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ORIGINAL REPORT

Bevacizumab Maintenance Versus No Maintenance During Chemotherapy-Free Intervals in Metastatic Colorectal Cancer: A Randomized Phase III Trial (PRODIGE 9)

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ABSTRACT

Purpose

Conflicting results are reported for maintenance treatment with bevacizumab during chemotherapy-free intervals (CFI) in metastatic colorectal cancer after induction chemotherapy.

Patients and Methods

In this open-label, phase III, randomized controlled trial, we compared the tumor control duration (TCD) observed with bevacizumab maintenance and with no treatment (observation) during CFI subsequent to induction chemotherapy with 12 cycles of fluorouracil, leucovorin, and irinotecan plus bevacizumab. After disease progression, the induction regimen was repeated for eight cycles, followed by a new CFI.

Results

From March 2010 to July 2013, 491 patients were randomly assigned. Disease progression or death occurred during induction chemotherapy in 85 patients (17%); 261 patients (53%) had at least one reinduction, 107 (22%) had two reinductions, and 56 (11%) had three or more reinductions. The median TCD was 15 months in both groups; the median progression-free survival (PFS) from randomization was 9.2 and 8.9 months in the maintenance group and observation groups, respectively. The TCD observed in both groups was higher compared with the TCD hypotheses of the trial. The median overall survival (OS) was 21.7 and 22.0 months in the maintenance and observation groups, respectively. In the per-protocol population, defined as patients with at least one reinduction after the first progression, the median duration of the first CFI was 4.3 months in both arms; the median TCD was 17.8 and 23.3 months ($P = .339$), the median PFS was 9.9 and 9.5 months, and the median OS was 27.6 and 28.5 months in the maintenance and observation groups, respectively. Multivariable analysis revealed that female gender, WHO performance status ≥ 2, and unresected primary tumors were associated with a shorter TCD.

Conclusion

Bevacizumab maintenance monotherapy did not improve TCD, CFI duration, PFS, or OS.

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INTRODUCTION

The prognosis of patients with metastatic colorectal cancer (mCRC) has been significantly improved by the use of several chemotherapy drugs, regardless of the sequence.[1] The addition of bevacizumab to first-line irinotecan plus fluorouracil chemotherapy resulted in a prolonged overall survival (OS)[2] and became a standard of care in mCRC. The duration of first-line combination chemotherapy is a matter of controversy because of the toxicity that occurs with prolonged treatment. The introduction of chemotherapy-free intervals (CFIs) was proposed in different studies with oxaliplatin- or irinotecan-based first-line chemotherapy.[3-5] More recently, several studies evaluated maintenance treatment with bevacizumab alone or in combination with fluoropyrimidine after induction chemotherapy.[6-9] All these studies, except one, investigated maintenance treatment or CFI without any treatment after oxaliplatin-based induction chemotherapy. Only the study by Koeberle et al[8] included some

ASSOCIATED CONTENT

Appendix
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patients treated with irinotecan-based induction chemotherapy. The primary end points varied across the studies, and none of them showed any difference in OS with respect to different strategies, except in the results of subgroup analysis. Maintenance with bevacizumab alone is attractive because it is a well-tolerated treatment in monotherapy. Nevertheless, previous results for bevacizumab used alone as maintenance therapy are conflicting. One study demonstrated the noninferiority of bevacizumab alone compared with fluoropyrimidine combined with bevacizumab with respect to the time to failure of the strategy, but did not show any improvement in the time to failure of the strategy when bevacizumab was compared with no treatment.[7] Another study failed to demonstrate the noninferiority of bevacizumab alone compared with continuation of induction chemotherapy with respect to progression-free survival (PFS).[6] However, bevacizumab monotherapy failed to show efficacy when given after front-line chemotherapy with irinotecan and a fluoropyrimidine.[10] In the randomized phase III PRODIGE 9 study, we aimed to assess the tumor control duration (TCD) with bevacizumab maintenance treatment or no treatment after irinotecan-based induction chemotherapy combined with bevacizumab.

PATIENTS AND METHODS

Patient Selection and Study Design

This open-label, randomized, multicenter, phase III study was conducted by the Fédération Francophone de Cancérologie Digestive and the PRODIGE (Partenariat de Recherche en Oncologie DIGEstive) intergroup in 66 French centers. The study design has been previously published,[11] and the protocol is provided in the Data Supplement. Main eligible criteria were histologically proven, nonresectable mCRC, WHO status ≤ 2, life-expectancy ≥ 3 months, and absence of previous chemotherapy or antiangiogenic therapy for metastatic disease. The study was approved by the Committee for the Protection of Persons Ile de France VIII. The trial was registered on ClinicalTrials.gov (NCT00952029).

Patients were randomly assigned to either induction chemotherapy plus bevacizumab followed by bevacizumab monotherapy in each CFI (maintenance arm) or to induction chemotherapy plus bevacizumab followed by no treatment in each CFI (observation arm). Patients were randomly assigned between the two treatment groups according to a ratio of one to one and using minimization techniques, taking into account the following stratification factors: site, previous primary tumor resection, and Köhne scoring (low versus intermediate versus high).[12]

Treatment Plan and Evaluation

Induction chemotherapy consisted of 12 cycles of fluorouracil, leucovorin, and irinotecan (FOLFIRI; irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, fluorouracil bolus 400 mg/m^2 followed by fluorouracil 2,400 mg/m^2 in continuous infusion for 46 hours) plus bevacizumab 5 mg/kg every 2 weeks. The disease status was assessed by computed tomography scan every 8 weeks and by clinical evaluation every 2 weeks. At the end of the induction treatment, patients with stable disease or with a tumor response according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria were either treated with bevacizumab monotherapy 5 mg/kg every 2 weeks (maintenance arm) or received no antitumor treatment (observation arm). When progression according to RECIST criteria occurred during the CFI, a sequence of eight cycles of FOLFIRI plus bevacizumab was reintroduced. If disease control had been achieved with these eight cycles, they were followed by another CFI (with bevacizumab monotherapy in the maintenance arm or no treatment in the observation arm). These sequences were repeated until progression occurred during chemotherapy. Throughout the entire treatment, including the chemotherapy sequence and the CFI, clinical and radiologic assessment was performed every 8 weeks or at any time progression was suspected. Safety was evaluated by means of laboratory and clinical testing before each cycle, during chemotherapy sequences, and before each bevacizumab infusion (maintenance arm) or every 8 weeks (observation arm) during CFIs. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0. *KRAS*, *NRAS*, and *BRAF* status was recorded after inclusion on the basis of determinations performed locally. Quality of life (QOL) was assessed using the Quality of Life Questionnaire C30 (QLQ-C30) from the European Organization for Research and Treatment of Cancer before randomization and every 8 weeks thereafter.[13] After progression during a chemotherapy sequence, the choice of second-line and additional treatment was at the discretion of the investigator.

