Effectiveness of bevacizumab in first- and second-line treatment for metastatic colorectal cancer: ITACa randomized trial

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Abstract

Background: Cancer trials involving multiple treatment lines substantially increase our understanding of therapeutic strategies. However, even when the primary end-point of these studies is progression-free survival (PFS), their statistical analysis usually focuses on each line separately, or does not consider repeated events, thus missing potentially relevant information. Consequently, the evaluation of the effectiveness of treatment strategies is highly impaired.

Methods: We evaluated the potentially different effect of bevacizumab (B) administered for the first- or second-line treatment of metastatic colorectal cancer (mCRC) in the ITACa (Italian Trial in Advanced Colorectal Cancer) randomized trial. The ITACa trial consisted of two arms: first-line chemotherapy (CT)+B followed by second-line CT alone *versus* first-line CT alone followed by second-line CT+B or CT+B+cetuximab according to KRAS status. Cox models for repeated disease progression were performed, and potential selection bias was adjusted using the inverse probability of censoring weighting method. Hazard ratios (HR) [95% confidence interval (CI)] for PFS (primary endpoint) were reported.

Results: The overall effect of B across the two lines resulted in a HR = 0.80 (95% CI 0.68–0.95, $p = 0.008$). Evaluating the differential effect of B in first- and second-line, the addition of B to first-line chemotherapy (CT) produced a 10% risk reduction (HR = 0.90, 95% CI 0.72–1.12, $p = 0.340$) *versus* CT alone; B added to second-line CT produced a 36% risk reduction (HR = 0.64, 95% CI 0.49–0.84, $p = 0.0011$) *versus* CT alone.

Conclusion: Our results seem to suggest that B confers a PFS advantage when administered in combination with second-line chemotherapy, which could help to improve current international guidelines on optimal sequential treatment strategies.

Keywords: metastatic colorectal cancer, repeated events, selection bias, sequential trial

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Introduction

Treatment for metastatic colorectal cancer (mCRC) is based on either cytotoxic drugs available in generic form, such as fluorouracil (5-FU), irinotecan, or oxaliplatin, or agents targeting specific pathways. Although the efficacy of the former is widely acknowledged, their impact on survival is still limited.[1] However, the addition of approved molecular-targeted agents directed against epidermal growth factor receptor (EGFR) – cetuximab and panitumumab – or vascular endothelial growth factor (VEGF) – bevacizumab (B) – could help to improve the survival benefit.[1–12]

In cases of unresectable mCRC, the combination of chemotherapy (CT) and a molecular-targeted

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agent is standard practice in first-line therapy. After disease progression (PD) at the end of full first-line therapy, the CT regimen is normally switched from 5-FU/oxaliplatin to 5-FU/irinotecan or vice versa. Other therapeutic options also comprise the sequential administration of molecular-targeted agents.[1,13]

In the present paper, which is based on the ITACa (Italian Trial in Advanced Colorectal Cancer) trial,[14] we provide original empirical evidence of the effectiveness of B with suggestions on the best sequential administration strategy. The ITACa trial was a randomized study aimed at assessing two treatment sequences within a pragmatic approach: the first arm received CT+B as first-line treatment followed by CT alone as second-line treatment, while the second arm received CT alone as first-line treatment followed by CT+B as second-line treatment.[14]

With regard to the role of B, Goldstein *et al*. conducted a cost-effectiveness analysis of B in first- and second-line settings.[15] A modest incremental benefit of B was obtained at a high incremental cost-per-QALY (quality-adjusted life-year) in both settings. This analysis was, however, based on limited empirical evidence and on an assumed equal efficacy of B in first- and second-line treatment.

A number of studies have analyzed either first- or second-line treatment,[2–13,16,17] and only a few have collected data on more than one treatment line.[18–20] Their primary endpoint was mainly overall survival (OS). However, each treatment line was considered separately when progression-free survival (PFS) was analyzed. This approach is not appropriate when the study aim is either to estimate the overall treatment effect, that is, considering the entire history of patients, or to compare treatment effects obtained in each line in presence of a patient selection process.

