203	164	120

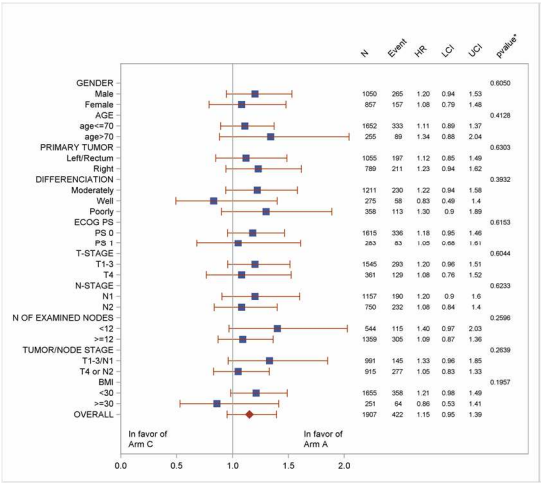
A


N
Event
HR
LCI
UCI
pvalue*
GENDER
Male 1017 256 1.20 0.94 1.54 0.3495
Female 898 192 1.45 1.09 1.95
AGE
age<=70 1681 370 1.33 1.08 1.63 0.5352
age>70 234 78 1.16 0.74 1.8
PRIMARY TUMOR
Left/Rectum 1072 231 1.49 1.14 1.93 0.1849
Right 784 200 1.13 0.86 1.49
DIFFERENCIATION
Moderately 1184 249 1.47 1.14 1.9 0.2916
Well 297 67 1.06 0.65 1.71
Poorly 372 108 1.09 0.75 1.59
ECOG PS
PS 0 1616 352 1.29 1.05 1.6 0.8852
PS 1 282 93 1.33 0.86 2
T-STAGE
T1-3 1569 326 1.44 1.15 1.8 0.1099
T4 345 122 1.01 0.71 1.44
N-STAGE
N1 1175 215 1.53 1.16 2 0.0807
N2 740 233 1.08 0.83 1.39
N OF EXAMINED NODES
<12 530 125 1.74 1.21 2.5 0.0601
>=12 1378 319 1.16 0.93 1.44
TUMOR/NODE STAGE
T1-3/N1 1001 163 1.68 1.23 2.3 0.0346
T4 or N2 913 285 1.08 0.86 1.37
BMI
<30 1643 384 1.41 1.15 1.73 0.0157
>=30 271 64 0.74 0.45 1.2
OVERALL 1915 448 1.29 1.07 1.55
In favor of Arm B
In favor of Arm A
0.0 0.5 1.0 1.5 2.0 2.5

