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ORIGINAL REPORT

A Randomized Phase IIIB Trial of Chemotherapy, Bevacizumab, and Panitumumab Compared With Chemotherapy and Bevacizumab Alone for Metastatic Colorectal Cancer

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Panitumumab, a fully human antibody targeting the epidermal growth factor receptor, is active in patients with metastatic colorectal cancer (mCRC). This trial evaluated panitumumab added to bevacizumab and chemotherapy (oxaliplatin- and irinotecan-based) as first-line treatment for mCRC.

Patients and Methods
Patients were randomly assigned within each chemotherapy cohort to bevacizumab and chemotherapy with or without panitumumab 6 mg/kg every 2 weeks. The primary end point was progression-free survival (PFS) within the oxaliplatin cohort. Tumor assessments were performed every 12 weeks and reviewed centrally.

Results
A total of 823 and 230 patients were randomly assigned to the oxaliplatin and irinotecan cohorts, respectively. Panitumumab was discontinued after a planned interim analysis of 812 oxaliplatin patients showed worse efficacy in the panitumumab arm. In the final analysis, median PFS was 10.0 and 11.4 months for the panitumumab and control arms, respectively (HR, 1.27; 95% CI, 1.06 to 1.52); median survival was 19.4 months and 24.5 months for the panitumumab and control arms, respectively. Grade 3/4 adverse events in the oxaliplatin cohort (panitumumab *v* control) included skin toxicity (36% *v* 1%), diarrhea (24% *v* 13%), infections (19% *v* 10%), and pulmonary embolism (6% *v* 4%). Increased toxicity without evidence of improved efficacy was observed in the panitumumab arm of the irinotecan cohort. *KRAS* analyses showed adverse outcomes for the panitumumab arm in both wild-type and mutant groups.

Conclusion
The addition of panitumumab to bevacizumab and oxaliplatin- or irinotecan-based chemotherapy results in increased toxicity and decreased PFS. These combinations are not recommended for the treatment of mCRC in clinical practice.

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INTRODUCTION

The treatment of metastatic colorectal cancer (mCRC) has undergone important advances in the past decade, including the introduction of multiagent chemotherapy and biologic agents. Bevacizumab, a humanized antibody against vascular endothelial growth factor-A (VEGF-A) has been shown to improve overall survival when combined with chemotherapy in first- or second-line treatment for mCRC.[1-3] Panitumumab and cetuximab, antibodies against epidermal growth factor receptor (EGFR), are active as monotherapy or in combination with chemotherapy for advanced disease.[4-13] Recently, it has been shown that the activity of EGFR antibodies is confined to patients whose tumors do not contain activating mutations in the *KRAS* gene.[14,15]

Early studies have suggested that blocking both the VEGF and EGFR pathways may increase antitumor activity.[16-20] The combination of bevacizumab and the small molecule EGFR inhibitor erlotinib yielded promising activity in non–small-cell lung cancer,[19] and the combination of cetuximab and bevacizumab either with or without irinotecan showed promising activity in irinotecan-refractory mCRC.[20] To formally explore the effectiveness of this combination, the Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) study, designed as a US community–based, randomized,

phase IIIB trial, evaluated the efficacy and safety of bevacizumab and chemotherapy with or without panitumumab in patients with previously untreated mCRC.

PATIENTS AND METHODS

Patients

Eligible patients had pathologic diagnosis of mCRC with measurable disease per modified Response Evaluation Criteria in Solid Tumors (RECIST).[21] Other inclusion criteria included Eastern Cooperative Oncology Group performance status of 0 or 1; adequate hematologic, hepatic, and renal functions; and available paraffin-embedded tumor tissue or unstained slides. Key exclusion criteria were prior chemotherapy or biologic therapy for metastatic disease; adjuvant chemotherapy within 6 months of undergoing random assignment; major surgery within 28 days of random assignment; pre-existing bleeding diathesis or coagulopathy or need for full-dose anticoagulation; and clinically significant cardiovascular disease within 1 year of random assignment. EGFR tumor expression was not required.

The study protocol was approved by institutional review boards at each participating center. All patients provided written informed consent before study-related procedures were performed.

Study Design

This was a randomized, open-label, multicenter, phase IIIB trial designed to evaluate the contribution of panitumumab to bevacizumab and chemotherapy for first-line treatment of mCRC. Patients were enrolled onto one of two cohorts per investigator choice: a fluorouracil, leucovorin, and oxaliplatin-based chemotherapy (Ox-CT) cohort or a fluorouracil, leucovorin, and irinotecan-based chemotherapy (Iri-CT) cohort, each with bevacizumab every 2 weeks (Q2W) with doses chosen by the investigator. The study design was intended to match first-line treatment of mCRC in US community practice at the time. Capecitabine-containing regimens were excluded. Patients were randomly assigned 1:1 to receive concomitant panitumumab 6 mg/kg Q2W or no additional treatment. Stratification factors were chemotherapy dose (Ox-CT, ≤ 85 mg/m^2, > 85 to ≤ 100 mg/m^2, > 100 mg/m^2; Iri-CT, one of three regimens; Fig 1), prior adjuvant therapy, Eastern Cooperative Oncology Group score, disease site (colon versus rectum), and number of metastatic organs (1 or > 1).