In the present study, we assessed the role of B through an original approach based on a recurrent event analysis of all PD events and the inverse probability of censoring weighting (IPCW) method to manage the patient selection process in a pragmatic trial comprising two sequential strategies and involving two treatment lines.[20–26] The importance of this aspect in terms of its impact on guidelines for patient management and in the light of the "continuum of care" concept is often underestimated, and trials focusing on single lines of therapy still dominate the literature, even though their results may be difficult to interpret and potentially misleading in this context.

Methods

Study design

ITACa was a comparative phase III multicenter randomized trial on two sequences of treatment for mCRC (Figure 1). Patients randomized to Arm A were scheduled to receive CT+B as first-line regimen followed by CT alone or CT+cetuximab as second-line treatment according to KRAS status. Patients randomized to Arm B were to receive CT alone as first-line regimen followed by CT+B or CT+B+cetuximab as second-line treatment according to KRAS status. The ITACa study included a second randomization for second-line cetuximab treatment. After the start of the trial, two studies reported a potentially detrimental effect of the combination of the two monoclonal antibodies, bevacizumab + cetuximab.[27,28] The Steering Committee of the ITACa trial evaluated the idea of amending the study by eliminating the CT+B+cetuximab arm. However, after a review of available literature data it was decided not to proceed with a modification because the trials in question were conducted before KRAS mutations were identified as a predictor of poor response to anti-EGFR monoclonal antibodies and so patients were not selected. Moreover, both were first-line trials and the CT regimens analyzed differed from those of the ITACa trial. All ITACa investigators were nonetheless instructed to monitor carefully for toxicity.[12] More details on the study design and procedures can be found in the paper by Passardi *et al*.[14]

Participants

The accrual period was 14 November 2007 to 6 March 2012. The end of follow up was 31 August 2016. Patients aged ⩾18 years with histologically confirmed mCRC, one or more unidimensionally measurable lesions not amenable to curative resection, an Eastern Cooperative Oncology Group performance status (ECOG PS) of ⩽2 (⩽1 if aged ⩾70 years), and an estimated life expectancy of ⩾12 weeks, were eligible for enrolment. Previous adjuvant CT for CRC or neoadjuvant/adjuvant chemoradiotherapy for rectal cancer were permitted only if completed ⩾6 months prior to recurrence. Patients who had previously undergone treatment with any

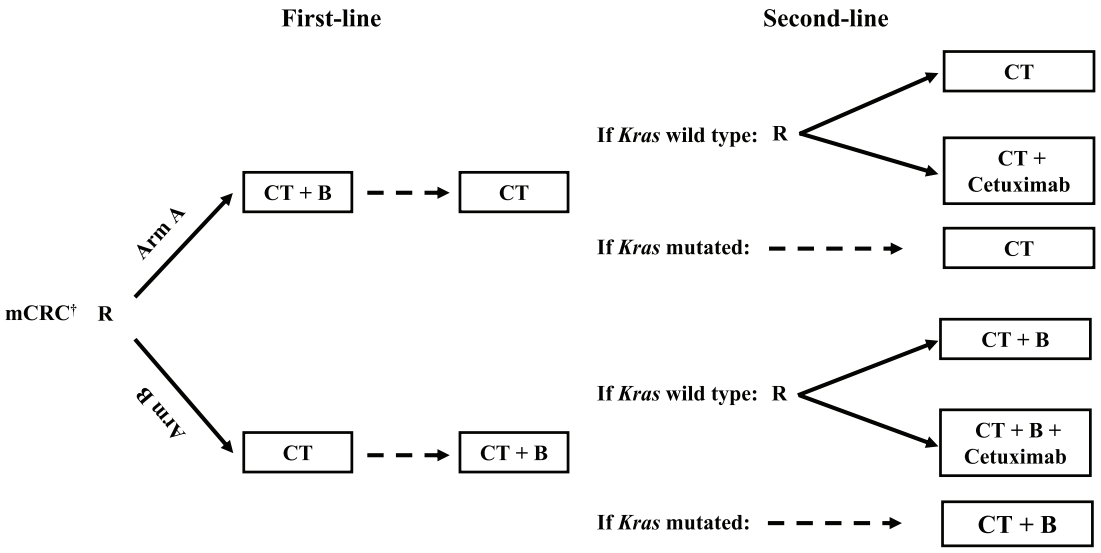

Figure 1. Study design of the ITACa trial.
B, bevacizumab; CT, chemotherapy (FOLFIRI or FOLFOX); ITACa, Italian Trial in Advanced Colorectal Cancer; mCRC, metastatic colorectal cancer; R, randomization.

anti-EGFR or anti-angiogenesis agent, or CT or immunotherapy for metastatic or advanced disease were not considered.

