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Continuation or reintroduction of bevacizumab beyond progression to first-line therapy in metastatic colorectal cancer: final results of the randomized BEBYP trial

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Background: The combination of bevacizumab with fluorouracil-based chemotherapy is a standard first-line treatment option in metastatic colorectal cancer (mCRC). We studied the efficacy of continuing or reintroducing bevacizumab in combination with second-line chemotherapy after progression to bevacizumab-based first-line therapy.

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Patients and methods: In this phase III study, patients with mCRC treated with fluoropyrimidine-based first-line chemotherapy plus bevacizumab were randomized to receive in second-line mFOLFOX-6 or FOLFIRI (depending on first-line regimen) with or without bevacizumab. The primary end point was progression-free survival. To detect a hazard ratio (HR) for progression of 0.70 with an α and β error of 0.05 and 0.20, respectively, 262 patients were required.

Results: In consideration of the results of the ML18147 trial, the study was prematurely stopped. Between April 2008 and May 2012, a total of 185 patients were randomized. Bevacizumab-free interval was longer than 3 months in 43% of patients in chemotherapy alone arm and in 50% of patients in the bevacizumab arm. At a median follow-up of 45.3 months, the median progression-free survival was 5.0 months in the chemotherapy group and 6.8 months in the bevacizumab group [adjusted HR = 0.70; 95% confidence interval (CI) 0.52–0.95; stratified log-rank $P = 0.010$]. Subgroup analyses showed a consistent benefit in all subgroups analyzed and in particular in patients who had continued or reintroduced bevacizumab. An improved overall survival was also observed in the bevacizumab arm (adjusted HR = 0.77; 95% CI 0.56–1.06; stratified log-rank $P = 0.043$). Responses (RECIST 1.0) were similar in the chemotherapy and bevacizumab groups (17% and 21%; $P = 0.573$). Toxicity profile was consistent with previously reported data.

Conclusions: This study demonstrates that the continuation or the reintroduction of bevacizumab with second-line chemotherapy beyond first progression improves the outcome and supports the use of this strategy in the treatment of mCRC.

Clinical Trials.gov number: NCT00720512.

Key words: metastatic colorectal cancer, bevacizumab, second-line, beyond progression

introduction

The combination of bevacizumab, a monoclonal antibody that inhibits the vascular endothelial growth factor (VEGF), with fluoropyrimidine-based chemotherapy is an effective treatment for metastatic colorectal cancer (mCRC), and it represents a standard option in the first-line setting [1–4] and in second-line in bevacizumab-naïve patients [5].

The prolonged treatment with bevacizumab by continuing the inhibition of VEGF beyond first-progression has a strong rationale. Indeed, several preclinical data demonstrated that VEGF is continuously expressed during tumor growth and it continues to be expressed throughout tumor progression, facilitating tumor angiogenesis, even if secondary signaling pathways emerged [6]. Data from preclinical models also demonstrated that longer exposure to anti-VEGF monoclonal antibodies lead to delayed tumor growth and extended survival in established tumors [7].

This concept was also evaluated in the clinical setting and the results of two non-randomized observational cohort studies (BRiTE and ARIES) showed a correlation between the use of bevacizumab beyond progression to first-line therapy and a substantial improvement in overall survival (OS) in advanced colorectal cancer patients [8, 9].

To determine the potential benefits of the continuation (bevacizumab interruption from <3 months) or reintroduction (bevacizumab interruption from more than 3 months) of bevacizumab after the first progression in patients with mCRC, two randomized trials were designed and conducted: the ML18147 trial and the BEBYP trial.

The ML18147 trial was an international multicenter trial that rapidly accrued a total of 820 patients who had interrupted bevacizumab from <3 months. Results were recently published [10] and demonstrated a significant improvement in progression-free survival (PFS) and OS continuing bevacizumab plus second-line chemotherapy.