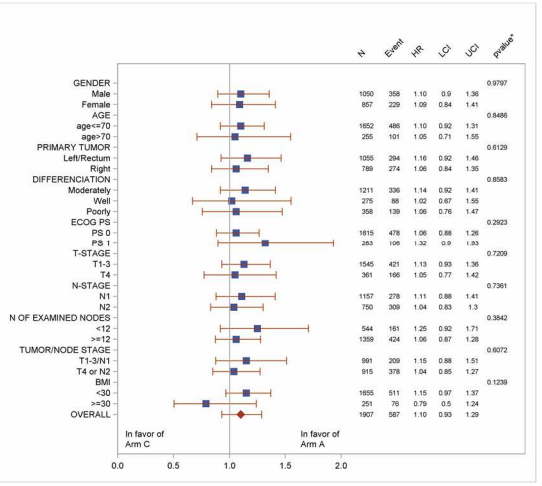
B


N
Event
HR
LCI
UCI
pvalue*
GENDER
Male 1017 341 1.07 0.86 1.32 0.1859
Female 898 267 1.33 1.04 1.7
AGE
age<=70 1681 516 1.20 1.01 1.42 0.4316
age>70 234 92 1.03 0.68 1.55
PRIMARY TUMOR
Left/Rectum 1072 322 1.34 1.07 1.67 0.1006
Right 784 265 1.00 0.79 1.28
DIFFERENCIATION
Moderately 1184 351 1.30 1.05 1.61 0.2027
Well 297 96 1.04 0.7 1.56
Poorly 372 136 0.93 0.66 1.3
ECOG PS
PS 0 1616 495 1.14 0.96 1.36 0.4603
PS 1 282 109 1.33 0.91 1.95
T-STAGE
T1-3 1569 454 1.27 1.06 1.53 0.1118
T4 345 154 0.94 0.68 1.29
N-STAGE
N1 1175 312 1.37 1.1 1.72 0.0328
N2 740 296 0.96 0.76 1.2
N OF EXAMINED NODES
<12 530 166 1.37 1.01 1.86 0.2426
>=12 1378 438 1.10 0.91 1.33
TUMOR/NODE STAGE
T1-3/N1 1001 241 1.52 1.17 1.96 0.0078
T4 or N2 913 367 0.96 0.78 1.17
BMI
<30 1643 525 1.23 1.03 1.46 0.0987
>=30 271 83 0.83 0.54 1.28
OVERALL 1915 608 1.16 0.99 1.36
In favor of Arm B
In favor of Arm A
0.0 0.5 1.0 1.5 2.0

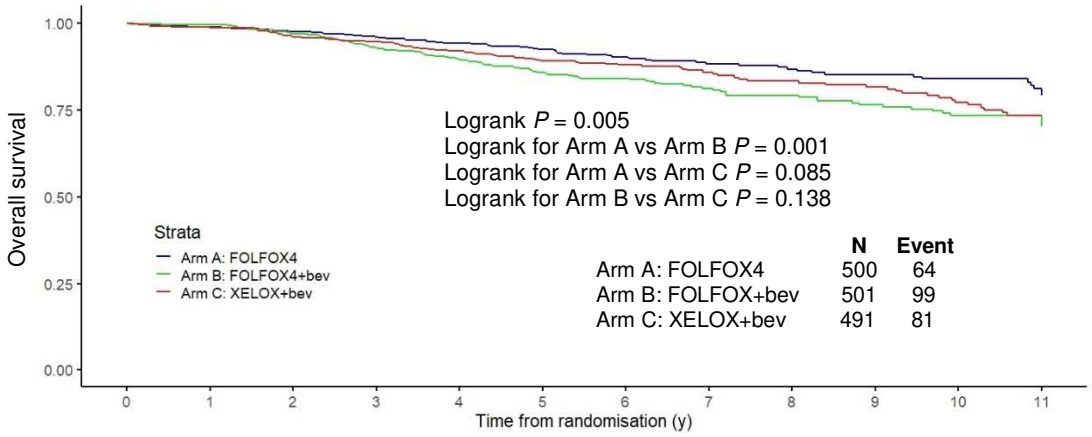
C


N
Event
HR
LCI
UCI
pvalue*
GENDER
Male 1050 265 1.20 0.94 1.53 0.6050
Female 857 157 1.08 0.79 1.48
AGE
age<=70 1652 333 1.11 0.89 1.37 0.4128
age>70 255 89 1.34 0.88 2.04
PRIMARY TUMOR
Left/Rectum 1055 197 1.12 0.85 1.49 0.6303
Right 789 211 1.23 0.94 1.62
DIFFERENCIATION
Moderately 1211 230 1.22 0.94 1.58 0.3932
Well 275 58 0.83 0.49 1.4
Poorly 358 113 1.30 0.9 1.89
ECOG PS
PS 0 1615 336 1.18 0.95 1.46 0.6153
PS 1 283 83 1.05 0.66 1.61
T-STAGE
T1-3 1545 293 1.20 0.96 1.51 0.6044
T4 361 129 1.08 0.76 1.52
N-STAGE
N1 1157 190 1.20 0.9 1.6 0.6233
N2 750 232 1.08 0.84 1.4
N OF EXAMINED NODES
<12 544 115 1.40 0.97 2.03 0.2596
>=12 1359 305 1.09 0.87 1.36
TUMOR/NODE STAGE
T1-3/N1 991 145 1.33 0.96 1.85 0.2639
T4 or N2 915 277 1.05 0.83 1.33
BMI
<30 1655 358 1.21 0.98 1.49 0.1957
>=30 251 64 0.86 0.53 1.41
OVERALL 1907 422 1.15 0.95 1.39
In favor of Arm C
In favor of Arm A
0.0 0.5 1.0 1.5 2.0