Outcomes

The primary end point was TCD, defined as the time elapsed between randomization and tumor progression during a chemotherapy sequence. Patients who did not progress during the chemotherapy sequence were censored at their last follow-up within the protocol or censored at the initiation of second line of chemotherapy or other therapeutic strategy. Patients with R0 resection or R1 resection without chemotherapy were censored at the date of surgery, and patients lost to follow-up were censored at the date of last news.

Secondary end points were PFS, defined as the time between randomization and first progression or death by any cause, and time to treatment failure, defined as the time between randomization and definitive discontinuation of the protocol treatment, whatever the cause. Patients alive and still under treatment were censored at date of last news; OS, defined as the time between randomization and death by any cause; duration of the first CFI, defined as the time between the end of induction chemotherapy and the first reintroduction of chemotherapy or the date of the last injection in the maintenance arm; total duration of CFIs, defined as the sum of the duration of successive CFI; objective response rate, defined according to RECIST 1.1 criteria; toxicity; and QoL assessed by the QLQ-C30 form completed at each evaluation.[11]

Because the randomization was performed before the induction chemotherapy, a significant number of patients were not fit enough to be subject to the CFI and reintroduction strategy. Since our study was designed, two other trials have been published, which showed that only 56% and 65% of patients screened before induction were enrolled into a trial designed to include maintenance or CFI.[7,14] Thus, we decided to perform an exploratory per-protocol analysis to describe our strategy in the subgroup of patients eligible for maintenance or CFI. The per-protocol population was defined as patients with at least one reintroduction of chemotherapy subsequent to a first disease progression during CFI.

Statistical Analyses

All efficacy analyses were based on a modified intent-to-treat analysis, defined as patients who had received at least one dose of the treatment, and a per-protocol analysis. TCD, OS, and PFS were analyzed using the unstratified Kaplan-Meier method. Treatment arms were compared using the conventional log-rank test. Sensitivity analyses with the stratified Cox model on the resected tumor and Köhne criteria (stratification factors at baseline) were also performed for TCD, OS, and PFS. The hypothesis was to extend from 10 to 14 months the median TCD with the maintenance of bevacizumab during CFI (hazard ratio [HR], 0.714). With a two-sided α risk of 5%, and a power of 90%, 396 events were required. Taking into account an interim analysis (IA) at 50% of the events and an assumption of 10 inclusions per month, and with a percentage of patients lost to follow-up of 10%, 492 patients had to be enrolled.[11] The data collected were analyzed at the Centre de Randomization, Gestion Analyze of the Fédération Francophone de Cancérologie Digestive. The follow-up ended in December 2016. Final analyses were performed on a database frozen in January 2017.

RESULTS

Between March 2010 and July 2013, 494 patients were randomly assigned to either FOLFIRI plus bevacizumab induction chemotherapy followed by bevacizumab maintenance during CFI (n = 247) or to the same induction chemotherapy followed by observation during CFI (n = 247) (Fig 1). An IA was performed as planned in the protocol after 203 events had been observed in March 2014. The IA showed no significant improvement of TCD with maintenance therapy. At the time of this analysis, the recruitment was completed so the IA had no effect on it. Investigators continued the follow-up of their patients according to the protocol. Baseline patient characteristics were well balanced between the two treatment groups (Table 1). The median follow-up was 51.2 (interquartile range [IQR], 48.8 to 58.8) months in the maintenance arm and 54.9 (IQR, 50.1 to 60.6) months in the observation arm. Six patients still remain in treatment (three in the maintenance arm and three in the observation arm), and 94 patients (19.3%) are alive, 46 (18.8%) in the maintenance arm and 48 (19.8%) in the observation arm.

Disease progression or death during induction chemotherapy occurred in 85 patients (17%), 39 (15.9%) in the maintenance arm and 46 (18.9%) in the observation arm. Chemotherapy reinduction after first progression during CFI was performed in 64.7% of the patients, who had not experienced progression during induction chemotherapy (60.2% in the maintenance arm and 69.5% in the observation arm). Eighty-two patients in the maintenance arm and 60 patients in the observation arm were alive or without progression after induction chemotherapy but did not undergo reinduction of FOLFIRI plus bevacizumab (Fig 1). The percentage of patients able to receive a second sequence of chemotherapy was not significantly different between the two arms, but more patients received a third sequence in the observation arm (Table 2). The median total number of chemotherapy cycles was 13 (IQR, 12 to 20) in the maintenance arm and 16 (IQR, 12 to 24) in the observation arm.