The BEBYP trial is an Italian multicenter trial that studied also patients who had interrupted bevacizumab from more than 3 months.

patients and methods

study design

The BEvacizumab BeYond Progression (BEBYP) trial was a prospective, randomized, open-label, multicenter, phase III study conducted in 19 Italian centers. Patients with unresectable, histologically confirmed colorectal adenocarcinoma with progressive disease (PD) after or during first-line therapy with fluoropyrimidine, FOLFIRI or FOLFOX plus bevacizumab, or more than 3 months after the last dose of FOLFOXIRI plus bevacizumab, were randomized to receive a second-line chemotherapy with or without bevacizumab. The original study design required a total of 262 patients to detect a hazard ratio (HR) for PFS of 0.70 in favor of the bevacizumab-containing arm. Accrual started on April 2008, but the trial was interrupted prematurely on May 2012, due to two main reasons: the first one was due to the announcement of the ML18147 study results that showed a survival improvement by the continuation of bevacizumab beyond progression; thus, we considered unethical to continue enrolling patients in the BEBYP trial that had a very similar design. The second reason was the very slow accrual rate of the trial. Indeed, we had problems in bevacizumab supply because of the limitations of AIFA grant, and therefore, the costs of the drug were charged to participating centers.

The study was approved by the ethics committees of all participating Institutions and it was conducted in full accordance with the Declaration of Helsinki and adhered to Good Clinical Practice Guidelines. All patients provided written, informed consent.

Patients were randomized 1:1 to receive a second-line chemotherapy alone (standard arm) or in combination with bevacizumab (experimental arm) using a centralized web-based system and a minimization algorithm. Stratification factors were Eastern Cooperative Oncology Group Performance Status (ECOG PS, 0 versus 1–2), chemotherapy-free interval (> versus ≤3 months) and the second-line chemotherapy regimen (FOLFIRI versus mFOLFOX-6). The choice of second-line chemotherapy was made by the investigators on the basis of the first-line chemotherapy administered.

patient eligibility

Patients were eligible if they had PD after or during first-line chemotherapy with fluoropyrimidine, FOLFIRI, FOLFOX plus bevacizumab or after at least 3 months from the last dose of first-line FOLFOXIRI plus bevacizumab. The other eligibility criteria were the following: histological diagnosis of

colorectal adenocarcinoma, age between 18 and 75 years, ECOG PS of 0–2, unresectable and measurable metastatic disease according to RECIST criteria version 1.0, adequate hematological, hepatic and renal functions, life expectancy longer than 3 months, urine dipstick for proteinuria <2+, at least 6 weeks from prior radiotherapy and 4 weeks from surgery. Patients were not eligible if they presented at least one of the following conditions: pregnancy or lactation, severe intestinal malabsorption (due to bowel obstruction, history of inflammatory enteritis or extensive intestinal resection), symptomatic peripheral neuropathy, presence or history of brain metastases, past or current history of malignancies other than colorectal cancer, active uncontrolled infections, active disseminated intravascular coagulation, clinically significant cardiovascular disease, uncontrolled hypertension, active uncontrolled bleeding, coagulopathy, serious non-healing wound, use of therapeutic anticoagulation, history of thromboembolic or hemorrhagic events within 6 months before treatment.

treatment

Patients received FOLFIRI or mFOLFOX-6 with or without bevacizumab according to the randomization arm. Chemotherapy was continued until a total of 12 cycles (or more upon investigator's judgment for the best interest of patient), PD, unacceptable toxicities or patient's refusal. Bevacizumab was continued until PD, unacceptable toxicities or patient's refusal.

Toxicity assessment was carried out before each cycle and adverse events (AEs) were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0.

statistical analysis

The primary end point of the study was PFS to second-line treatment. Considering that a second-line chemotherapy alone in mCRC patients achieved a median PFS of ~4 months [5] and in order to demonstrate an HR for PFS of 0.70 in favor of the experimental arm, corresponding to an increase in the median PFS from 4.0 to 5.7 months, with a two-sided α-error of 0.05 and a power of 80%, we estimated the need to observe a total of 249 events. Assuming an accrual time of 24 months and a further minimum follow-up time of 12 months, we required to enroll a total of 262 patients. As previously specified, the accrual was interrupted prematurely after the enrollment of 185 patients.

PFS was defined as the time from the randomization until the first documentation of objective disease progression or death due to any cause, whichever occurred first. PFS was censored on the date of the last follow-up information for patients who were alive and progression-free at the time of the analysis.