D


N
Event
HR
LCI
UCI
pvalue*
GENDER
Male 1050 358 1.10 0.9 1.36 0.9797
Female 857 229 1.09 0.84 1.41
AGE
age<=70 1652 486 1.10 0.92 1.31 0.8486
age>70 255 101 1.05 0.71 1.55
PRIMARY TUMOR
Left/Rectum 1055 294 1.16 0.92 1.46 0.6129
Right 789 274 1.06 0.84 1.35
DIFFERENCIATION
Moderately 1211 336 1.14 0.92 1.41 0.8583
Well 275 88 1.02 0.67 1.55
Poorly 358 139 1.06 0.76 1.47
ECOG PS
PS 0 1615 478 1.06 0.88 1.26 0.2923
PS 1 283 106 1.32 0.9 1.93
T-STAGE
T1-3 1545 421 1.13 0.93 1.36 0.7209
T4 361 166 1.05 0.77 1.42
N-STAGE
N1 1157 278 1.11 0.88 1.41 0.7361
N2 750 309 1.04 0.83 1.3
N OF EXAMINED NODES
<12 544 161 1.25 0.92 1.71 0.3842
>=12 1359 424 1.06 0.87 1.28
TUMOR/NODE STAGE
T1-3/N1 991 209 1.15 0.88 1.51 0.6072
T4 or N2 915 378 1.04 0.85 1.27
BMI
<30 1655 511 1.15 0.97 1.37 0.1239
>=30 251 76 0.79 0.5 1.24
OVERALL 1907 587 1.10 0.93 1.29
In favor of Arm C
In favor of Arm A
0.0 0.5 1.0 1.5 2.0

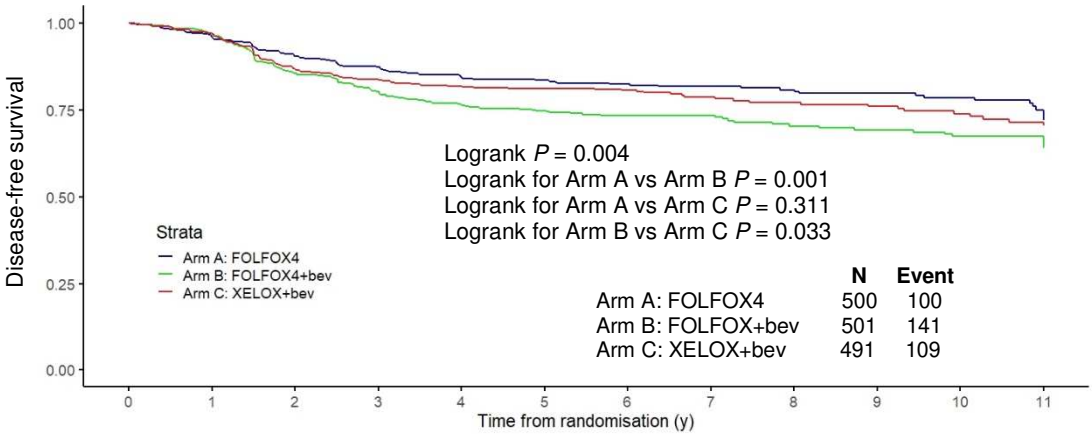
A



Number at risk

Arm A: FOLFOX4	500	486	474	463	451	412	314	198	166	153	126	82
Arm B: FOLFOX4+bev	501	485	466	443	419	381	273	178	150	133	107	72
Arm C: XELOX+bev	491	475	461	448	426	394	286	171	154	140	109	80