All patients provided written informed consent and the study was performed in accordance with the principles of Good Clinical Practice and the ethical standards of the Declaration of Helsinki. The protocol was approved by the local ethics committee (Comitato Etico Area Vasta Romagna) on 19 September 2007 and was registered in our National Clinical Trials Observatory (Osservatorio delle Sperimentazioni Cliniche) and in the European Clinical Trials Database (EudraCT no. 2007-004539-44) before patient recruitment began.

Registration on ClinicalTrials.gov [ClinicalTrials.gov identifier: NCT01878422] was not mandated but was carried out at a later date. The authors confirm that all ongoing and related trials for drugs are registered.

Treatment

All eligible patients were randomized to either Arm A (CT+B→CT) or Arm B (CT→CT+B). CT was FOLFIRI or FOLFOX4 for both arms at the clinician's discretion. B was administered as a 30- to 90-min intravenous infusion at a 5 mg/kg dose on day 1 of each 2-week cycle. Treatment was to be continued until PD, withdrawal of consent, or unacceptable toxicity, whichever came first. Pre-specified CT dose modifications were made after the occurrence and resolution of severe hematologic or non-hematologic toxicity. If a patient became eligible for curative resection of metastatic disease, B would have to be stopped at least 6–8 weeks prior to surgery. After surgery, the choice of treatment was at the clinician's discretion, and patients could either resume treatment with CT (with or without B in Arm A) after ⩾28 days of surgery or complete wound healing, until PD. By "surgery" we mean curative resection of the metastatic disease, and by "toxicity" (NCI-CTC criteria V3) all non-hematologic grade 3 and 4 adverse events.

Outcomes and other clinical measures

The primary outcome was PFS, defined as the time from the random assignment to the first documented events, PD, or death from any cause, whichever occurred first. The main baseline characteristics between study arms are shown in Table 1.

Statistical analysis

Our analysis had two objectives: (a) evaluation of the efficacy of B; and (b) comparison between the two B administration strategies (arm A *versus* B). Given that a patient could potentially experience more than one PD event, PFS was considered as a recurrent event. In the present study, the

Table 1. Main baseline patient characteristics by randomization arm.

	All ($n = 370$)		Arm A ($n = 176$)		Arm B ($n = 194$)	
	n	(%)	*n*	(%)	*n*	(%)
Gender						
Female	147	(39.7)	68	(38.6)	79	(40.7)
Male	223	(60.3)	108	(61.4)	115	(59.3)
Age, years						
Mean ± SD	64.5 ± 10.3		64.6 ± 10.2		64.5 ± 10.4	
Chemotherapy regimen						
FOLFOX4	221	(59.7)	103	(58.5)	118	(62.8)
FOLFIRI	149	(40.3)	73	(41.5)	76	(39.2)
KRAS						
Wild type	235	(63.5)	112	(63.6)	123	(63.4)
Mutated	135	(36.5)	64	(36.4)	71	(36.6)
Tumor localization						
Rectum	92	(24.9)	41	(23.3)	51	(26.3)
Colon	278	(75.1)	135	(76.7)	143	(73.7)
ECOG PS						
0	298	(80.5)	144	(81.8)	154	(79.4)
⩾1	72	(19.5)	32	(18.2)	40	(20.6)
LDH						
⩽UNL	200	(58.1)	101	(62.9)	99	(54.7)
>UNL	144	(41.9)	62	(38.0)	82	(45.3)

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; SD, standard deviation; UNL, upper normal limit.

analysis was limited to the first and second PD, or death.