Panitumumab doses were withheld for grade 3 skin/nail-related toxicities and for nonskin/nail-related toxicities requiring intervention, eventually followed by escalation back to the original dose if tolerated or resolution. For nonskin/nail-related toxicities requiring intervention, chemotherapy was reduced per standard of care before panitumumab dose modifications. For grade 4 toxicities, panitumumab was discontinued.

Study Assessments

Radiographic tumor assessments were performed every 12 weeks until disease progression using modified RECIST by local and central review. Central review was performed by a single radiologist. Response confirmation was not required. Stable disease was first assessed at week 12. Adverse events (AEs) were graded using National Cancer Institute Common Terminology Criteria of Adverse Events version 3.0. An external independent data monitoring committee (DMC; 2 oncologists and 1 biostatistician) reviewed safety and efficacy according to a prespecified DMC charter.

Study Objectives and End Points

The primary objective was to assess whether panitumumab plus bevacizumab and Ox-CT extended progression-free survival (PFS) compared to

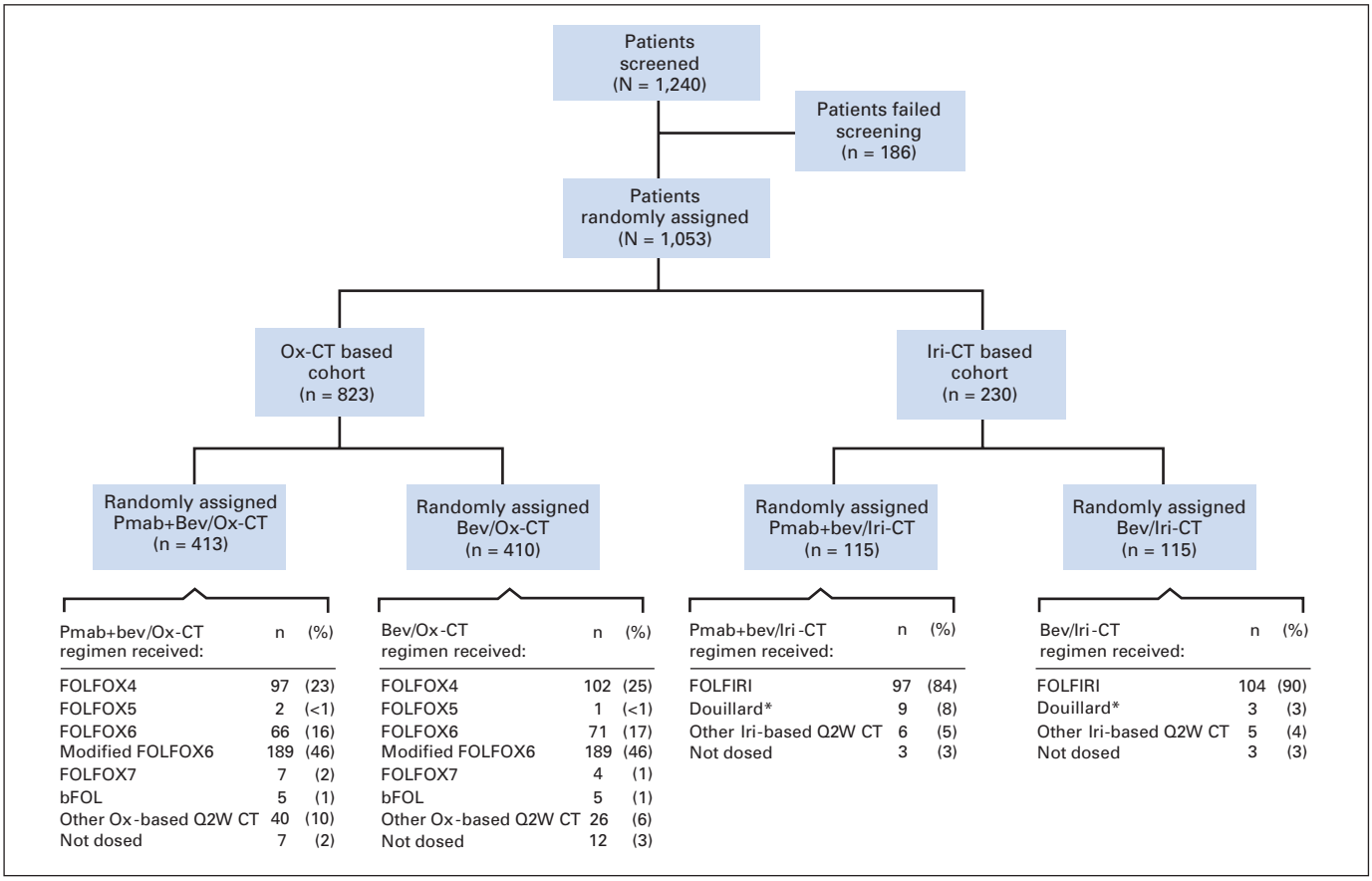

Fig 1. CONSORT diagram. Ox-CT, oxaliplatin-based chemotherapy; Iri-CT, irinotecan-based chemotherapy; Pmab, panitumumab; Bev, bevacizumab; FU, fluorouracil; FOLFOX, oxaliplatin, FU, and leucovorin; bFOL, bolus FU and low-dose leucovorin with oxaliplatin. (*) Douillard et al.[20a]

bevacizumab and Ox-CT alone by central review. The primary objective for the Iri-CT cohort was to describe safety. Secondary end points for both cohorts included objective response rate (RR), overall survival (OS), and safety. All end points in the Iri-CT cohort were descriptive.

Exploratory analyses by *KRAS* mutational status were performed in both cohorts. *KRAS* testing was done using allele-specific PCR (DxS, Manchester, UK) in paraffin-embedded tumor tissue as previously described.[14]

Statistical Analyses

For the primary analysis of the Ox-CT cohort, 462 PFS events were required to detect a hazard ratio (HR) of 0.769 with at least 80% power for a two sided, .05-level test. This HR, assuming exponential PFS, would translate to a 30% improvement in median PFS for panitumumab versus control, assuming a median PFS of 12 months in the control arm and follow-up of approximately 24 months. Planned sample sizes were 800 and 200 patients for the Ox-CT and the Iri-CT cohorts, respectively. An interim analysis of PFS was planned at 50% of the required events (approximately 231 PFS events). The Wald χ^2 test based on a Cox model adjusted for randomization factors was used to test a difference in PFS. To control the overall type I error, the Lan-DeMets alpha-spending function with O'Brien-Fleming boundaries was used: 0.00305 at the interim analysis and 0.04900 at the final analysis. Kaplan-Meier methodology estimated time to event end points, including 95% CI for event-free rates and rate differences. PFS was calculated from the day of randomization until radiologic progression or death. Patients alive without progression or having nonradiologic progression (ie, clinical