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ORIGINAL ARTICLE

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

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Background: The bevacizumab-Avastin® adjuVANT (AVANT) study did not meet its primary end point 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 randomly assigned to FOLFOX4, FOLFOX4-bevacizumab, or XELOX-bevacizumab.

Results: A total of 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 5.51—10.54), 672 patients died, of whom 198 (20.7%), 250 (26.0%), and 224 (23.5%) were in the FOLFOX4, FOLFOX4-bevacizumab, and XELOX-bevacizumab arms, respectively. The 10-year overall survival (OS) rates were 74.6%, 67.2%, and 69.9%, ($P = 0.003$) and 5-year disease-free survival (DFS) rates were 73.2%, 68.5%, and 71.0% ($P = 0.174$), respectively. OS and DFS hazard ratios were 1.29 [95% confidence interval (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 arms, respectively ($P = 0.789$). Treatment arm, sex, 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.

Key words: adjuvant, bevacizumab, colon cancer, FOLFOX, XELOX

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]

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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 bevacizumab-Avastin® adjuvant (AVANT) 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 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).

PATIENTS AND METHODS

Patients

Complete eligibility criteria have been previously reported.[9] Briefly, eligible patients who 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 carried out 4—8 weeks before randomization.

The main exclusion criteria included: the presence of a remaining tumor, carcinoembryonic antigen $>1.5\times$ 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. All patients provided informed consent for Avant study. The S-AVANT protocol was approved by the Ethics Review Committee or Institutional Review Board at participating sites.

Trial design

AVANT was a prospective, multicenter, randomized, parallel, open-label, three-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 the study and locked data on 30 June 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

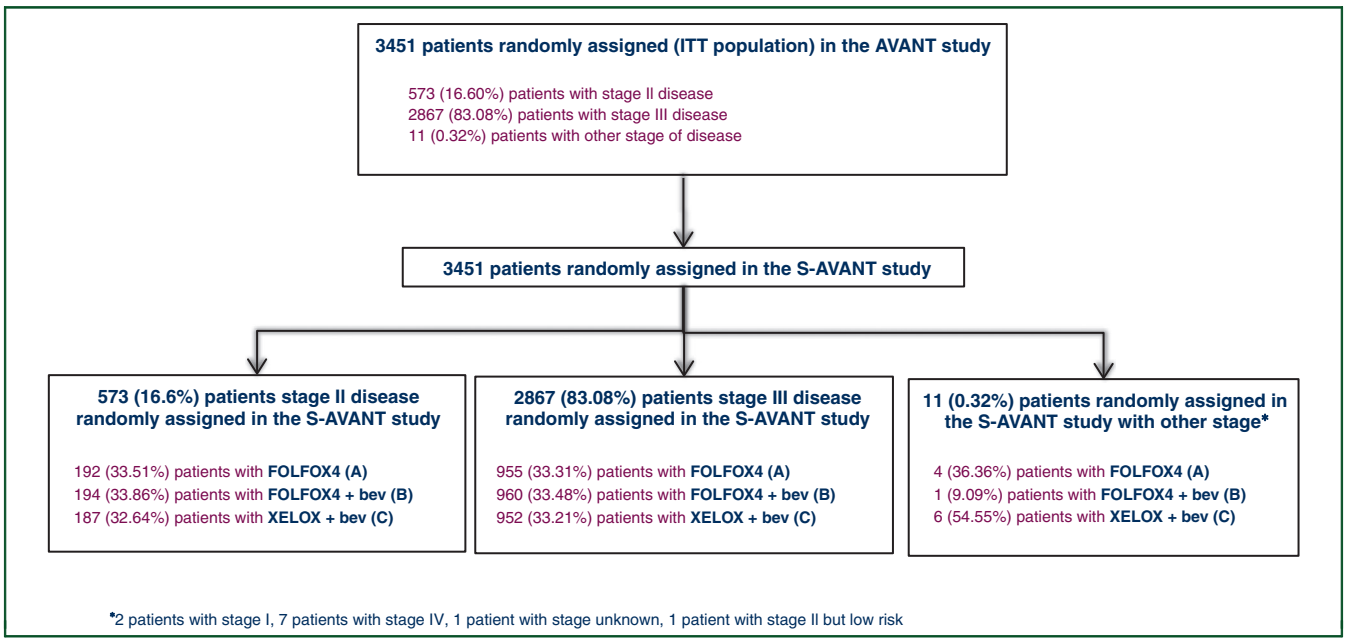

Figure 1. Flow-chart.
bev, bevacizumab; ITT, intent-to-treat.