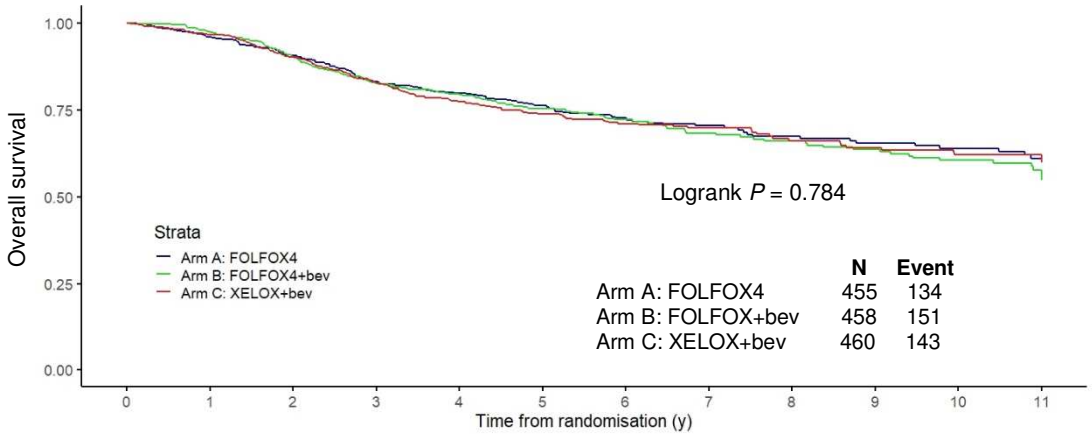
B



Number at risk

Arm A: FOLFOX4	500	471	440	423	406	374	289	183	154	144	119	77
Arm B: FOLFOX4+bev	501	473	413	384	359	334	241	161	131	118	96	65
Arm C: XELOX+bev	491	468	417	397	378	358	257	151	136	123	97	73

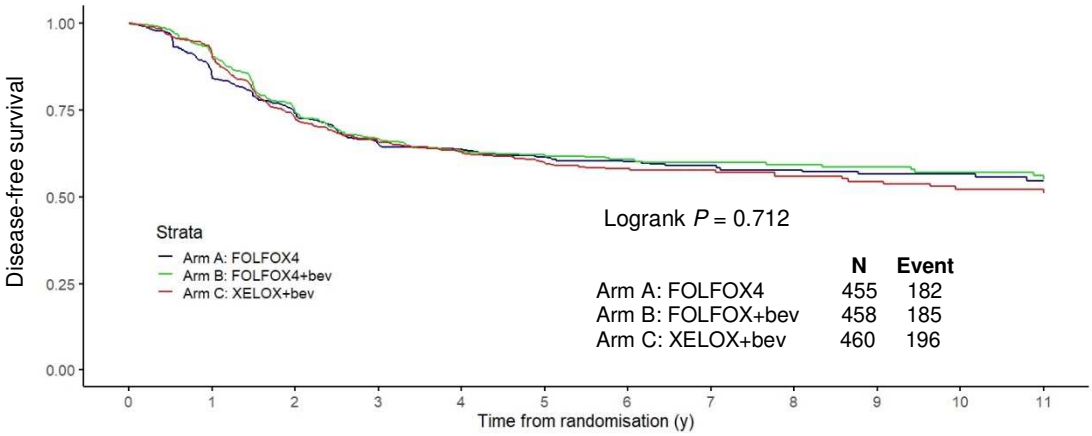
A



Number at risk

Arm A: FOLFOX4	455	420	394	359	341	304	214	126	107	99	85	59
Arm B: FOLFOX4+bev	458	443	408	372	355	313	225	134	110	104	84	59
Arm C: XELOX+bev	460	436	404	366	336	302	232	134	107	97	82	58