progression) were censored. Central review censoring was based on the last available scan read centrally; local review censoring was based on the last day of patient contact or visit without known disease progression. OS was calculated from the day of randomization until death, censoring patients at the last day known to be alive. To obtain descriptive safety information following review of the interim results of the PFS end point, an unplanned interim analysis of OS in the Ox-CT cohort was conducted. Descriptive statistics were provided for patient demographics, baseline characteristics, and incidence of AEs. Efficacy analyses included any patient who was randomly assigned (intent-to-treat). Safety analyses included patients who received at least one dose of study treatment.

RESULTS

Patient Disposition and Demographics

From March 2005 through October 2006, 1,240 patients were screened and 1,053 patients were enrolled and randomly assigned in 200 US centers: 823 patients to the Ox-CT cohort and 230 patients to the Iri-CT cohort (Fig 1). Approximately 20% of patients in each arm in the Ox-CT cohort were enrolled by sites that enrolled $\leq$ three patients. The most common reasons for screening failure were inadequate hepatic function (n = 51), inability to comply with study procedures (n = 37), and inadequate hematologic function (n = 16).

Three planned safety reviews were conducted by the DMC after approximately 25, 75, and 150 patients were randomly assigned. An additional unplanned analysis of safety and response on approximately 500 patients was conducted at the DMC request, resulting in no study modifications. After the fifth (planned) analysis of safety and response on approximately 800 patients, the DMC recommended changes to the patient informed consent because of imbalances in diarrhea, dehydration, and infections favoring the control arm. An investigator letter informed of these imbalances and highlighted guidelines for toxicity management and dose modifications for severe diarrhea and infections. A planned interim analysis of safety and efficacy was conducted at approximately 50% progression or death events in the Ox-CT cohort using a data cutoff of October 30, 2006. Because of decreased PFS and increased toxicity observed in the panitumumab arm, panitumumab was discontinued in both cohorts on March 22, 2007, by the sponsor. The trial continued without panitumumab treatment, and no further protocol-prespecified, hypothesis-testing analyses were conducted. An updated descriptive analysis of efficacy and safety was conducted on data available as of May 31, 2007. Results from both the primary analysis (October 2006) and the descriptive update (May 2007) are included herein.

Baseline demographics and clinical characteristics were well balanced among treatment arms within each chemotherapy cohort (Table 1). Median follow-up time was 7.5 months (range, 0.0 to 19.3 months) for the Ox-CT cohort and 6.2 months (range, 0.2 to 18.6 months) for the Iri-CT cohort at the October 2006 cutoff, and 12.3 months (range, 0.2 to 26.2 months) for the Ox-CT cohort and 9.0 months (range, 0.3 to 24.0 months) for the Iri-CT cohort at the May 2007 cutoff.