The median TCD was 15 months in both arms (HR, 1.07; 95% CI, 0.85 to 1.34; $P = .57$; Fig 2A). The median PFS was 9.2 months in the maintenance arm and 8.9 months in the observation arm (HR, 0.91; 95% CI, 0.76 to 1.09; $P = .316$; Fig 2B). The 12-month PFS was 30.2% (± 2.9) in the maintenance arm and 21.01 (± 2.6) in the observation arm. The median time to treatment failure was 11.1 months in the maintenance arm and 12.1 months in the observation arm (HR, 1.17; 95% CI, 0.97 to 1.40; $P = .092$). The median duration of first CFI was 4.1 months in the maintenance

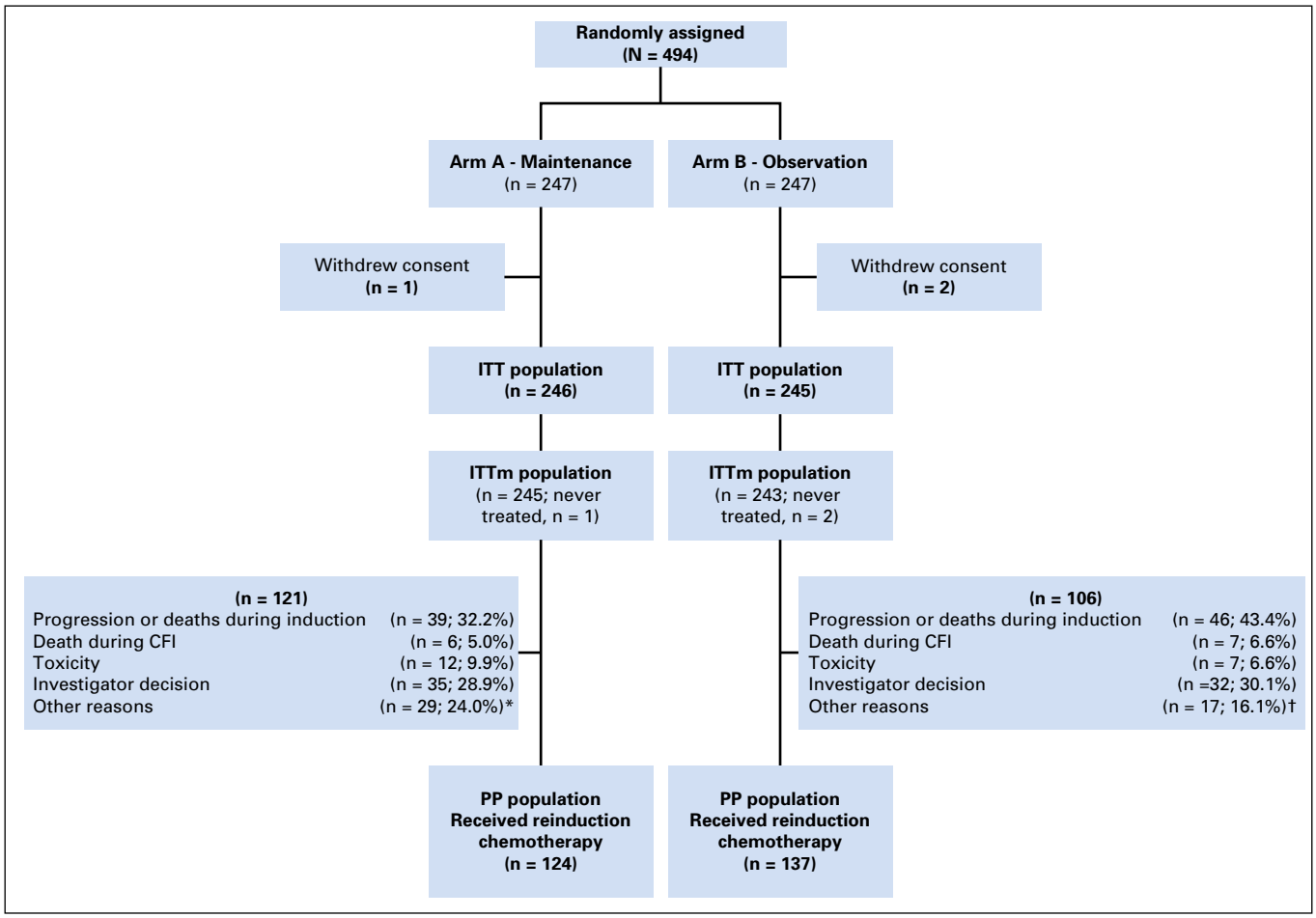

Fig 1. Flow chart. CFI, chemotherapy-free intervals; ITT, intent to treat; ITTm; modified intent to treat; PP, per protocol; PS, performance status. (*) Other reasons: intercurrent event or contra-indication (n = 9); metastasis surgery (n = 6); primary or other surgery (n = 5); lost to follow-up (n = 4); PS alteration (n = 5). (†) Other reasons: intercurrent event or contra-indication (n = 6); metastasis surgery (n = 2); primary or other surgery (n = 6); lost to follow-up (n = 2); PS alteration (n = 1).

Table 1. Baseline Characteristics

Characteristic	Maintenance (n = 245)	Observation (n = 243)
Median age, years (Q1, Q2)	64.2 (57.3, 72.3)	65.0 (57.8, 72.7)
Male gender, No. (%)	152 (62.0)	164 (67.5)
Primary tumor resected, No. (%)	141 (57.8)	140 (57.6)
WHO performance status, No. (%)		
0	118 (48.2)	115 (47.3)
1	112 (45.7)	104 (42.8)
2	15 (6.1)	24 (9.9)
Köhne criteria, No. (%)		
Low	97 (39.6)	84 (34.6)
Intermediate	104 (42.4)	112 (46.1)
High	44 (18.0)	47 (19.3)
Number of metastatic sites, No. (%)		
1	103 (42.0)	89 (36.6)
> 1	142 (58.0)	154 (63.4)
Location (n = 356), No. (%)		
Right colon	58 (41.7)	42 (35.0)
Left colon	80 (57.6)	77 (64.2)
Rectum	43 (17.8)	56 (23.9)
Median CEA (n = 473), μg/L (Q1, Q3)	66.4 (12.2, 525.1)	59.4 (8.5, 372.0)
Median CA 19.9 (n = 468), U/mL (Q1, Q2)	87.0 (11.0, 700.0)	70.5 (15.0, 656.0)
Mutated *KRAS* (n = 375)	85 (45.7)	88 (46.6)
Mutated *BRAF* (n = 245)	12 (9.6)	9 (7.5)

Abbreviations: CA, cancer antigen; CEA, carcinoembryonic antigen; Q, quartile.