B



Number at risk

Arm A: FOLFOX4	455	372	321	283	274	250	178	106	90	84	74	52
Arm B: FOLFOX4+bev	458	411	337	300	282	257	186	111	90	87	73	51
Arm C: XELOX+bev	460	407	325	291	272	243	185	106	86	79	66	46

Table 1. Clinical characteristics of stage III patients

	Stage III (*N* = 2867)		FOLFOX4 (*N* = 955)		FOLFOX4+ bev (*N* = 960)		XELOX+ bev (*N* = 952)		
	n	***%***	***n***	***%***	***n***	***%***	***n***	***%***	***P****
Gender*									0.0836
Male	1537	53.61	530	55.50	487	50.73	520	54.62	
Female	1330	46.39	425	44.50	473	49.27	432	45.38	
Age*, years									0.7262
Mean (SD)	57.89 (11.21)		57.71 (11.30)		57.89 (10.91)		58.08 (11.45)		
Median	59.01		59.01		58.87		59.19		
Q1-Q3	51.12-66.14		50.66-66.27		51.62-65.79		51.18-66.37		
Min-Max	19.09-83.94		21.86-83.94		19.09-82.79		19.77-82.65		
Localization									
Left/Rectum	1598	57.32	529	57.0	543	58.14	526	56.80	
Right	1177	42.22	396	42.67	388	41.54	393	42.44	
Both	13	0.47	3	0.32	3	0.32	7	0.76	0.6473
Missing	79		27		26		26		
Differentiation									0.1467
Poorly differentiated	534	19.26	196	21.19	176	18.97	162	17.63	
Well/Moderately	2238	80.74	729	78.81	752	81.03	757	82.37	
Missing	95		30		32		33		
ECOG PS									0.9808
0	2422	85.07	809	85.25	807	85.04	806	84.93	
1	425	14.93	140	14.75	142	14.96	143	15.07	
Missing	20		6		11		13		
BMI									
<30	2467	86.08	831	87.11	812	84.58	824	86.55	
≥30	399	13.92	123	12.89	148	15.42	128	13.45	0.2450

Missing	1		1		0		0		
No. of examined nodes									
<12	805	28.17	269	28.23	261	27.33	275	28.95	
≥12	2053	71.83	684	71.77	694	72.67	675	71.05	0.7340
Missing	9		2		5		2		
T stage									0.3889
T1	26	2.69	26	2.72	31	3.23	20	2.10	
T2	216	7.54	80	8.38	66	6.88	70	7.36	
T3	2050	71.55	665	69.63	701	73.10	684	71.92	
T4	522	18.22	184	19.27	161	16.79	177	18.61	
Missing	2		0		1		1		
N stage *									0.8019
N1	1747	60.93	585	61.26	590	61.46	572	60.08	
N2	1120	39.07	370	38.74	370	38.54	380	39.92	
TN stage									0.9434
T1-3/N1	1492	52.08	500	52.36	501	52.24	491	51.63	
T4 or N2	1373	47.92	455	47.64	458	47.76	460	48.37	
Missing	2		0		1		1		
Follow-up median AVANT (IQR), years***	6.02053 (5.10609 - 6.65572)		6.02327 (5.10335- 6.68857)		6.01780 (5.09788- 6.65845)		6.02875 (5.1170- 6.64203)		0.5503
Follow-up median S-AVANT (IQR), years***	6.7269 (5.5058- 10.5407)		6.7844 (5.4976- 10.4997)		6.7269 (5.5003- 10.5435)		6.6557 (5.5250- 10.5435)		0.9781

Abbreviations: SD, Standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, body mass index; IQR, interquartile range

*No missing data

** *P* value computed with chi-square test or Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables

***log-rank test

Table 2. OS and DFS according to treatment arms in all stage III patients and in stage III patients relapse-free and still alive at 4 years