Secondary end points were OS, response rate (RR) and safety profile. OS was calculated from the date of randomization to the date of death due to any cause. The assessment of response was done according to RECIST criteria version 1.0 with a computed tomography (CT) scan of the chest and abdomen, repeated every 8 weeks until PD. Response and progression evaluation was based on investigator-reported measurements, subsequently confirmed by an independent, not blinded, central review. The centrally confirmed RR and PFS were reported in the manuscript. Survival curves were estimated by the use of the Kaplan–Meier method and compared with the stratified log-rank test, taking into account ECOG PS, chemotherapy-free interval and second-line regimen. Adjusted HRs and corresponding 95% CIs for PFS and OS were estimated with the Cox proportional hazard regression model. The median period of follow-up was calculated for the entire study cohort according to the reverse Kaplan–Meier method. Responses and toxicities were compared by the use of χ^2 test or Fisher's exact test when appropriate. Subgroup analyses of PFS were carried out by means of interaction test to determine the consistency of the treatment effect according to key baseline characteristics. All efficacy analyses were carried out on an intention-to-treat basis. All statistical tests were two sided, and *P*-values of 0.05 or less were considered to be statistically significant. No adjustment for multiple comparisons was made.

This study is registered in ClinicalTrials.gov with the number NCT00720512.

results

patient characteristics and treatment

Between 8 April 2008 and 11 May 2012, a total of 185 patients were randomized; 184 patients (92 in the standard arm and 92 in the experimental arm) were evaluable for the intention-to-treat analysis because one patient was erroneously randomized twice (supplementary Figure S1, available at *Annals of Oncology* online).

Patients' characteristics were well balanced between the two arms with the exception of a slight imbalance in sex and age (Table 1). The median first-line PFS was 10.9 and 10.3 months in the control and experimental arms, respectively, and the chemotherapy-free interval was longer than 3 months in 66% of patients in both groups. Bevacizumab-free interval resulted longer than 3 months in 43% of patients in the control arm and in 50% in the experimental arm (Table 1).

With regard to the second-line chemotherapy, 66% and 34% of patients in both arms received FOLFOX and FOLFIRI, respectively. The type of second-line chemotherapy, chosen by investigators on the basis of the first-line treatment administered, is showed in supplementary Table S1, available at *Annals of Oncology* online.

activity and efficacy

After a median follow-up of 45.3 months, the number of events for PFS was 182 (99%). A significant improvement of PFS in

Table 1. Patients' characteristics

Characteristics	CT (92 patients) (%)	CT + BV (92 patients) (%)
Age, median (range)	66.5 years (38–75)	62 years (38–75)
Sex (M/F)	75/25	57/43
ECOG PS 0/1/2	82/17/1	82/16/2
Sites of disease (single/multiple)	24/76	24/76
Liver-only metastases	15	13
KRAS[a] (wt/mut/NA)	36/32/33	32/40/28
BRAF[a] (wt/mut/NA)	64/3/33	65/7/28
First-line CT		
Fluoropyrimidine	4	1
FOLFIRI	58	59
FOLFOX	25	24
FOLFOXIRI	13	16
First-line PFS, median	10.9 months	10.3 months
CT-free interval >3 months	66%	66%
BV-free interval >3 months	43%	50%

[a]Centralized analysis.
ECOG PS, Eastern Cooperative Oncology Group Performance Status; wt, wild-type; mut, mutated; NA, not applicable; CT, chemotherapy; PFS, progression-free survival; BV, bevacizumab.

the experimental arm was observed. The median PFS was 5.0 months with chemotherapy alone and 6.8 months with bevacizumab plus chemotherapy (adjusted HR = 0.70, 95% CI 0.52–0.95; stratified log-rank $P = 0.010$) (Figure 1).

Data from subgroup analysis for PFS were consistent with those of the overall population. In particular, patients who continued bevacizumab beyond progression (bevacizumab-free interval ≤3 months) or those who had reintroduced bevacizumab after progression (bevacizumab-free interval >3 months) had a similar benefit (Figure 2).

With regard to secondary end points, our results demonstrated that the continuation or reintroduction of bevacizumab beyond progression did not significantly increase RR neither disease control rate. Overall, RR was 17% in the standard arm and 21% in the experimental arm ($P = 0.573$), disease control rate was 58% and 70%, respectively ($P = 0.124$), as reported in Table 2.