Table 2. Treatment Received

Treatment	Maintenance (n = 245) No. (%)	Observation (n = 243) No. (%)	*P*
No reintroduction	121 (49.4)	106 (43.6)	.034
One sequence postinduction	78 (31.8)	76 (31.3)	
Two sequences postinduction	28 (11.4)	23 (9.5)	
Three sequences or more postinduction	18 (7.3)	38 (15.6)	
Second-line	159 (65)	158 (65)	
Chemotherapy alone	53 (22)	58 (24)	
Chemotherapy plus anti-VEGF	77 (31)	77 (32)	
Chemotherapy plus anti-EGFR	29 (12)	23 (9)	
R0 surgery	15 (6)	10 (4.1)	.700

Abbreviations: EGFR, endothelial growth factor receptor; VEGF, vascular endothelial growth factor.

arm and 4.2 in the observation arm. The median total duration of cumulative CFI was 4.9 months in the maintenance arm and 5.5 months in the observation arm, but in the case of patients with at least two successive CFIs, these values were 8.6 months and 10.7 months, respectively. The median OS was 21.7 months in maintenance arm and 22 months in the observation arm (HR, 1.07; 95% CI, 0.88 to 1.29; $P = .500$; Fig 2C). The best response was a partial or complete tumor response in 53.0% of patients in the maintenance arm and 56.5% of patients in the observation arm. Second-line treatment and the R0 resection rate were similar in both arms (Table 2).

The per-protocol analysis was performed on 261 patients (53% of all enrolled patients). In this population, the median TCD was 17.8 months in the maintenance arm and 23.3 months in the observation arm (HR, 1.16; 95% CI, 0.86 to 1.57; $P = .339$). The PFS was 9.9 months in the maintenance arm and 9.5 months in the observation arm (HR, 0.89; 95% CI, 0.70 to 1.13; $P = .339$). The median duration of first CFI was 4.3 months in both arms. The median OS was 27.6 months in the maintenance arm and 28.5 months in the observation arm (HR, 1.11; 95% CI, 0.86 to 1.45; $P = .424$).

Univariable analyses for TCD, PFS, and OS are presented in the Appendix (Tables A1, A2, and A3, online only). Multivariable analysis revealed that female gender, WHO performance status ≥ 2, and unresected primary tumor were associated with a shorter TCD. WHO performance status ≥ 2, unresected primary tumor, and age older than 65 years were associated with a shorter OS (Table 3).

Results of the subgroup of patients with tumor *BRAF* status available are listed in Appendix Table A4. Subgroup analysis revealed no condition favoring bevacizumab maintenance for either TCD (Appendix Fig A1, online only), PFS (Appendix Fig A2, online only), or OS (Appendix Fig A3, online only).

Treatment-related adverse events of grades 3, 4, and 5 were observed in 80% of patients in the maintenance arm and 79% of patients in the observation arm (Table 4). More toxicities, and especially cardiovascular toxicities, were observed in the maintenance arm during the CFI. QoL was assessed only in 162 patients in the maintenance arm and 173 patients in the observation arm. No significant difference was observed between arms. The median time to QoL global degradation was 14.7 (95% CI, 11.9 to 18.1) months in the maintenance arm and 14.4 (95% CI, 12.7 to 19.4) months in the observation arm. It was 3.7 (95% CI, 2.3 to 5.2) months and 5.1 (95% CI, 3.6 to 8.0) months for the physical functional subscale and 19.8 (95% CI, 17.8 to 24.1) months and 21.5 (95% CI, 15.4 to 21.1) months for the asthenia subscale in the maintenance and observation arms, respectively.

DISCUSSION

The PRODIGE 9 trial investigated bevacizumab alone as maintenance treatment after induction chemotherapy and after each reinduction sequence. This is the first trial to have addressed this strategy in a large number of patients treated with irinotecan-based induction chemotherapy. This strategy resulted in a unexpected prolonged TCD in both arms compared with our initial hypotheses.[11] Our trial failed to demonstrate a difference in TCD between the two treatment strategies of administering and not administering bevacizumab monotherapy during the maintenance period. In the AIO 0207 trial, the time to failure of the strategy after induction chemotherapy did not differ significantly between the bevacizumab monotherapy arm (6.1 months) and the observation arm (6.4 months).[7] Thus, the results of both trials are concordant. In the AIO 0207 trial, PFS after induction chemotherapy was slightly but significantly improved by bevacizumab compared with observation (4.6 *v* 3.5 months; $P = .0018$).[7] In the SAKK 41/06 trial, the time to progression was 4.1 months in the bevacizumab arm and 2.9 in the observation arm, but the difference was not significant.[8] The computed tomography or magnetic resonance imaging scans were performed every 6 weeks in the AIO 0207 and SAKK 41/06 trials, but every 8 weeks in the PRODIGE 9 trial. Thus,