We fitted four variants of the survival Cox model: (a) the Andersen-Gill (AG) model,[21] a simple extension of the Cox model that assumes a common baseline hazard of PD irrespective of previous PD history; (b) the Prentice, Williams and Peterson (PWP) conditional model,[22] which specifies different baseline hazards depending on the PD time sequence and is therefore more suitable if the PD hazard varies between first and second recurrence. Both AG and PWP models were used to assess the efficacy of B; (c) the PWP model, with the inclusion of an interaction term between B and the PD rank (PWP-I), to test the differential effect of B in first- and in second-line treatment, and (d) the PWP model with a frailty random term to test the presence of residual heterogeneity among patients.[24]

The AG model is a simple, easy-to-understand benchmark for recurrent event analysis. In general, simpler and parsimonious models guarantee a greater external validity than more complex ones, which may be influenced by chance characteristics of the single dataset, especially when sample size is not large. Formal comparison between these

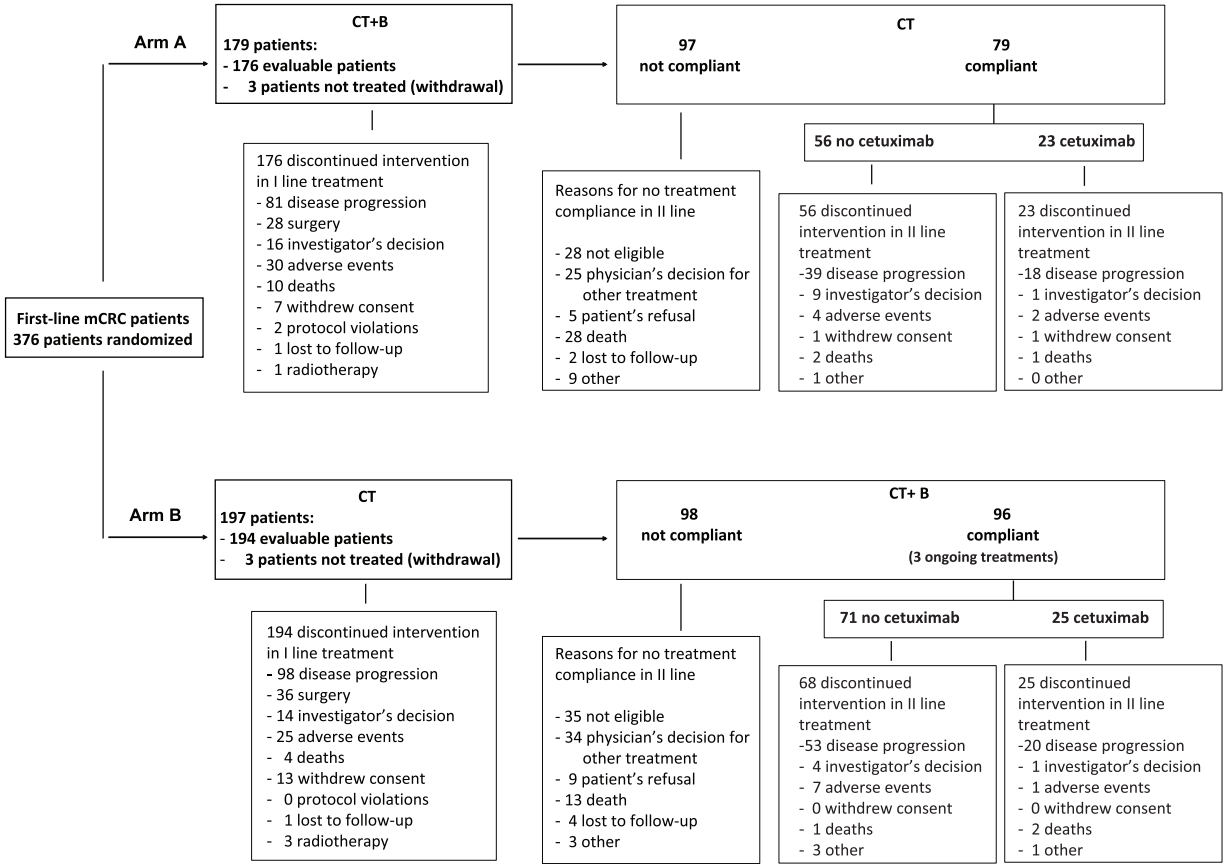

Figure 2. CONSORT diagram of the ITACa trial.
B, bevacizumab; CT, chemotherapy (FOLFIRI or FOLFOX); ITACa, Italian Trial in Advanced Colorectal Cancer; mCRC, metastatic colorectal cancer.