As of the May 2007 cutoff, 94% of patients in the Ox-CT cohort and 87% in the Iri-CT cohort had ended study treatment. Most patients in both cohorts discontinued treatment because of nonprogressive events (68% and 65% for Ox-CT and Iri-CT cohorts, respectively); the most frequent reasons were AEs, treatment refusal, and requirement for alternative therapy. More patients in the panitumumab arms ended treatment for progressive events (progression or death) than in the control arms (Appendix Table A1, online only).

Efficacy

PFS. A planned interim analysis of the primary end point of PFS in the Ox-CT cohort by blinded central review was conducted on 257 Ox-CT events. PFS was significantly worse in the panitumumab arm of the Ox-CT cohort (HR, 1.44; 95% CI, 1.13 to 1.85; $P = .004$). Median PFS time was 8.8 months (95% CI, 8.3 to 9.5 months) for panitumumab and 10.5 months (95% CI, 9.4 to 12.0 months) for the control arm.

As of May 2007, there were 467 (57%) PFS events. By central review, PFS continued to favor the control arm (HR, 1.27; 95% CI, 1.06 to 1.52). Median PFS times were 10.0 months (95% CI, 8.9 to 11.0 months) for panitumumab and 11.4 months (95% CI, 10.5 to 11.9 months) for control (Fig 2A). By local review, median PFS times were 9.6 months (95% CI, 8.8 to 10.7 months) and 11.0 months (95% CI, 10.2 to 11.8 months) for panitumumab and control, respectively (HR, 1.27; 95% CI, 1.07 to 1.5; Appendix Fig A1A, online only).

For the Iri-CT cohort, median PFS (secondary end point) by central review in the October 2006 analysis was 10.1 month for panitumumab and 11.9 months for the control (HR, 1.57; 95% CI, 0.71 to 3.46). In the May 2007 analysis, median PFS was 10.1 month for panitumumab and 11.7 months for control by central review (HR, 1.19; 95% CI, 0.79 to 1.79; Fig 2A) and 11.0 months for panitumumab and 10.7 months for control by local review (HR, 0.92; 95% CI, 0.63 to 1.34; Appendix Fig A1B, online only).

Secondary End Points

In the updated May 2007 analysis, RR by central review were similar between the panitumumab and control arms in both chemotherapy cohorts (46% and 48%, respectively, for the Ox-CT cohort [odds ratio, 0.92; 95% CI, 0.70 to 1.22] and 43% and 40%, respectively, for the Iri-CT cohort [odds ratio, 1.11; 95% CI, 0.65 to 1.90]; Table 2). Similar findings were observed by local review, with the

Table 1. Patient Baseline Demographics and Clinical Characteristics

Characteristic	Pmab + Bev/ Ox-CT (n = 413)		Bev/Ox-CT (n = 410)		Pmab + Bev/ Iri-CT (n = 115)		Bev/Iri-CT (n = 115)	
	No.	%	No.	%	No.	%	No.	%
Male	233	56	238	58	56	49	71	62
Race								
White	343	83	330	80	86	75	85	74
Black	35	8	41	10	18	16	16	14
Hispanic	25	6	25	6	6	5	14	12
Asian	10	2	10	2	2	2	0	0
Other	0	0	4	1	3	3	0	0
Age, years								
Median	61		62		60		59	
Range	28-88		22-89		35-84		23-80	
≥ 65	162	39	178	43	44	38	32	28
ECOG status								
0	253	61	239	58	68	59	74	64
1	160	39	171	42	47	41	41	36
Prior adjuvant therapy	80	19	77	19	38	33	36	31
Time since primary diagnosis of CRC, months								
Median	1.8		1.9		3.1		2.0	
Range	0.1-250.6		0.1-164		0.2-84.6		0.2-84.2	
Time since diagnosis of metastases, months								
Median	1.1		1.2		1.1		1.1	
Range	0-42.8		0-129.8		0.2-84.6		0-23.8	
Number of metastatic organs								
1	204	49	199	49	46	40	53	46
> 1	208	50	211	51	69	60	62	54
LDH								
> 1.5 times ULN	79	19	85	21	20	17	21	18

Abbreviations: Pmab, panitumumab; Bev, bevacizumab; Ox-CT, oxaliplatin-based chemotherapy; Iri-CT, irinotecan-based chemotherapy; ECOG, Eastern Cooperative Oncology Group; CRC, colorectal cancer; LDH, lactate dehydrogenase; ULN, upper limit of normal.

exception of a numerically higher RR in the panitumumab arm of the Iri-CT cohort (Appendix Table A2, online only).