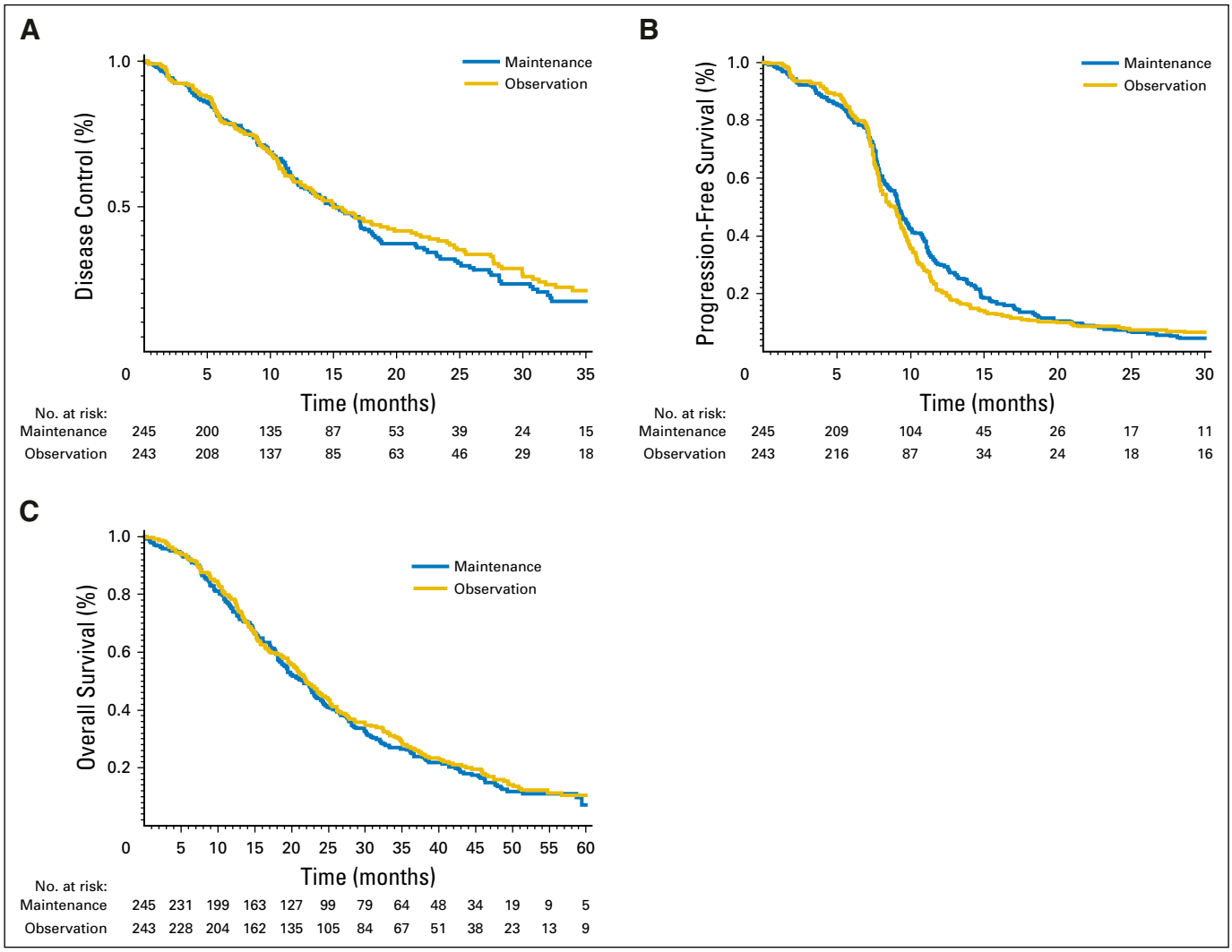

Fig 2. Kaplan-Meier curves according to study treatment. (A) Tumor control duration. (B) Progression-free survival. (C) Overall survival.

it cannot be ruled out that the PRODIGE 9 trial design was unable to detect a small difference in the time to first progression between patients treated with bevacizumab and those in the observation group.

The OS was not modified by bevacizumab monotherapy compared with observation after induction chemotherapy in the PRODIGE 9 trial as in the two previous randomized trials that made this comparison.[7,8] Furthermore, in our trial, subgroup exploratory analyses did not find any subgroup benefitting from bevacizumab maintenance treatment. Altogether, it could be concluded that bevacizumab monotherapy after induction chemotherapy in mCRC has little or no beneficial effect.

It is suspected that discontinuation of bevacizumab promotes a rebound in cancer growth. Our results show that bevacizumab

Table 3. Multivariable Analysis for TCD, PFS, and OS

Prognostic Factors	TCD (n= 487) HR (95% CI)	PFS (n = 487) HR (95% CI)	OS (n = 487) HR (95% CI)
Sex (women *v* men)	1.29 (1.01 to 1.63); *P* = .038	—	—
WHO performance status (2 *v* 0)	2.84 (1.59 to 5.06); *P* < .001 (overall *P* = .002)	2.02 (1.23 to 3.31); *P* =.005 (overall *P* =.02)	2.53 (1.53 to 4.18); *P* < .001 (overall *P* = .0015)
Primary tumor resected (no *v* yes)	1.34 (1.06 to 1.70); *P* = .014	1.15 (0.95 to 1.39); *P* = .140	1.26 (1.03 to 1.54); *P* = .027
Age (> 65 *v* ≤ 65 years)	—	—	1.34 (1.10 to 1.64); *P* = .004
Number of metastatic sites (> 1 *v* 1)	—	—	2.18 (1.05 to 4.56); *P* = .037

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TCD, tumor control duration.

Table 4. Maximum Grade 3, 4, and 5 of Major Toxicities During the Protocol Treatment (according NCI-CTC v2.0 classification)

Toxicities	Maintenance (n = 245) No. (%)	Observation (n = 243) No. (%)
Total severe toxicities during chemotherapy*	182 (74.3)	186 (76.5)
Cardiovascular	49 (20.0)	37 (15.2)
Cardiovascular/general-other		1 (0.4)
Edema	1 (0.4)	1 (0.4)
Hypertension	16 (6.5)	12 (4.9)
Hypotension	1 (0.4)	1 (0.4)
Peripheral arterial ischemia	9 (3.7)	5 (2.1)
Pulmonary embolism	2 (0.8)	4 (1.6)
Supraventricular arrhythmias		1 (0.4)
Thrombosis/embolism	20 (8.2)	13 (5.3)
Vasovagal episode	3 (1.2)	1 (0.4)
Hematologic	64 (26.1)	78 (32.1)
Gastrointestinal	63 (25.7)	74 (30.5)
Hemorrhage	3 (1.2)	4 (1.6)
Total severe toxicities during chemotherapy-free interval	81 (33.1)	34 (14,0)
Cardiovascular	21 (8.6)	5 (2.1)
Cardiovascular/general-other	3 (1.2)	1 (0.4)
Hypertension	15 (6.1)	2 (0.8)
Peripheral arterial ischemia	1 (0.4)	1 (0.4)
Thrombosis/embolism	5 (2.0)	1 (0.4)
Hematologic	2 (0.8)	2 (0.8)
Gastrointestinal	10 (4.1)	9 (3.7)
Hemorrhage	0 (0.0)	0 (0.0)
GGT	37 (15.1)	10 (4.1)
Alkaline phosphatase	11 (4.5)	4 (1.6)
Bilirubin	8 (3.3)	2 (0.8)
AST	6 (2.4)	1 (0.4)

Abbreviations: GGT, gamma-glutamyl transferase; NCI-CTT, National Cancer Institute Common Toxicity Criteria.