models is not possible because, as in our case, the empirical evidence is insufficient to discriminate between these models. We chose to report all the fitted models to illustrate the different way in which each one summarizes the empirical information: the AG model provides an overall estimate of the effect of B without assumptions on the baseline hazard, whereas the PWP model stratifies on treatment line which seems *a priori* a reasonable assumption; PWP(I) is a nested model for assessing the differential effect of B; and the frailty model is fitted as a sensitivity analysis to assess the effect of B in the presence of residual patient heterogeneity. Given the potentially negative influence of cetuximab on the effect of B, we performed a sensitivity analysis for those receiving cetuximab that did not consider patient history after second-line randomization. The IPCW method was used to manage the potential bias of the patient selection process (Figure 2 and Table 2).[25,26,29]

All relevant variables that can explain the selection process are included in the calculation of IPCW. Thus, all the statistical models are indirectly adjusted for covariates by using IPCW in a way similar to adjustment by propensity score. Given the fact that some values were missing for lactase dehydrogenase (LDH), which is used in the computation of the IPC weights, all the models were fitted on 344 patients. Among these, 321 PDs or deaths were observed during first-line treatment, whereas 161 PDs or deaths were registered during second-line therapy.

Patient characteristics are summarized using means ± standard deviation (SD), frequencies, and percentages, when appropriate. Hazard ratios (HRs) are reported with 95% confidence intervals (CIs). Two-sided *p* values are reported when testing the differential effect of B in first-line *versus* second-line treatment).[30] All analyses were performed using STATA Statistical Software Release 14 (StataCorp LP, College Station, TX, USA) and R Version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria). Inverse probability of censoring weights was computed in

Table 2. Patient characteristics by compliance to second-line treatment.

	No (No. 195)		Yes (No. 175)	
	n	(%)	*n*	(%)
Gender				
Female	81	(41.5)	66	(37.7)
Male	114	(58.5)	109	(62.3)
Mean age (years) ± SD	65.7 ± 9.8		63.2 ± 10.6	
First-line randomization arm				
FOLFOX4 + bevacizumab	56	(28.7)	47	(26.9)
FOLFIRI + bevacizumab	42	(21.5)	31	(17.7)
FOLFOX4	67	(34.4)	51	(29.1)
FOLFIRI	30	(15.4)	46	(26.3)
KRAS status				
Wild type	134	(68.7)	101	(57.7)
Mutated	61	(31.3)	74	(42.3)
Center				
Other	132	(67.7)	89	(50.9)
IRST	63	(32.3)	86	(49.1)
Tumor localization				
Rectum	48	(24.6)	44	(25.1)
Colon	147	(75.4)	131	(74.9)
ECOG PS				
0	155	(79.5)	143	(81.7)
⩾1	40	(20.5)	32	(18.3)
LDH				
⩽UNL	110	(61.8)	90	(54.2)
>UNL	68	(38.2)	76	(45.8)
Surgery				
No	152	(77.9)	151	(86.3)
Yes	43	(22.1)	24	(13.7)
Hematologic toxicity				
No	146	(74.9)	142	(81.1)
Yes	49	(25.1)	33	(18.9)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; UNL, upper normal limit.

R using the *ipw* package.[31] A full description of the statistical analyses is given in the Supplemental Material.

Results

Between 14 November 2007 and 6 March 2012, 376 patients were randomly assigned to the two study arms, 179 to Arm A (CT+B→CT) and 197 to Arm B (CT→CT+B). The study design is reported in Figure 1. Of the 376 patients, 6 (1.6%) were excluded due to consent withdrawal or eligibility criteria violation, thus leaving 176 patients in Arm A and 194 in Arm B. A total of 96 patients (55%) in Arm A and 98 patients (51%) in Arm B did not comply with the second-line treatment, the main reasons being the patient's physical conditions or the physician's decision, as reported in the CONSORT diagram (Figure 2).