The number of events for OS was 82 and 81 in the standard and experimental arms, respectively. The median OS was 15.5 months with chemotherapy alone and 14.1 months with bevacizumab plus chemotherapy because of curves intersection, but the adjusted HR = 0.77 (95% CI 0.56–1.06; stratified log-rank $P = 0.043$) was in favor of the experimental arm (Figure 3).

safety

One hundred and eighty-three patients received at least one cycle of second-line therapy and were evaluable for safety. One patient in arm B did not receive any cycles of second-line treatment due to early deterioration of PS. The median number of cycles of treatment was 8 (range 1–19) in the standard arm and 9 (range 1–13) in the experimental arm. No differences in terms of any grade (93% versus 94%), grade 3–4 (43% versus 44%) and serious (7% versus 7%) AEs were observed between the two arms. One toxic death due to central nervous system ischemia occurred in the bevacizumab group.

The incidence of bevacizumab-related toxicities, in particular hypertension, bleeding and proteinuria, was higher in the experimental arm, even if this difference was not statistically significant and grade 3–4 toxicities did not differ between the two arms (supplementary Table S2, available at *Annals of Oncology* online).

subsequent anti-cancer therapy

At least one subsequent anti-cancer therapy was received by 75% and 73% of patients in the standard and the experimental arm, respectively. Only few patients received a further treatment containing bevacizumab (1% versus 4%). Fifty percent of patients in the control arm and 32% of patients in the experimental arm received a subsequent therapy containing cetuximab or panitumumab.

discussion

We designed the present trial of second-line chemotherapy with or without bevacizumab to verify the potential benefit of the continuation or reintroduction of bevacizumab after first progression in patients with mCRC who had received a first-line chemotherapy plus bevacizumab. Results demonstrate that the continuation or reintroduction of bevacizumab with second-line chemotherapy improves PFS (primary end point), with a median PFS of 6.8 months in the bevacizumab group and 5.0 months in the chemotherapy group (adjusted HR = 0.70; 95% CI 0.52–0.95; stratified log-rank $P = 0.010$). Subgroup analyses for PFS were consistent with the primary findings in all subgroups. Even if the median OS in the bevacizumab group was slightly inferior than the median OS in the chemotherapy group (14.1 versus 15.5 months) due to curves intersection, an adjusted HR = 0.77 (95%

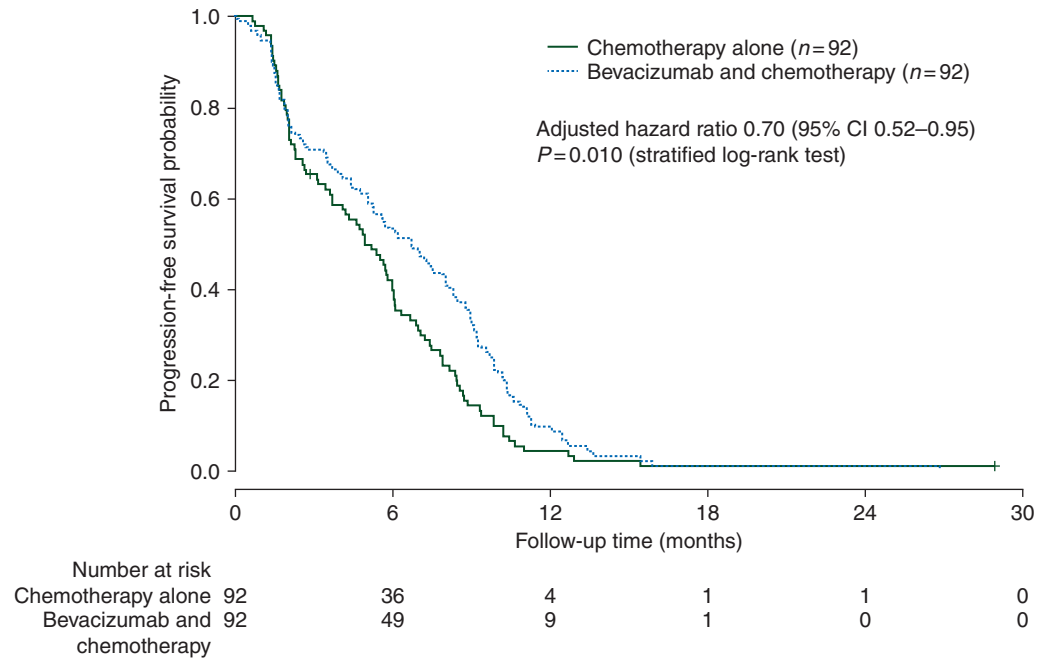

Figure 1. Kaplan–Meier analysis of progression-free survival comparing patients treated with chemotherapy alone (green line) versus patients treated with bevacizumab and chemotherapy (blue line).