*Two patients in the maintenance arm had a grade 5 event: one patient for occlusion and one patient for gastrointestinal perforation. Two patients in the observation arm had a grade 5 event for dyspnea.

monotherapy maintenance did not delay reprogression. From a health care economic point of view, avoiding unnecessary bevacizumab treatment can result in substantial cost savings.

Several large phase III trials addressed the question of maintenance therapy previously.[3,7,9] Comparison of OS across trials is difficult because of different trial schedules and times of randomization, which occurred before or after induction chemotherapy; in addition, we enrolled only patients with definitively nonresectable metastases and patients were not selected according to *RAS* mutation, contrary to other recent phase III trials.[15,16] The question of a detrimental effect of CFI could be raised but was not assessed by the PRODIGE 9 trial. The patient selection rules to give a maintenance treatment or a CFI without any treatment deserve additional evaluation. Moreover, patients with *BRAF* mutations should probably not be enrolled in a de-escalation strategy because of their distinct biology and a poor prognosis compared with the rest of the population.

Chemotherapy reinduction after first progression during CFI was performed in 53% of the modified intent-to-treat population, but this proportion reached 69.5% in the subgroup of patients with no disease progression during induction chemotherapy in the observation arm. This is a higher proportion than in the observation arm of the AIO 0207 trial (36%) but comparable to that in the CAIRO 3 trial (58%). In these previous trials, as in PRODIGE 9, investigator decision is frequently observed and suggests that some investigators are reluctant to use the reinduction strategy. The planned duration of induction chemotherapy was 24 weeks in the AIO 0207 trial, 18 weeks in the CAIRO 3 trial, and 24 weeks in the PRODIGE 9 trial. Given the lack of cumulative toxicity, especially neurotoxicity, reinduction using irinotecan-based chemotherapy may be more feasible than using oxaliplatin-based chemotherapy. It was possible to perform several reinductions of chemotherapy in some patients, resulting in a prolonged TCD. It is noteworthy that fewer successive reinductions of chemotherapy took place in the maintenance arm. Although there is not a clear explanation for this finding, it may have affected the primary end point. We observed more toxicities and especially cardiovascular toxicities in the maintenance arm during the CFI. This is in line with the result observed with the bevacizumab monotherapy arm in the study by Giantonio et al,[10] with more than 30% of patients with any grade 3 to 4 toxicity and more than 8% with cardiovascular grade 3 to 4 toxicity. This increased toxicity in the maintenance arm might partly explain the lack of reinduction of chemotherapy in this arm. Nevertheless, we could not rule out that part of this increasing toxicity could be a result of more intensive monitoring of adverse events in the maintenance arm.

In the PRODIGE 9 trial, unresected primary tumor, WHO performance status $>$ 2, *BRAF* mutation, and more than one metastatic site were associated with a shorter OS. Tumor *BRAF* mutation was also reported as a poor prognostic factor in previous trials.[7,17] This finding encourages the conduct of a specific trial in this subgroup of patients. An unresected primary tumor was associated with poor OS in several mCRC first-line chemotherapy trials.[18] Moreover, in the CAIRO 3 trial, a better OS was observed in patients with metachronous metastases and in patients with synchronous metastases but with a resected primary tumor than in those without a resected primary tumor. Interestingly, in this trial, the OS benefit of maintenance chemotherapy with bevacizumab compared with observation was mainly obtained in patients with synchronous metastases but with a resected primary tumor.[9]

A poorer prognosis was reported for patients with a right-sided tumor compared with those with a left-sided tumor.[19] In the PRODIGE 9 trial, univariable analysis showed a right-sided tumor to be significantly associated with a poor OS compared with a rectal tumor, but this was not demonstrated in multivariable analysis. However, age older than 65 years was associated with a poor prognosis in multivariable analysis. Thus, age seemed to be more related to prognosis than primary location. However, the prognostic value of primary location seemed more important when therapy targeting anti–epidermal growth factor receptor rather than bevacizumab was used as front-line treatment.[20] Nevertheless, all the results derived from primary location should be viewed with caution because the analysis was a subgroup post hoc analysis.

In previous trials that have compared maintenance chemotherapy with observation after induction chemotherapy combined with bevacizumab, maintenance treatment had no significant effect on OS.[7-9] Thus, observation or maintenance chemotherapy with fluoropyrimidine combined with bevacizumab are valuable options. Moreover, in the PRODIGE 9 trial, we observed that the strategy of reinduction with irinotecan-based chemotherapy combined with bevacizumab resulted in a prolonged TCD and OS.

In conclusion, the PRODIGE 9 trial demonstrated that bevacizumab monotherapy has no effect when used as maintenance treatment after induction chemotherapy. Additional research is needed to better define subgroups of patients who should receive maintenance chemotherapy after induction treatment or could undergo a true chemotherapy-free interval.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Appendix