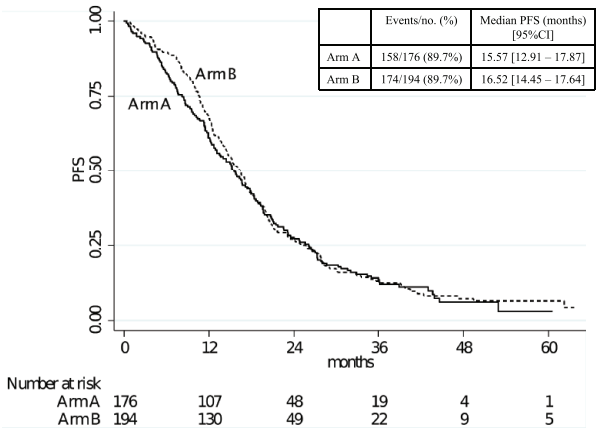

Figure 3. Kaplan Meier survival curves from first randomization to second disease progression or death, whichever came first, by arm (Arm A: CT+B→CT; Arm B: CT→CT+B).
PFS, progression-free survival.

The characteristics of the patients receiving or not receiving second-line treatment are reported in Table 2. We modeled the probability of selective withdrawal from the second-line treatment fitting a Cox model for time to second-line treatment. The most important factors were patient age at randomization, study arm, ECOG PS, LDH, and surgery/curative resection of metastatic disease. This model was used for the calculation of the stabilized IPCW alongside a simpler model with only the observed time-fixed covariates, as explained in the statistical analysis section.

The observation of the patients in second-line treatment was weighted using stabilized IPCW to reconstruct the complete population. Therefore, all patient clinical histories post-first PD are, after weighting, representative of the starting population as though the selective withdrawal had never occurred.

Preliminary analysis of sequential treatment strategy

The standard approach in a randomized study of sequential therapeutic strategy involving multiple-lines is to compare the two strategies using Kaplan–Meier curves (Figure 3). This analysis considers only the time elapsed between first randomization to second PD or death for each subject. Patients who did not progress were censored at the date of the last tumor assessment. No difference between the two arms in the Kaplan–Meier survival curves was evident. This approach ignores the selection process which affects mainly more advanced patients, overlooking most of the information in patient clinical history from randomization to first and second PD.

Efficacy of bevacizumab

We fitted an IPC-weighted Cox model for repeated events to understand the role of B by considering all available information from randomization to the first and possibly second PD. The AG model was the first model to be considered. We estimated a 0.83 (95% CI 0.69–1.00) HR for B (Table 3) ($p=0.046$). This model assumes a baseline hazard common to the first and second PD. This may appear implausible either for clinical reasons or selection process. Indeed, we observed that the hazard for the second PD was higher than that for the first PD. The PWP conditional model, which takes into account different baseline hazards for first and second PD, was fitted. The HR for B was 0.80 (95% CI 0.68–0.95). Treatment with B reduced the risk of PD or death by 20%, with 95% CI of 5–32% ($p=0.008$). In the paper by Passardi *et al.*,[14] the HR for B was 0.86 (95% CI 0.70–1.07), corresponding to a risk reduction of 14%, with 95% CI of 30%, 7%.

Differential efficacy of bevacizumab in first- and second-line treatment

The test for the differential effect of B, that is, the test on the two treatment strategies (Arm A *versus* Arm B) resulted in a p value of 0.067. The addition of B to CT in first-line treatment produced a

Table 3. Results from the variants of the Cox model for the effect of bevacizumab.*

	AG		PWP		PWP-I[a]	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
B						
No	1		1		1	
Yes	0.83 (0.69–1.00)	0.046	0.80 (0.68–0.95)	0.008	0.90 (0.72–1.12)	0.340
B×rank of PD					0.64 (0.49– 0.84)	0.001