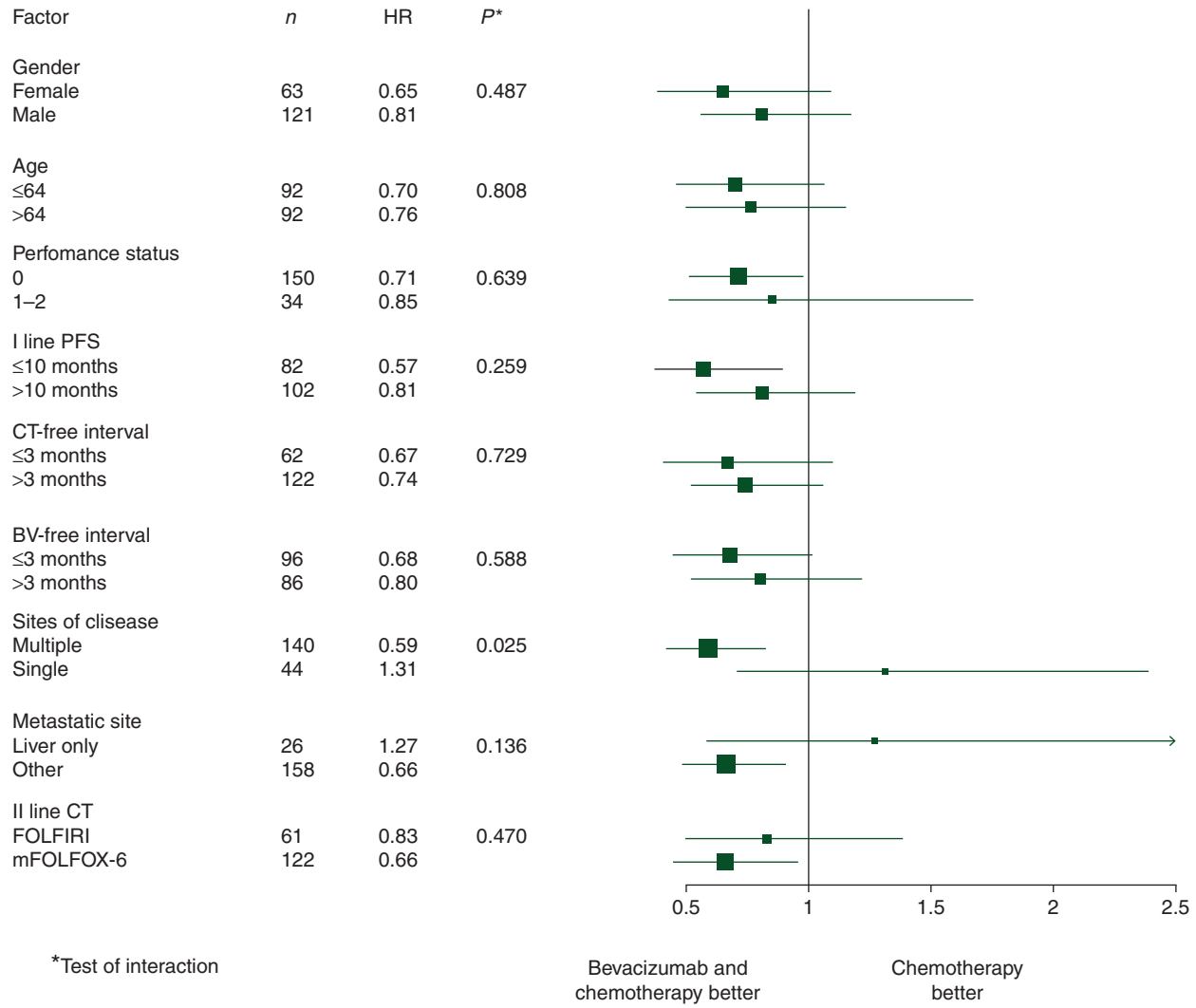

Figure 2. Subgroups analysis of progression-free survival. CT-free, chemotherapy-free; BV-free, bevacizumab-free; I line PFS, first-line progression-free survival; II line CT, second-line chemotherapy.