An unplanned interim analysis of survival was performed in October 2006 after results of the primary end point demonstrated shorter PFS time in the panitumumab arm. In this analysis, median OS time in the Ox-CT cohort was 18.4 months for panitumumab and was not reached for control (HR, 1.56; 95% CI, 1.11 to 2.19). In the updated analysis (Fig 2B), median OS time for the Ox-CT cohort was 19.4 months (95% CI, 18.4 to 20.8 months) for panitumumab and 24.5 months (95% CI, 20.4 to 24.5 months) for control (HR, 1.43; 95% CI, 1.11 to 1.83). In the Iri-CT cohort, median OS time for the panitumumab arm was 20.7 months (95% CI, 17.8 to not estimable months) and 20.5 months (95% CI, 19.8 to not estimable months) for the control arm (HR, 1.42; 95% CI, 0.77 to 2.62; Fig 2B).

KRAS Analyses

KRAS mutational status was determined in 82% of patient tumor samples (865/1053; 664 [81%] in the Ox-CT cohort; 201 [87%] in the Iri-CT cohort). Mutations were found in 40% (346/865) of all samples (39% in the Ox-CT cohort, 43% in the Iri-CT cohort, both arms combined). Correlations with efficacy were conducted using centrally reviewed data from the May 2007 data cutoff. PFS favored the control arm in both chemotherapy cohorts regardless of *KRAS* status (Table 3 and Appendix Fig A3, online only). For the Ox-CT cohort, RR was similar between arms in both KRAS groups. For Iri-CT cohort, RR was numerically higher in the wild-type (WT) group for the panitumumab arm and in the mutant group for the control arm (Table 3). A difference in OS favoring the control arm was observed in the WT subset of the Ox-CT cohort (HR, 1.89; 95% CI, 1.30 to 2.75; $P = .045$, not adjusted for multiplicity). In the Iri-CT cohort, OS favored the control arm regardless of *KRAS* status; for WT *KRAS* (panitumumab: control), the HR was 1.28 (95% CI, 0.50 to 3.25; $P = .445$; Table 3 and Appendix Fig A3, online only).

Drug Exposure

Of all patients receiving panitumumab, more than 97% received panitumumab 6 mg/kg Q2W as their first dose. Approximately 95% of all patients received bevacizumab at approximately 5 mg/kg Q2W as their first dose.

In both the Ox-CT and Iri-CT cohorts, the proportion of patients with chemotherapy and/or antibody dose delays was higher in the panitumumab arms, with a difference in favor of the control arms ranging from 6% to 17% (Appendix Table A3, online only). While small differences in relative dose intensity for each individual agent favored the control arms, the proportion of patients receiving a relative dose intensity of ≥ 85% of bevacizumab and each chemotherapy agent in both chemotherapy cohorts was lower in the panitumumab arms (33% for panitumumab *v* 42% for control for Ox-CT; 34% for panitumumab *v* 44% for control for Iri-CT).