Variable	FOLFOX4	FOLFOX4 + bev	XELOX + bev
Overall			
No.	955	960	952
OS			
No. of events	198	250	224
3 year, % (95% CI)	89.8 (87.9-91.6)	88.0 (85.6- 89.9)	88.9 (86.7-90.8)
5 year, % (95% CI)	84.7 (82.2-86.9)	80.8 (78.1-83.2)	81.7 (79.1-84.1)
10 year, % (95% CI)	74.6 (70.9-77.9)	67.2 (63.1-70.9)	69.9 (65.8-73.6)
DFS			
*N*o. of events	282	326	305
3 year, % (95% CI)	76.9 (74.1-79.5)	73.7 (70.8-76.4)	75.2 (72.3-77.8)
5 year, % (95% CI)	73.2 (70.2-75.9)	68.5 (65.4-71.4)	71.0 (67.9-73.8)
10 year, % (95% CI)	68.1 (64.6-71.3)	62.4 (58.6-65.9)	63.6 (59.7-67.2)
Patients alive without relapse at 4 years			
No.	680	642	651
OS			
No. of events	33	35	33
5 year, % (95% CI)	99.1 (98.0-99.6)	99.5 (98.5-99.8)	99.4 (98.4-99.8)
10 year, % (95% CI)	93.1 (89.6-95.4)	90.7 (86.5-93.6)	89.9 (85.4-93.1)
DFS			
No. of events	47	45	52
5 year, % (95% CI)	98.1 (96.7-98.9)	97.8 (96.3-98.7)	97.5 (96.0-98.5)
10 year, % (95% CI)	91.3 (87.9-93.8)	89.0 (84.9-92.1)	87.3 (83.0-90.6)

Abbreviations: OS, overall survival; DFS, disease-free survival; bev, bevacizumab

Table 3. Multivariate analysis of prognostic factors for OS and DFS

Variable		*N* (event)	HR	95% CI	*P*-value	Global *P*-value
OS						
		2677 (617)				
Arm	A: FOLFOX		1			
	B: FOLFOX4-bev		1.373	1.129-1.671	0.0015	
	C:XELOX-bev		1.206	0.987-1.473	0.0673	0.0065
Gender	Female		1			
	Male		0.782	0.666-0.920	0.0029	0.0029
Age, year	<70		1			
	≥70		1.658	1.351-2.036	<0.0001	<0.0001
Differentiation	Poorly		1			
	Well		0.666	0.513-0.865	0.0023	
	Moderately		0.730	0.604-0.883	0.0012	0.0014
ECOG PS	0		1			
	1		1.560	1.280-1.902	<0.0001	<0.0001
T stage	T1-3		1			
	T4		1.744	1.457-2.087	<0.0001	<0.0001
N stage	N1		1			
	N2		1.755	1.494-2.061	<0.0001	<0.0001
Primary tumor	Left/Rectum		1			
	Right		1.215	1.034-1.427	0.0182	
	Both		1.634	0.672-3.973	0.2783	0.0410
DFS						
		2677 (847)				
Arm	A: FOLFOX		1			
	B: FOLFOX4-bev		1.197	1.014-1.414	0.0337	
	C:XELOX-bev		1.112	0.939-1.316	0.2177	0.1039
Gender	male		1			
	female		0.850	0.741-0.975	0.0204	0.0204
Age, year	<70		1			
	≥70		1.278	1.057-1.544	0.0113	0.0113
Differentiation	Poorly		1			
	Well		0.850	0.679-1.062	0.1527	
	Moderately		0.832	0.703-0.985	0.0325	0.0971
ECOG PS	0		1			
	1		1.338	1.122-1.595	0.0012	0.0012
T stage	T1-3		1			
	T4		1.655	1.415-1.934	<0.0001	<0.0001
N stage	N1		1			
	N2		1.667	1.453-1.913	<0.0001	<0.0001
Primary tumor	Left/Rectum		1			
	Right		1.144	0.996-1.313	0.0569	
	Both		1.409	0.627-3.166	0.4060	0.1281

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; DFS, disease-free survival; bev, bevacizumab