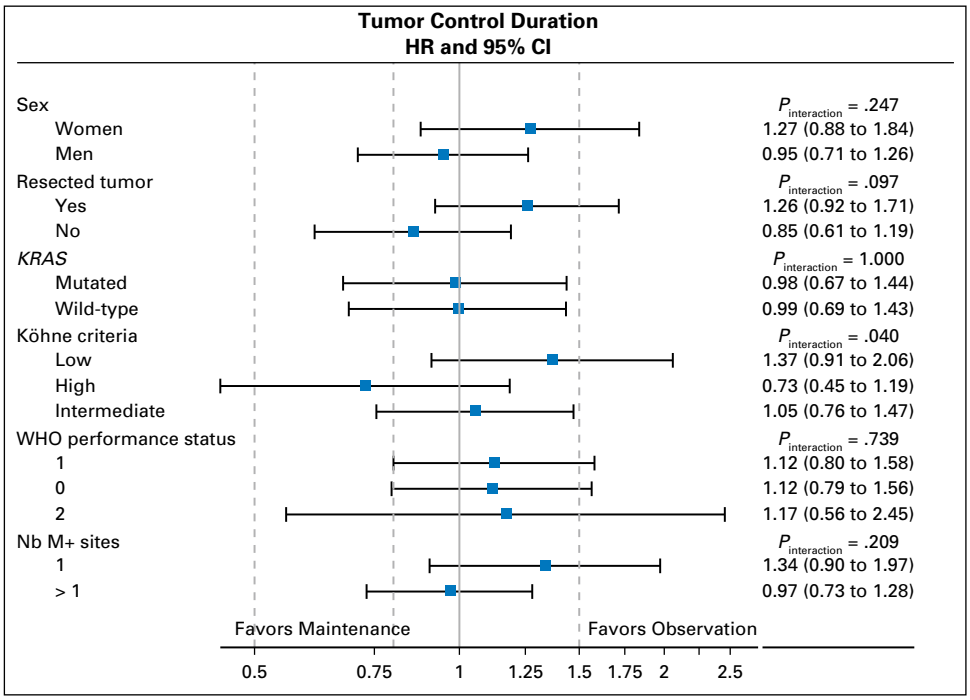

Fig A1. Subgroup analysis for tumor control duration.

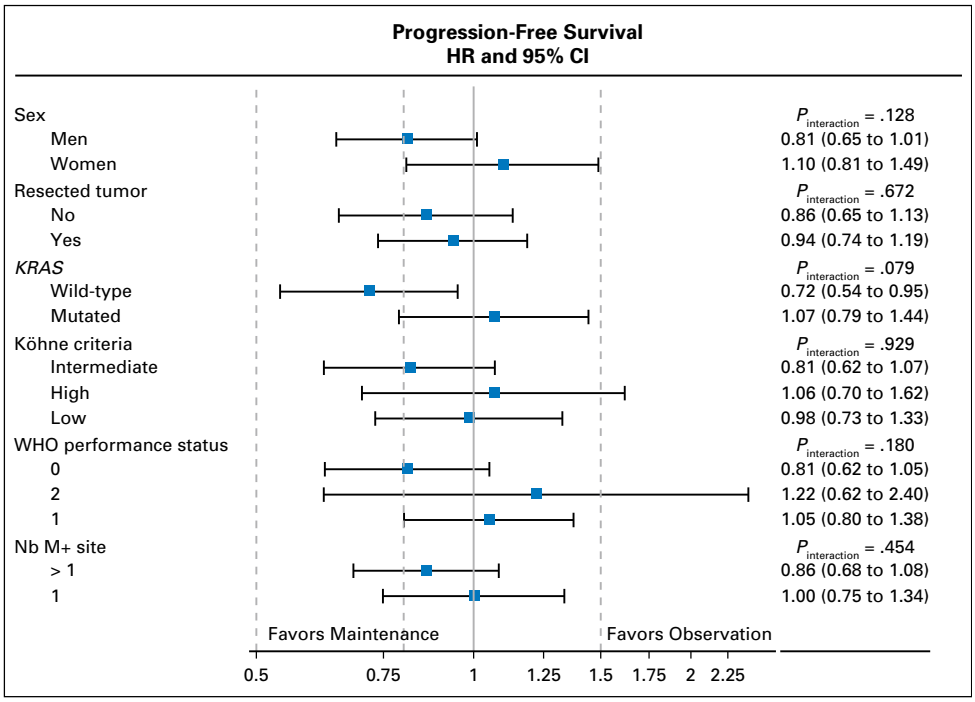

Fig A2. Subgroup analysis for progression-free survival.

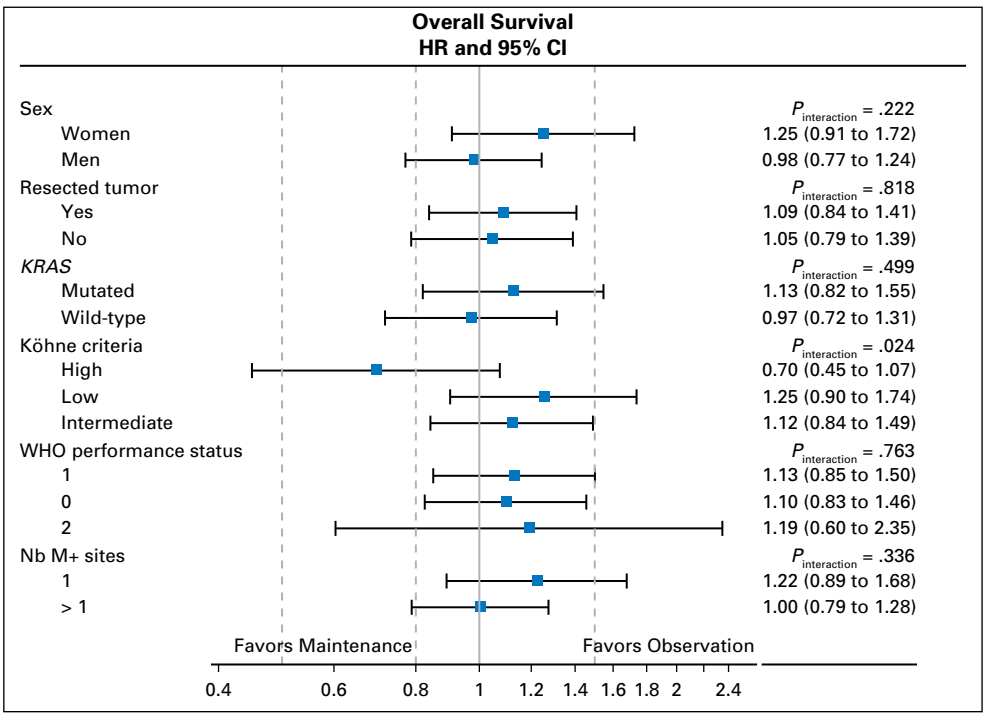

Fig A3. Subgroup analysis for overall survival.