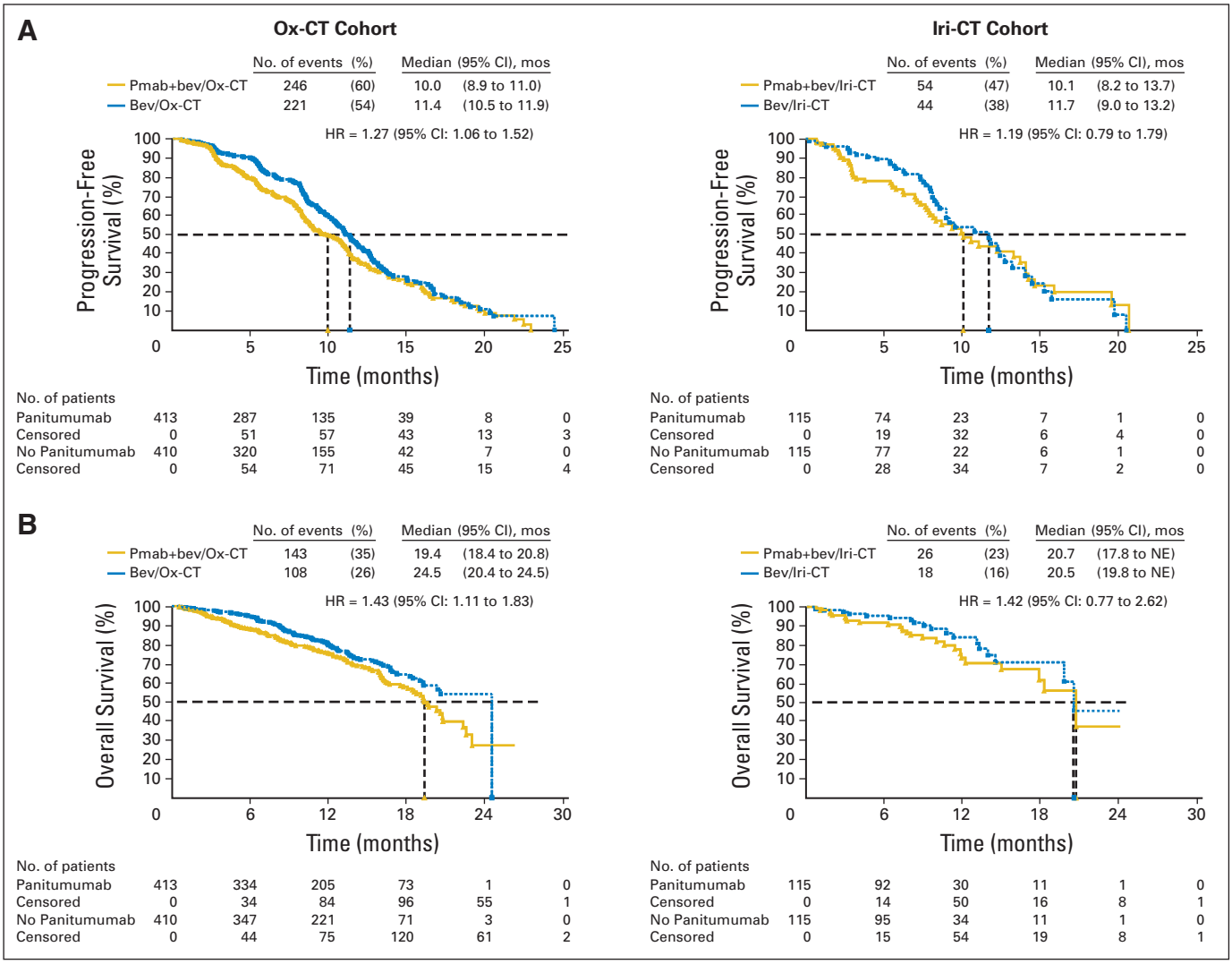

Fig 2. (A) Progression-free survival (central review) and (B) overall survival for the oxaliplatin-based chemotherapy (Ox-CT) and irinotecan-based chemotherapy (Iri-CT). NE, not estimable; mos, months.

Safety

The safety analysis set included 804 patients in the Ox-CT cohort and 224 patients in the Iri-CT cohort. In both cohorts, more patients experienced worst grade 3 or higher AEs in the panitumumab arm than the control arm: Ox-CT cohort, 367 (90%) versus 305 (77%), respectively; Iri-CT cohort, 100 (90%) versus 71 (63%), respectively.

Table 2. Objective Response Rate by Blinded Central Review

	Pmab + Bev/Ox-CT (n = 413)		Bev/Ox-CT (n = 410)		Pmab + Bev/Iri-CT (n = 115)		Bev/Iri-CT (n = 115)	
Response	No.	%	No.	%	No.	%	No.	%
Best ORR	190	46	196	48	49	43	46	40
Complete response	0	0	2	< 1	0	0	0	0
Partial response	190	46	194	47	49	43	46	40
Stable disease	121	29	137	33	31	27	42	37
Progressive disease*	28	7	18	4	15	13	4	3
Not done/nonevaluable†	74	18	59	14	20	18	23	20

NOTE: Intent-to-treat set. Computed tomography scans performed every 12 weeks; responses did not require confirmation.
Abbreviations: Pmab, panitumumab; Bev, bevacizumab; Ox-CT, oxaliplatin-based chemotherapy; Iri-CT, irinotecan-based chemotherapy; ORR, overall response rate.
*Central review unable to evaluate clinical disease progression (ie, non-radiographic progressive disease); central review unable to accurately evaluate progressive disease after surgical resections.
†Included missing and unreadable scans.

Table 3. Efficacy by *KRAS* Status (Central Review)

Outcome	Ox-CT (n = 664)					
	Wild-Type *KRAS*, n = 404 (61%)			Mutant *KRAS*, n = 260 (39%)		
	Panitumumab (n = 201)	Control (n = 203)	HR	Panitumumab (n = 135)	Control (n = 125)	HR
Response rate, %*	50	56	n/a	47	44	n/a
PFS*						
Median, months	9.8	11.5	1.36	10.4	11.0	1.25
95% CI	8.4 to 11.3	10.6 to 12.3	1.04 to 1.77	9.1 to 11.3	9.9 to 12.8	0.91 to 1.71
OS						
Median, months	20.7	24.5	1.89	19.3	19.3	1.02
95% CI	17.7 to NE	NE	1.30 to 2.75	16.2 to 23.0	16.7 to NE	0.67 to 1.54
	Iri-CT (n = 201)					
	Wild-Type *KRAS*, n = 115 (57%)			Mutant *KRAS*, n = 86 (43%)		
Outcome	Panitumumab (n = 57)	Control (n = 58)	HR	Panitumumab (n = 47)	Control (n = 39)	HR
Response rate, %*	54	48	n/a	30	38	n/a
PFS*						
Median, months	10.0	12.5	1.50	8.3	11.9	1.19
95% CI	8.2 to 14.1	9.0 to 15.7	0.82 to 2.76	6.3 to 14.3	8.1 to 13.2	0.65 to 2.21
OS						
Median, months	NE	19.8	1.28	17.8	20.5	2.14
95% CI	NE	19.8 to NE	0.50 to 3.25	11.9 to NE	20.5 to NE	0.82 to 5.59

Abbreviations: Ox-CT, oxaliplatin-based chemotherapy; HR, hazard ratio; PFS, progression-free survival; n/a, not applicable; NE, not estimable; OS, overall survival; Iri-CT, irinotecan-based chemotherapy.
*Central review.