CI 0.56–1.06; stratified log-rank $P = 0.043$) in favor of the experimental arm was observed. Safety profile was coherent with previously reported data confirming a good safety profile for continuing or reintroducing bevacizumab after first progression.

The role of the continuation of bevacizumab after first progression was also evaluated in the randomized phase III trial ML18147 [10]. In this trial, a total of 820 patients with mCRC progressing up to 3 months after discontinuing first-line bevacizumab plus chemotherapy were randomly assigned to second-line chemotherapy with or without bevacizumab. The OS (primary end point) was significantly improved with bevacizumab plus chemotherapy, achieving a median OS of 11.2 versus 9.8 months with chemotherapy alone (HR = 0.83; 95% CI 0.71–0.97; log-rank $P = 0.0211$). The continuation of bevacizumab with second-line chemotherapy improved also PFS (HR = 0.67; 95% CI 0.58–0.78; log-rank $P < 0.0001$). On the basis of these results, bevacizumab has been recently approved by the American and European regulatory agencies in combination with second-line fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy in mCRC patients who have progressed on a first-line bevacizumab-containing regimen.

Table 2. Response rate according to RECIST v1.0 criteria

	CT ($n = 92$) (%)	CT + BV ($n = 92$) (%)
Complete response (CR)	2	1
Partial response (PR)	15	20
Overall response rate (RR)*	17	21
Stable disease (SD)	41	49
Disease control rate (DCR)	58	70
Progressive disease	40	29
Not evaluable	2	1

*$P = 0.573$.
CT, chemotherapy; BV, bevacizumab.

The main limitations of the BEBYP trial are the low statistical power due to small sample size and the slow accrual rate, which probably might explain the intersection between OS curves (Figure 3). Nevertheless, this study could demonstrate an

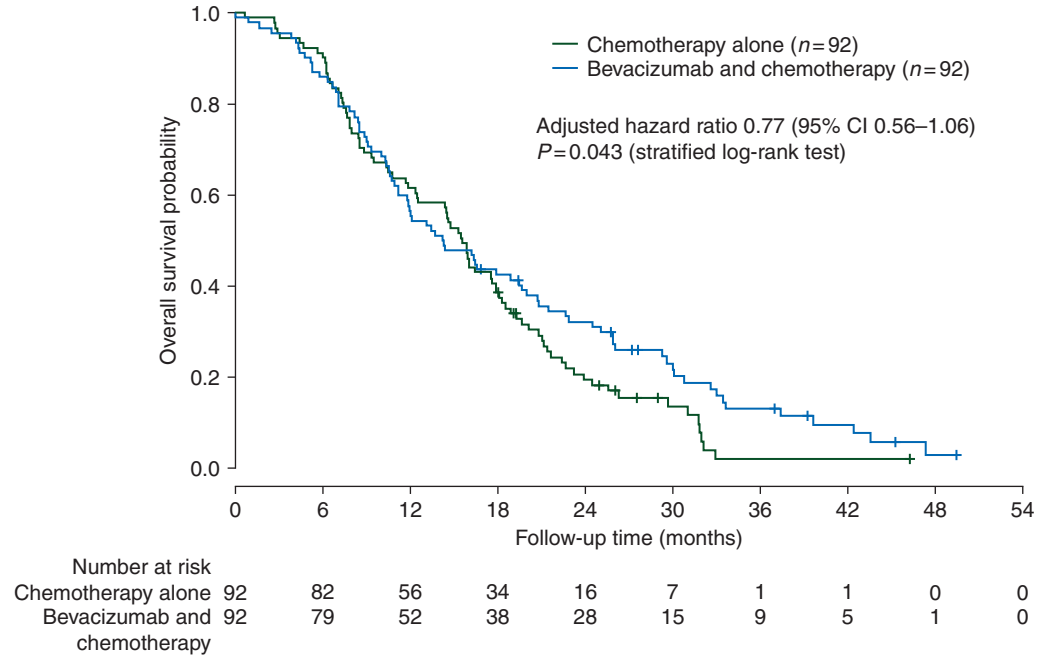

Figure 3. Kaplan–Meier analysis of overall survival comparing patients treated with chemotherapy alone (green line) versus patients treated with bevacizumab and chemotherapy (blue line).