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 30–90 minutes as an intravenous infusion on day 1 before 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 were discontinued due to toxicity, the patient could continue bevacizumab, but not oxaliplatin.

End points

The primary end point of S-AVANT was OS of the stage III population randomized in the AVANT study. Secondary end points 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 cut-off

Table 1. Clinical characteristics of stage III patients

	Stage III (*N* = 2867)		FOLFOX4 (*N* = 955)		FOLFOX4 + bev (*N* = 960)		XELOX + bev (*N* = 952)		*P*[b]
	n	%	*n*	%	*n*	%	*n*	%	
Sex[a]									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[a] (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[a]									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[c]	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[c]	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

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; SD, standard deviation.
[a] No missing data.
[b] *P* value computed with chi-square test or Fisher's exact test for categorical variables and Kruskal–Wallis test for continuous variables.
[c] log-rank test.

date were censored at the date at which they were last confirmed to be alive. DFS was defined as the time from randomization to the first relapse, second primary cancer, or death from any cause. Event-free patients at the clinical cut-off 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. The 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). The median values (interquartile range) for continuous variables were compared using the 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). Causes of death (CC-related, non-CC-related, cardiovascular-related, and sudden deaths) were described and compared among arms. The follow-up duration was calculated using a reverse Kaplan–Meier estimation.[13]

Cox proportional hazard models were carried out 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 <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 carried out and summarized with forest plots. The interaction term in each subgroup was obtained by considering the 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 carried out. All analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC) 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 hypotheses were formulated for this analysis, P values are shown for exploratory purposes. All tests were two-sided.

RESULTS

Patient characteristics

From December 2004 to June 2007, 3451 CC patients were randomized at 330 centers in 34 countries (the intention-to-treat 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 the groups (Table 1). The median follow-up for the whole population was 6.73 years [interquartile range (IQR): 5.51–10.54] with no difference among the treatment arms

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			
No. 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)

bev, bevacizumab; CI, confidence interval; DFS, disease-free survival; OS, overall survival.

(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% to 77.9%), 67.2% (95% CI 63.1% to 70.9%), and 69.9% (95% CI 65.8% to 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