AEs of interest (treatment-related and unrelated) from the updated analysis are summarized (Table 4). As expected, skin-related toxicities were the most common grade 3 events in the panitumumab arms (35% and 38% for the Ox-CT and Iri-CT cohorts, respectively). Other AEs occurring more frequently in the panitumumab arm for both cohorts included diarrhea, dehydration, hypomagnesemia, infections, and pulmonary embolism. In the Iri-CT cohort, there was also a higher incidence of deep venous thrombosis in the panitumumab arm. Approximately 19% of patients had a panitumumab-related serious AE.

Two-hundred fifty (31%) and 43 (19%) patients had died in the Ox-CT and Iri-CT cohorts, respectively. For both cohorts combined, deaths within 60 days of the first dose occurred in 15 (2.9%) and eight (1.6%) patients in the panitumumab and control arms, respectively. For both cohorts combined, deaths within 30 days after the last dose occurred in 41 (8%) and 17 (3%) patients in panitumumab and control arms, respectively. There were seven (1%) deaths attributed by the investigator to be panitumumab-related: five in the Ox-CT cohort (pulmonary embolism, cardiac arrest, cancer progression, arrhythmia, and intestinal perforation) and two in the Iri-CT cohort (intestinal perforation and sepsis).

DISCUSSION

In the PACCE trial, the combination of panitumumab with bevacizumab and chemotherapy resulted in a decrease in PFS and in excess serious toxicity, particularly diarrhea, infections, and pulmonary embolism in patients with mCRC. Results were largely consistent between the oxaliplatin and irinotecan cohorts.

While the exact explanation for these results is unknown, several hypotheses can be postulated. Although pharmacokinetic interactions between antibodies or between antibodies and chemotherapy are uncommon, we cannot exclude this possibility, as drug concentration levels were not collected in this study. Toxicity was exacerbated by dual-pathway inhibition in combination with chemotherapy. Bevacizumab with an anti-EGFR antibody and chemotherapy could have enhanced diarrhea and skin toxicity by inhibiting tissue repair, and more complete inhibition of the VEGF axis could have increased the incidence of pulmonary embolism. Toxicity likely contributed to the increases in dose delays and reductions, decreases in dose intensity, and increases in mortality in the panitumumab arm. Lower dose intensity could explain the similar response rates observed with worse results of time-dependent end points. In contrast with the safety profile observed in this study, panitumumab given with fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or with fluorouracil, leucovorin, and irinotecan (FOLFIRI) in the absence of bevacizumab appears to be well tolerated.[22,23]

Potentially, a pharmacodynamic interaction induced by EGFR inhibition could have led to a blunting of the therapeutic effects of bevacizumab and/or chemotherapy. Possible mechanisms include EGFR-mediated alterations of downstream targets required for the activity of bevacizumab and/or chemotherapy or the induction of EGFR-mediated cell-cycle arrest leading to resistance to cytotoxics. Since both classes of agents improve outcome when combined with chemotherapy in mCRC, cell-cycle mediated effects appear less likely, although definitive data on the role of EGFR-inhibiting antibodies in combination with oxaliplatin-based chemotherapy in mCRC is still awaited.

Table 4. Adverse Events of Interest for the Ox-CT and Iri-CT Cohorts

	Pmab + Bev/Ox-CT (n = 407)						Bev/Ox-CT (n = 397)					
	Any Grade		Grade 3		Grade 4		Any Grade		Grade 3		Grade 4	
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Skin toxicity*	387	95	142	35	3	1	120	30	3	1	0	0
Diarrhea	300	74	89	22	8	2	264	66	49	12	2	1
Nausea/vomiting	287	71	51	13	0	0	297	75	23	6	3	1
Infections†	232	57	66	16	10	2	190	48	33	8	8	2
Neutropenia	146	36	56	14	41	10	172	43	67	17	27	7
Dehydration	134	33	63	15	9	2	68	17	21	5	1	< 1
Hypomagnesemia	115	28	14	3	6	1	9	2	0	0	0	0
Neuropathy	86	21	14	3	1	< 1	113	28	26	7	0	0
Hypertension	72	18	16	4	0	0	83	21	21	5	0	0
Paronychia	35	9	4	1	0	0	0	0	0	0	0	0
Deep venous thrombosis	27	7	27	7	0	0	30	8	30	8	0	0
Pulmonary embolism‡	27	7	0	0	24	6	16	4	0	0	16	4
Gastrointestinal perforations§	2	< 1	0	0	0	0	0	0	0	0	0	0