improvement in PFS and OS with a magnitude similar to the ML18147 trial. In terms of absolute values, our trial achieved better results in both arms compared with the ML18147 (median PFS of 5.0 and 6.8 months in the BEBYP trial versus 4.1 and 5.7 months in the ML18147 trial; median OS of 15.5 and 14.1 versus 9.8 and 11.2 months, respectively; RR of 17.5% and 21% versus 4% and 5%, respectively). A possible explanation for this difference might be the different inclusion criteria between the two trials and patients' general conditions. In the ML18147 study, patients who had interrupted bevacizumab for more than 3 months were excluded and patients with PS 0 were ~43%, whereas in our study, patients who had reintroduced bevacizumab after more than 3 months were 43% in the chemotherapy group and 50% in the bevacizumab group and those with PS 0 were 82% in both arms.

The results of both trials, BEBYP and ML18147, show a smaller benefit in continuing bevacizumab if compared with the results of the two observational trials, BRITE and ARIES [8, 9]. This difference is probably due to the potential biases of the observational trials.

The biological concept of benefit associated with continuing angiogenesis inhibition after disease progression is also supported by the results from two recent trials, the VELOUR and the CORRECT trial. In the phase III VELOUR study [11], aflibercept (an antiangiogenic recombinant fusion protein that blocks the activity of VEGFA, VEGFB and PlGF) was added to FOLFIRI treatment in patients who had tumor progression to oxaliplatin-based first-line treatment. Aflibercept improved outcomes to almost the exact extent as bevacizumab in the ML18147 study, independently of whether patients had received bevacizumab in first-line treatment or not [12]. In the CORRECT trial [13], treatment with regorafenib (an orally administered multikinase inhibitor with potent inhibitory activity on VEGFR-1, VEGFR-2 and VEGFR-3) was beneficial in patients with mCRC progressing after receiving all approved standard treatments, included bevacizumab.

The concept of continuing angiogenesis inhibition beyond a first-line containing bevacizumab has been recently strengthened also by the announcement of positive results of the phase III study RAISE evaluating the combination of ramucirumab with second-line FOLFIRI. Although all the limitations of our study, first of all its premature interruption and the small sample size, we can conclude that the BEBYP trial results support the idea that a strategy of continuing to inhibit angiogenesis beyond first progression can improve the outcome of mCRC patients treated in first line with chemotherapy plus bevacizumab without a significant worsening of toxicities. Furthermore, the BEBYP results could suggest that also the reintroduction of bevacizumab with second-line chemotherapy in patients who had a discontinuation of more than 3 months might be beneficial. This strategy has a cost, but we think that it is important to consider globally the additional benefit of the combination of bevacizumab with first-line chemotherapy and then with maintenance therapy and then with second-line therapy. In this view, in our opinion, this strategy is cost-effective.

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disclosure

GM has received honoraria and expenses for travel, accommodations and meetings from Amgen, Merck, Bayer and Roche. FL reports serving on advisory board for Amgen, and Sanofi-Aventis, receiving payment for the development of educational presentations from Roche, Amgen and receiving lecture fees from Sanofi-Aventis, Bayer, Roche and receiving grant support from Roche and Merck Serono. CC reports serving on advisory board for Roche and Bayer and receiving payment for the development of educational presentations from Bayer. CB has received honoraria and expenses for travel, accommodations and meetings from Sanofi, Roche, Bayer, Merck and Celgene. SC reports receiving payment for the development educational presentation from Amgen, Roche, Merk Serono. AF reports serving on advisory board for Amgen, Bayer, Merck Serono, Roche and Sanofi-Aventis, receiving payment for the development of educational presentations from Amgen, Bayer, Merck Serono, Roche and Sanofi-Aventis and receiving lecture fees from Amgen, Bayer, Merck Serono, Roche and Sanofi-Aventis and receiving grant support from Amgen, Merck Serono and Roche. All remaining authors have declared no conflicts of interest.

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