[a]*p* value for the interaction between bevacizumab and event = 0.067.
AG, Andersen and Gill model; B, bevacizumab; CI, confidence interval; HR, hazard ratio; PD, progressive disease; PWP, Prentice, Williams, and Peterson conditional model; PWP-I, Prentice, Williams, and Peterson conditional model with interaction.
*Caution is needed when testing the main effect in the presence of interactions. Thus, in the Results section we based our reasoning on the *p* value for the interaction ($p = 0.067$) rather than the *p* values for the HRs in the first- ($p = 0.340$) and in second-line treatments ($p = 0.0011$).[36]

10% (95% CI –28%, +12%) risk reduction (HR = 0.90, 95% CI 0.72–1.12, *p* value = 0.340) with respect to CT alone and a 36% (95% CI –51%, –16%) risk reduction (HR = 0.64, 95% CI 0.49–0.84, *p* value = 0.0011) when B was added to CT in second-line treatment compared with CT alone. Our findings thus provide some evidence of a greater effect of B in second-line treatment (Table 3).

Since, after the start of ITACa trial, two studies reported a potential detrimental effect of the combination of the two monoclonal antibodies, bevacizumab and cetuximab, a sensitivity analysis not considering the patients' history after randomization to second-line treatment of the subgroup of patients receiving cetuximab ($n = 23$ receiving CT+cetuximab and $n = 25$ receiving CT+B+cetuximab), was performed. The effect of B in first-line treatment was equal to an HR of 0.96 (95% CI 0.76–1.20, $p = 0.732$) and the effect of B in second-line treatment with an HR = 0.60 (95% CI 0.45–0.79, $p = 0.0005$). The test for differential effect of B resulted in a *p* value = 0.014.

Patient heterogeneity

In order to provide some idea of the extent and clinical importance of patient heterogeneity, we calculated the percentage of patients with HR $\geqslant 2$, that is, more than twofold the hazard of PD regardless of all observed patient characteristics and treatments. This percentage is governed by the variance parameter of the frailty model. The higher the percentage, the greater the heterogeneity. We estimated that 20% of patients would have a more than twofold higher than average HR of PD. This means that one out of five patients has a double or more risk of PD that is not explained by the clinical or tumor variables measured in the study.

Discussion

Given that the ITACa trial was a pragmatic sequential strategy study considering first- and second-line treatment, we were able to assess both the overall effect of B and the effect of B when administered in first- and second-line. Our results are based on the recurrent event analysis of all progression episodes adjusting for patient selection. In a previous paper limited to the first PD, we reported a 14% (95% CI –30%, 7%) risk reduction,[14] whereas in the present paper, a 20% (95% CI of –32%, –5%) reduction in the risk of progression or death was observed. Our approach allowed for a more precise estimate of the effect of B, with a 72% gain in precision. Consequently, the half-width of the CI reduced from 18.5 [(–30–7)/2 = 18.5] to 13.5 [(32–5)/2 = 13.5]. We thus addressed the estimation of the effect of B when administered in first-line treatment only *versus* second-line treatment only. A 10% (95% CI –28%, +12%) risk reduction was observed when B was added to CT in first-line treatment and a 36% (95% CI –51%, –6%) reduction in the risk was registered when B was added to CT in second-line treatment (interaction *p* value = 0.067). We considered the adjustment for the potential selective withdrawal at second-line treatment in all our analyses. The addition of B to CT has been shown to significantly increase median time to PD in the majority of randomized clinical trials.[4–12] These studies are based mainly on the analysis of the first

PD. To the best of our knowledge, there are still no published randomized studies investigating the effect of B in first- or second-line treatment in a unified framework using a repeated event analysis and IPCW to control for selection bias.

The interpretation of published results on second-line treatment is difficult and potentially misleading because:

(1) First, the reference group may or may not have undergone previous treatment with B;
(2) Secondly, the patient population in the second-line treatment may be affected by the selection process as a high percentage of patients undergoing first-line treatment are often ineligible for a second-line study.

Second-line effect estimates should always be considered cautiously, especially in comparisons with first-line treatment effects. Clinicians generally have insufficient information to plan a course of treatment for individual patients as it is incorrect to evaluate the estimated effect of B obtained separately in first- and second-line treatment. The sequential strategy can be assessed by an appropriate study design and statistical analysis such as that of the present study.