	Pmab + Bev/Iri-CT (n = 111)						Bev/Iri-CT (n = 113)					
	Any Grade		Grade 3		Grade 4		Any Grade		Grade 3		Grade 4	
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Skin toxicity*	105	95	42	38	0	0	29	26	0	0	0	0
Diarrhea	92	83	30	27	1	1	89	79	10	9	0	0
Nausea/vomiting	88	79	12	11	2	2	84	74	9	8	0	0
Infections†	64	58	13	12	2	2	42	37	10	9	0	0
Neutropenia	38	34	16	14	3	3	37	33	19	17	5	4
Dehydration	32	29	15	14	0	0	23	20	7	6	0	0
Hypomagnesemia	34	31	3	3	2	2	5	4	0	0	1	1
Hypertension	15	14	2	2	0	0	23	20	3	3	0	0
Paronychia	16	14	4	4	0	0	0	0	0	0	0	0
Deep venous thrombosis	14	13	14	13	0	0	7	6	7	6	0	0
Pulmonary embolism‡	13	12	0	0	12	11	6	5	0	0	6	5

Abbreviations: Ox-CT, oxaliplatin-based chemotherapy; Iri-CT, irinotecan-based chemotherapy; Pmab, panitumumab; Bev, bevacizumab.
*Skin toxicity included multiple terms from the skin and subcutaneous and infections system organ class per *Medical Dictionary for Regulatory Activities* v9.0.
†Grade 5 infections occurred in three (1%) Pmab + Bev/Ox-CT pts, three (1%) Bev/Ox-CT patients, and in two (2%) Pmab + Bev/Iri-CT patients.
‡Grade 5 pulmonary embolism occurred in three (1%) Pmab + Bev/Ox-CT patients and in one (1%) Pmab + Bev/Iri-CT patient.
§Grade 5 gastrointestinal perforations occurred in two (< 1%) Pmab + Bev/Ox-CT patients.

There are methodological and design factors in PACCE that could have affected outcomes. First, the chemotherapy treatments were not uniform, possibly confounding outcomes and complicating the ability to provide standardized dose modification instructions with consequent excess toxicity. Nevertheless, the arms were well-balanced with respect to regimens and doses. Second, the open-label nature of the study may have resulted in toxicity-reporting bias. Lastly, a high degree of PFS censoring due to treatment discontinuation before disease progression could have masked treatment effects emerging later in the course of therapy.

Despite the above observations, recently reported data strongly suggest that the results of PACCE are generalizable to the triple combination of anti-EGFR agents, bevacizumab, and chemotherapy in mCRC. A recent report from a phase III study investigating capecitabine, oxaliplatin, and bevacizumab with or without cetuximab in first-line mCRC (CAIRO2)[24] also showed inferior PFS in the investigational arm with excess toxicity, particularly skin toxicity and diarrhea, without significant differences in RR or OS. A phase II study examining FOLFOX plus bevacizumab and erlotinib in mCRC likewise demonstrated poor tolerability.[25]

The positive predictive value of *KRAS* mutations as an exclusion marker for EGFR antibody treatment has been demonstrated.[8,9,14,15,26–28] However, in the PACCE study, a trend towards worse survival was observed with panitumumab in the WT *KRAS* group of the oxaliplatin cohort. Differential exposure to EGFR antibodies in later lines of therapy could also have affected survival in the WT *KRAS* group. Similarly, in the CAIRO2 study, the triple combination of cetuximab, bevacizumab, and capecitabine plus oxaliplatin did not provide additional benefit in the WT *KRAS* group.[24] This observation raises the possibility of a negative interaction between anti-EGFR antibodies and bevacizumab when combined with chemotherapy, even in a setting where anti-EGFR antibodies can effectively inhibit EGFR signaling. Understanding this potential interaction would help identify patient populations, therapeutic combinations, and, potentially, sequencing schedules that are more likely to result in clinical benefit. The ongoing CALGB 80405 phase III trial investigating bevacizumab, cetuximab, and chemotherapy for first-line mCRC,[29,30] which was recently amended to include only patients with WT *KRAS* tumors (Alan Venook, personal communication), may provide further insights.

In conclusion, our results do not support the use of panitumumab in combination with bevacizumab and oxaliplatin- or irinotecan-based chemotherapy for the treatment of mCRC. Administration of chemotherapy and dual EGFR/VEGF inhibition should be conducted only in a research setting, using selected populations and/or novel administration schedules or combinations. Molecular markers in this setting should expand beyond the *KRAS* biomarker.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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