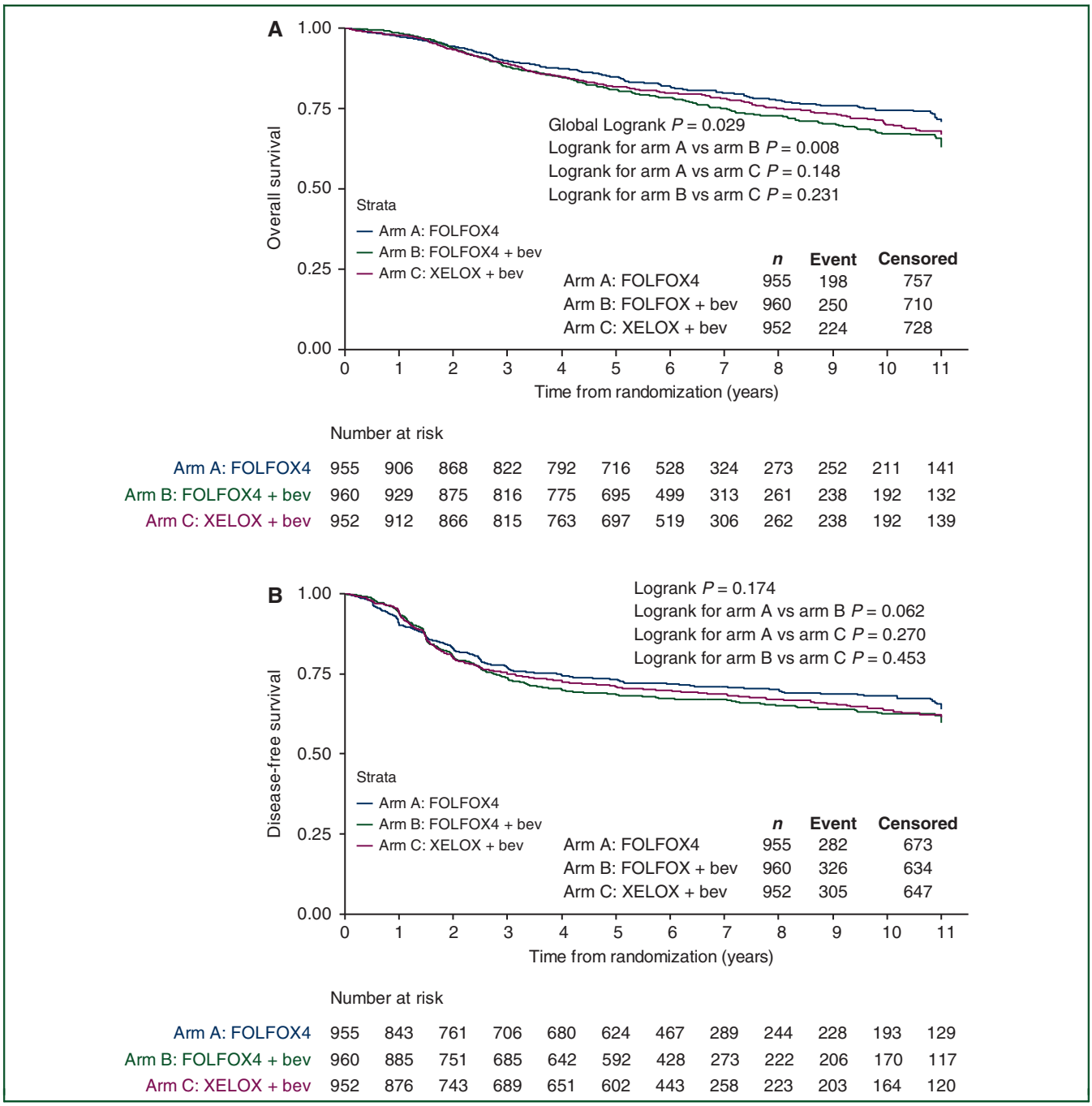

Figure 2. Overall survival (A) and disease-free survival (B) according to treatment arm in stage III patients.
bev, bevacizumab.

70.2% to 75.9%), 68.5% (95% CI 65.4% to 71.4%), and 71% (95% CI 67.9% to 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 the FOLFOX4 arm and 1.10 (95% CI 0.93—1.29; $P = 0.269$) for the XELOX-bevacizumab arm versus the 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%) treated with FOLFOX4-bevacizumab, and 33 (5.1%) and 52 (8.0%) treated with XELOX-bevacizumab experienced OS and DFS events, 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, sex, age (<70 versus ≥70), differentiation (well/moderately versus poorly), Eastern Cooperative Oncology Group (ECOG) performance status (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 not differentiation and primary tumor localization, remained as independent prognostic factors for DFS (Table 3).

Similar associations of the treatment arms and outcomes were found in multivariate analysis after adjusting for other prognostic factors. The forest plots for main OS and DFS prognostic factors are shown in Figure 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 subgroups (interaction *P* value of 0.035) with a detrimental effect observed in T1—3N1 patients. A similar observation was made for DFS (Figure 3).

In patients at low risk of recurrence (T1—3N1), the 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—

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

Variable		HR	95% CI	*P* value	Global *P* value
OS					
No. of events	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
Sex	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					
No. of events	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
Sex	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

bev, bevacizumab; CI, confidence interval; DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival.