Regardless of the drug being considered, only five mCRC trials have been published on multiple treatment lines.[18,20,32–34] Of these, one is still ongoing (STRATEGIC-1),[33] and only the study protocol has been published to date. However, all five studies use an approach that ignores the repeated event feature of disease progression and the potential selection process of patients that often characterize these kinds of trials. Our study, through its statistical approach to repeated events and the IPCW method for the correction of selection bias, provides valid, unbiased evidence of the impact of B in either first- or second-line treatment only.[23,26] Given that our estimate of a 36% risk reduction of B in second-line treatment is undoubtedly of clinical relevance, we would suggest administering B in second-line rather than first-line treatment as an initial choice in the mCRC setting. Our findings confirm the conclusions of the cost-effectiveness analysis by Goldstein *et al.*,[15] which, however, were not based on empirical data. Literature data show that around 50% of patients initially enrolled in a protocol entered second-line treatment. This fact, combined with our estimate of the effect of B (HR 0.80 or 0.63 in second-line treatment), supports the indication of B in second-line treatment from a cost-effectiveness perspective.

However, the greater effect of B in second-line treatment still needs to be reproduced in other studies on sequential treatment strategy and should be thus considered carefully. Furthermore, although our results were affected by the high percentage of patient withdrawals, other randomized trials also suffered from the same problem.[18–20]

Another reason for caution is that the statistical analysis used, which takes into account the selection process with the IPCW method, is based on the assumed absence of unmeasured confounders. A second effect of a high percentage of patients not entering second-line treatment is a low power in estimating differential effects at second-line. Consequently, in the design phase of a trial on a multiple-line sequential strategy, adequate inflation of the initial sample size calculation is recommended.

We did not evaluate other more recently introduced therapeutic drugs because the ITACa trial was designed in 2007 when anti-EGFR therapies were still unavailable for first-line treatment. As the number of therapeutic options has increased substantially, appropriate trials such as ITACa are especially important. The ITACa trial included a nested second randomization with a treatment arm of second-line cetuximab. Thus, the two arms were balanced and no additional covariate was needed in the statistical analysis. Our results on B in second-line treatment may be an underestimation of the efficacy of B given the presence of the CT+B+cetuximab arm ($N=25$ KRAS wild type patients and $N=23$ KRAS wild type patients in the CT+cetuximab arm). Indeed, the results of a subgroup analysis not considering the patient history after second-line randomization for patient treated with cetuximab showed the effect of B in first-line treatment with an HR = 0.96 (95% CI 0.76–1.20) and the effect of B in second-line treatment with HR = 0.60 (95% CI 0.45–0.79). The test for the differential effect of B gave a $p$value = 0.014.

In the present analysis, we adopted a combined endpoint, that is, disease progression or death, whichever occur first. Future research could consider the effect of the treatment separately using a competing risk approach. Moreover, the evaluation of OS would add another clinical dimension

to strategy trials but was not addressed in the present study.

In the sensitivity analysis from model *d*, up to one in five patients showed a twofold or higher risk of PD than the average, which cannot be attributed to any of the clinical or tumor characteristics measured in this study. This can be interpreted as an upper bound of the benefit that can be obtained through new research on diagnostic biomarkers. Patient profiling could therefore be useful to identify frail subjects in future studies. For example, resistant markers such as NRAS, BRAF, PIKCa, and HER2 or other microsatellite instability (MSI)/DNA mismatch-repair (MMR) deficiency biomarkers[35] may be unevenly distributed, thus contributing to this heterogeneity. However, such information was not available for all of the randomized patients.

In conclusion, our results should be interpreted within the context of the more recent trials assessing the addition of angiogenesis inhibitors after progression. Overall, four randomized studies showed that prolonging angiogenesis inhibition beyond disease progression improves survival in mCRC patients, with a comparable, limited, but statistically significant, magnitude of benefit across trials (about a 1.5-month advantage in median OS, with HR around 0.8).[8,9,16,17] As the clinical significance of these results and the cost-effectiveness of this strategy are still not widely accepted, our results are consistent with the suggestion that second-line could be an ideal setting for angiogenesis inhibitors.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

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