Table A1. Univariable Analysis of Prognostic Factors Associated With Tumor Control Duration

Prognostic Factor		n/N Event	% Event	HR (95% CI); *P*
Treatment arm	A (maintenance)	151/245	61.63	1.07 (0.85 to 1.34); .573
	B (observation)	151/243	62.14	Reference
Sex	Women	115/172	66.86	1.30 (1.03 to 1.64); .026
	Men	187/316	59.18	Reference
Age	≤ 65 years	150/249	60.24	Reference
	> 65 years	152/239	63.60	1.11 (0.88 to 1.39); .3724
Köhne criteria	Low	96/181	53.04	Reference
	High	67/91	73.63	2.74 (1.99 to 3.78); < .001
	Intermediate	139/216	64.35	1.15 (0.88 to 1.49); .302
WHO performance status	0	135/233	57.94	Reference
	1	134/216	62.04	1.33 (1.04 to 1.69); .020
	2	33/39	84.62	5.12 (3.43 to 7.65); < .001
Primary tumor resected	No	141/206	68.45	1.55 (1.24 to 1.95); < .001
	Yes	160/281	56.94	Reference
No. of metastatic sites	1	105/192	54.69	Reference
	>1	197/296	66.55	1.28 (1.01 to 1.62); .043
KRAS status	Mutant	108/173	62.43	1.09 (0.84 to 1.41); .532
	Wild-type	115/202	56.93	Reference
BRAF status	Mutant	14/21	66.67	1.94 (1.11 to 3.39); .020
	Wild-type	134/224	59.82	Reference
Localization	Right colon	68/100	68.00	1.35 (0.96 to 1.91); .086
	Left colon	94/157	59.87	1.11 (0.80 to 1.52); .537
	Rectum	63/99	63.64	Reference

Abbreviation: HR, hazard ratio.

Table A2. Univariable Analysis of Prognostic Factors Associated With Progression-Free Survival

Prognostic Factor		n/N Event	% Event	HR (95% CI); *P*
Treatment arm	A (maintenance)	240/245	97.96	0.91 (0.76 to 1.09); .316
	B (observation)	237/243	97.53	Reference
Sex	Women	167/172	97.09	0.96 (0.80 to 1.16); .686
	Men	310/316	98.10	Reference
Age	≤ 65 years	244/249	97.99	Reference
	> 65 years	233/239	97.49	0.90 (0.75 to 1.08); .257
Köhne criteria	Low	175/181	96.69	Reference
	High	91/91	100.00	2.12 (1.64 to 2.75); < .001
	Intermediate	211/216	97.69	1.16 (0.95 to 1.42); .148
WHO performance status	0	226/233	97.00	Reference
	1	212/216	98.15	1.14 (0.95 to 1.38); .169
	2	39/39	100.00	3.05 (2.16 to 4.31); < .001
Primary tumor resected	No	203/206	98.54	1.25 (1.04 to 1.51); .015
	Yes	273/281	97.15	Reference
No. of metastatic sites	1	186/192	96.88	Reference
	>1	291/296	98.31	1.26 (1.05 to 1.52); .014
KRAS status	Mutant	172/173	99.42	1.07 (0.87 to 1.32); .509
	Wild-type	195/202	96.53	Reference
BRAF status	Mutant	20/21	95.24	1.60 (1.01 to 2.54); .046
	Wild-type	218/224	97.32	Reference
Localization	Right colon	99/100	99.00	1.17 (0.89 to 1.55); .266
	Left colon	151/157	96.18	1.02 (0.79 to 1.31); .887
	Rectum	97/99	97.98	Reference

Abbreviation: HR, hazard ratio.

Table A3. Univariable Analysis of Prognostic Factors Associated With Overall Survival

Prognostic Factor		n/N Event	% Event	HR (95% CI); *P*
Treatment arm	A (maintenance)	214/245	87.35	1.07 (0.88 to 1.29); .500
	B (observation)	209/243	86.01	Reference
Sex	Women	153/172	88.95	1.09 (0.89 to 1.32); .415
	Men	270/316	85.44	Reference
Age	≤ 65 years	213/249	85.54	Reference
	> 65 years	210/239	87.87	1.28 (1.05 to 1.54); .013
Köhne criteria	Low	146/181	80.66	Reference
	High	88/91	96.70	2.94 (2.24 to 3.87); < .001
	Intermediate	189/216	87.50	1.22 (0.98 to 1.52); .073
WHO performance status	0	193/233	82.83	Reference
	1	192/216	88.89	1.30 (1.06 to 1.58); .011
	2	38/39	97.44	4.26 (2.98 to 6.09); < .001
Primary tumor resected	No	191/206	92.72	1.40 (1.15 to 1.69); .001
	Yes	231/281	82.21	Reference
No. of metastatic sites	1	156/192	81.25	Reference
	>1	267/296	90.20	1.39 (1.14 to 1.70); .001
KRAS status	Mutant	153/173	88.44	1.16 (0.93 to 1.45); .183
	Wild-type	169/202	83.66	Reference
BRAF status	Mutant	19/21	90.48	1.73 (1.07 to 2.77); .024
	Wild-type	187/224	83.48	Reference
Localization	Right colon	87/100	87.00	1.39 (1.03 to 1.89); .031
	Left colon	133/157	84.71	1.11 (0.85 to 1.47); .440
	Rectum	83/99	83.84	Reference

Abbreviation: HR, hazard ratio.

Table A4. Multivariable Analyses for TCD, PFS, and OS in *BRAF* Subpopulation

Prognostic Factor	TCD (n = 245), HR (95% CI); *P*	PFS (n = 245), HR (95% CI); *P*	OS (n = 245), HR (95% CI); *P*
BRAF status (mutated *v* wild-type)	2.29 (1.27 to 4.14);.006	1.77 (1.07 to 2.92); .03	2.08 (1.26 to 3.44); .004
WHO performance status (2 *v* 0)	2.48 (1.14 to 5.41); .02 (overall *P* = .06)	2.69 (1.32 to 5.51); .007 (overall *P* = .01)	2.34 (1.11 to 4.91); .03 (overall *P* = .05)
Primary tumor resected (no *v* yes)	1.44 (1.02 to 2.04); .038	—	1.53 (1.14 to 2.06); .005
No. of metastatic sites (> 1 *v* 1)	—	—	4.24 (1.16 to 15.49); .03

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TCD, tumor control duration.

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