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), the 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 of 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%),

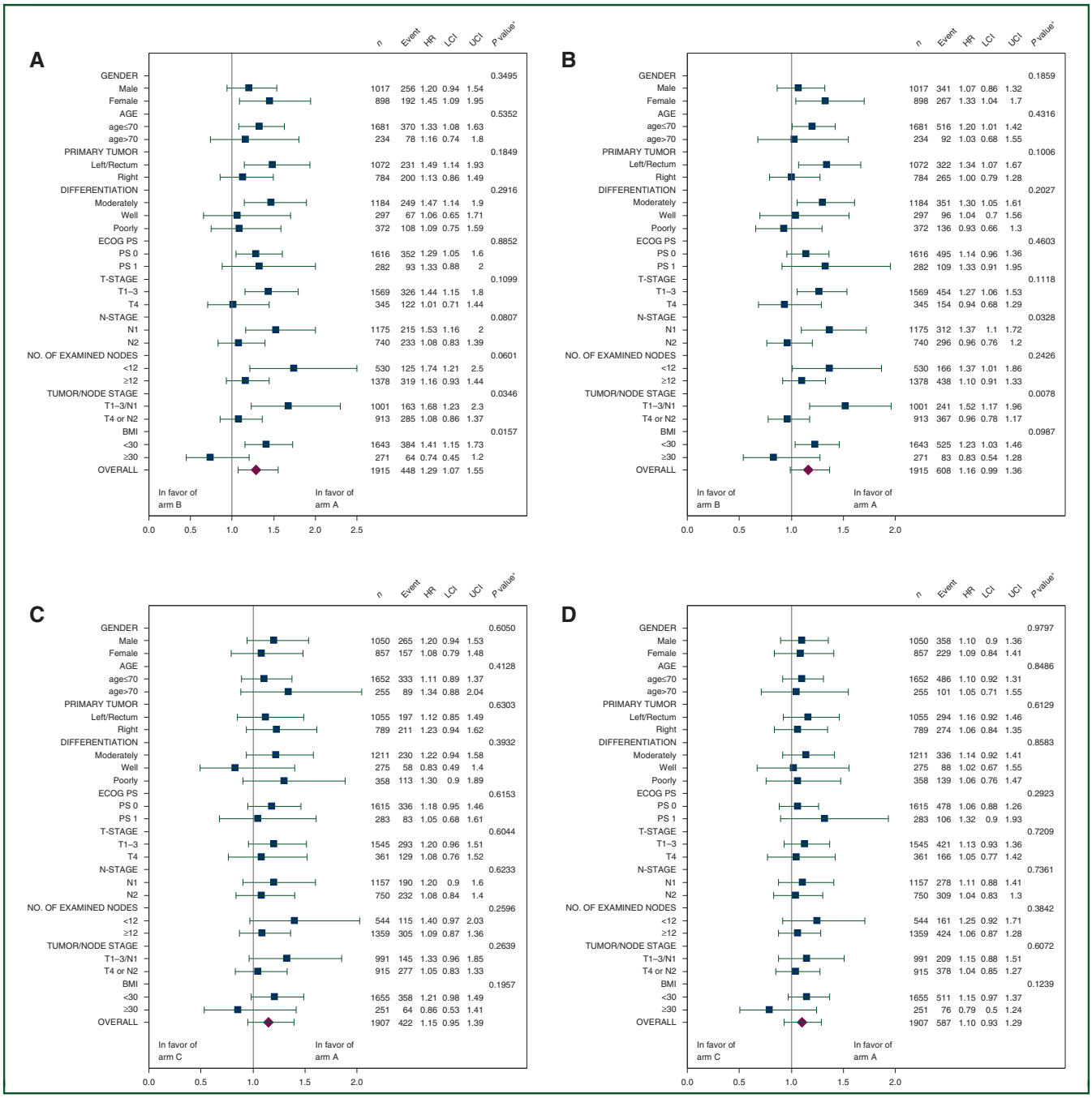

Figure 3. Forest-plots for overall survival (OS) and disease-free survival (DFS) between FOLFOX4 versus FOLFOX4-bevacizumab (A, B) and FOLFOX4 versus XELOX-bevacizumab (C, D).

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

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

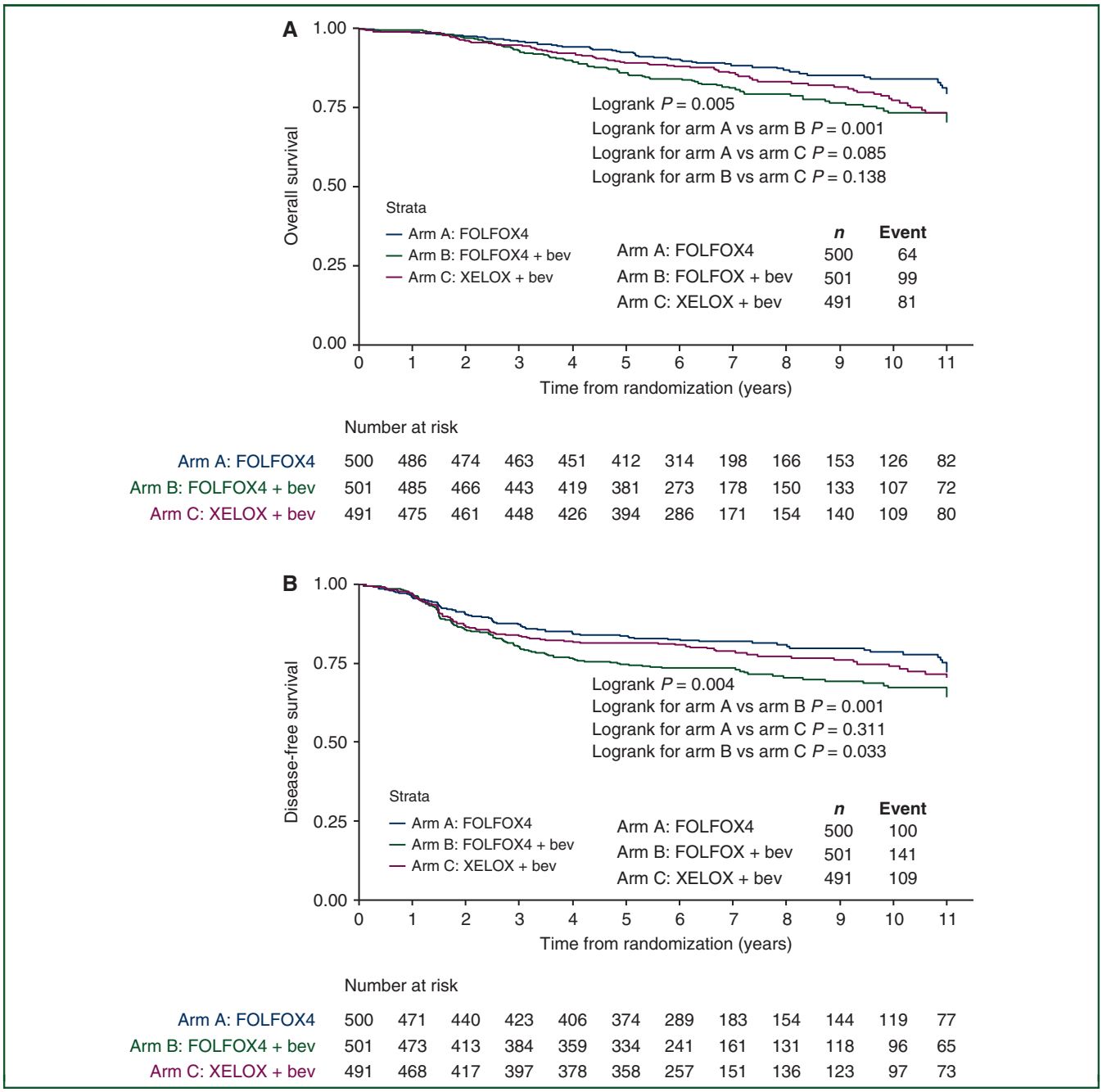

Figure 4. Overall survival (A) and disease-free survival (B) according to treatment arm in stage III patients with T1–3N1.
bev, bevacizumab.

and XELOX-bevacizumab: 180/224 (80.4%; $P = 0.764$). Non-CC-related deaths occurred in 130 patients with stage III disease, in whom those related to cardiovascular diseases and sudden deaths were reported in 13/41 non-CC-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 causes 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 Figure 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 a detrimental effect on OS with bevacizumab and oxaliplatin-based adjuvant chemotherapy [FOLFOX4 (HR = 1.29) or XELOX (HR = 1.15)],

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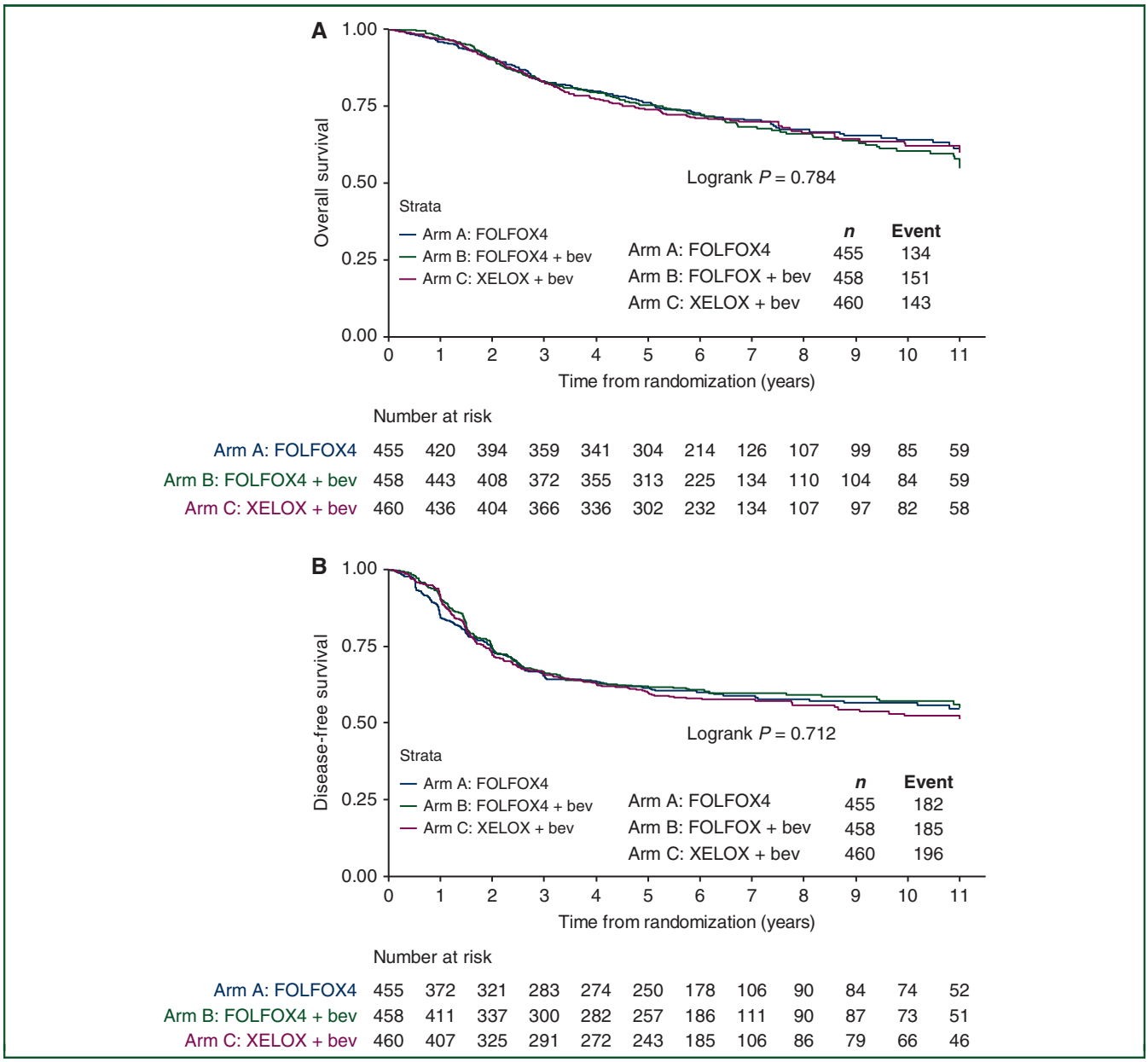

Figure 5. Overall survival (A) and disease-free survival (B) according to treatment arm in stage III patients with T4 or N2.
bev, bevacizumab.

without increase in non-CC-related deaths. The negative effects of bevacizumab- and oxaliplatin-based chemotherapy on OS (FOLFOX4 versus FOLFOX4-bevacizumab) support the fact 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 T1–3N1 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 a 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 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-CC-related deaths. Therefore, bevacizumab should not be used in adjuvant treatment of patients with curatively resected stage III CC.

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DISCLOSURE

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/accommodation/expenses from Roche/Genentech, MSD Oncology, 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, 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.