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ORIGINAL REPORT

Randomized Phase III Study of Panitumumab With Fluorouracil, Leucovorin, and Irinotecan (FOLFIRI) Compared With FOLFIRI Alone As Second-Line Treatment in Patients With Metastatic Colorectal Cancer

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ABSTRACT

Purpose
Panitumumab is a fully human anti–epidermal growth factor receptor (EGFR) monoclonal antibody that improves progression-free survival (PFS) in chemotherapy-refractory metastatic colorectal cancer (mCRC). This trial evaluated the efficacy and safety of panitumumab plus fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone after failure of initial treatment for mCRC by tumor *KRAS* status.

Patients and Methods
Patients with mCRC, one prior chemotherapy regimen for mCRC, Eastern Cooperative Oncology Group performance status 0 to 2, and available tumor tissue for biomarker testing were randomly assigned 1:1 to panitumumab 6.0 mg/kg plus FOLFIRI versus FOLFIRI every 2 weeks. The coprimary end points of PFS and overall survival (OS) were independently tested and prospectively analyzed by *KRAS* status.

Results
From June 2006 to March 2008, 1,186 patients were randomly assigned 1:1 and received treatment. *KRAS* status was available for 91% of patients: 597 (55%) with wild-type (WT) *KRAS* tumors, and 486 (45%) with mutant (MT) *KRAS* tumors. In the WT *KRAS* subpopulation, when panitumumab was added to chemotherapy, a significant improvement in PFS was observed (hazard ratio [HR] = 0.73; 95% CI, 0.59 to 0.90; $P = .004$); median PFS was 5.9 months for panitumumab-FOLFIRI versus 3.9 months for FOLFIRI. A nonsignificant trend toward increased OS was observed; median OS was 14.5 months versus 12.5 months, respectively (HR = 0.85, 95% CI, 0.70 to 1.04; $P = .12$); response rate was improved to 35% versus 10% with the addition of panitumumab. In patients with MT *KRAS*, there was no difference in efficacy. Adverse event rates were generally comparable across arms with the exception of known toxicities associated with anti-EGFR therapy.

Conclusion
Panitumumab plus FOLFIRI significantly improved PFS and is well-tolerated as second-line treatment in patients with WT *KRAS* mCRC.

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INTRODUCTION

Worldwide, 1 million patients are diagnosed annually with colorectal cancer (CRC), and 50% of these will develop metastatic disease.[1] Ultimately, more than 500,000 patients die every year from CRC. Most patients with metastatic CRC (mCRC) will receive chemotherapy. Since the introduction of oxaliplatin and irinotecan, combinations of fluorouracil (FU), leucovorin, and oxaliplatin and of FU, leucovorin, and irinotecan (FOLFIRI) are considered standard chemotherapy for mCRC.[2-6] Clinical trials have shown the benefit of adding bevacizumab or cetuximab to chemotherapy in the treatment of mCRC.[7-9] Approximately 70% of patients who progress after one line of chemotherapy will receive

at least one subsequent line of systemic treatment.[6] Of note, in patients receiving FOLFIRI after prior FU, leucovorin, and oxaliplatin treatment, the response rate of 4% and median progression-free survival (PFS) of 2.5 months are modest.[6] These data indicate that further investigations to optimize patient treatment strategies and treatment selection are needed.

Panitumumab is a fully human monoclonal antibody (mAb) directed against the epidermal growth factor receptor (EGFR) that is approved in the United States as monotherapy for mCRC after disease progression with standard chemotherapy and in the European Union and other regions for patients with wild-type (WT) *KRAS* tumor status.[10,11]

KRAS mutations occur in approximately 35% to 43% of patients with mCRC.[12,13] Retrospective analyses of phase II and III studies have demonstrated that *KRAS* mutations are predictive of resistance to anti-EGFR therapies; patients with mCRC with mutant (MT) *KRAS* tumor status do not derive clinical benefit.[8,14-19]

We conducted this global, phase III trial to evaluate the effect of the addition of panitumumab to FOLFIRI chemotherapy as second-line treatment for mCRC. Originally designed to compare the treatment effect in the all randomized population, based on compelling external data, the study was amended before any efficacy analyses so that these analyses could be performed prospectively by tumor *KRAS* status.

PATIENTS AND METHODS

Patients

Eligible patients were ≥ 18 years of age with Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 with a diagnosis of adenocarcinoma of the colon or rectum. Only one prior chemotherapy regimen for mCRC consisting of first-line fluoropyrimidine-based chemotherapy was allowed. Radiographically confirmed disease progression must have occurred during or within 6 months of prior first-line chemotherapy. In addition, at least one unidimensionally measurable lesion (≥ 20 mm) was required for enrollment. A pretreatment paraffin-embedded tumor tissue from the primary tumor or metastasis had to be available for central analyses of EGFR and biomarker testing. Neither EGFR expression nor *KRAS* status was required for enrollment.

Patients were excluded if they had received prior irinotecan or prior anti-EGFR therapy. Before random assignment, systemic chemotherapy, hormonal therapy, immunotherapy, approved proteins/antibodies, or any experimental agent or therapy (within 30 days) or radiotherapy (within 14 days) were not allowed. Patients must not have had major surgery ≤ 28 days before random assignment.

The study protocol was approved by the independent ethics committee at participating study centers, and all patients provided signed informed consent before any study-related procedures were performed.

Study Design and Treatment Schedule

This was an open-label, randomized, multicenter, phase III trial that compared the efficacy of panitumumab plus chemotherapy versus chemotherapy alone in patients with previously treated mCRC. The study was not blinded because of the expected skin toxicity related to panitumumab administration. Patients were randomly assigned one:one to panitumumab 6.0 mg/kg every 2 weeks plus FOLFIRI or FOLFIRI alone. Random assignment was stratified by three factors: prior treatment with oxaliplatin (no, yes) or bevacizumab (no, yes) for mCRC and ECOG performance status (0 or 1 *v* 2). Panitumumab was administered by a 60-minute infusion before chemotherapy; if the first panitumumab dose was well tolerated, subsequent infusions could be administered over 30 minutes. All patients received FOLFIRI: 180 mg/m^2 irinotecan and 400 mg/m^2 racemic leucovorin (or 200 mg/m^2 *l*-leucovorin) by intravenous (IV) infusion on day 1 and FU 400 mg/m^2 IV bolus on day 1, followed by 2,400 mg/m^2 continuous infusion administered over days 1 and 2. Patients received chemotherapy ± panitumumab until disease progression or intolerability.

Tumor response was assessed by the investigator and by an independent central radiology review blinded to treatment and outcomes using a modification of Response Evaluation Criteria in Solid Tumors (RECIST) every 8 weeks until disease progression. Responses (complete response or partial response) were confirmed ≥ 28 days after the criteria for response were first met.[20] Patients were followed-up for safety for at least 30 days after the last study drug administration and for survival every 3 months.

Adverse events (AEs) were collected during the treatment and safety follow-up phases and were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 with modifications

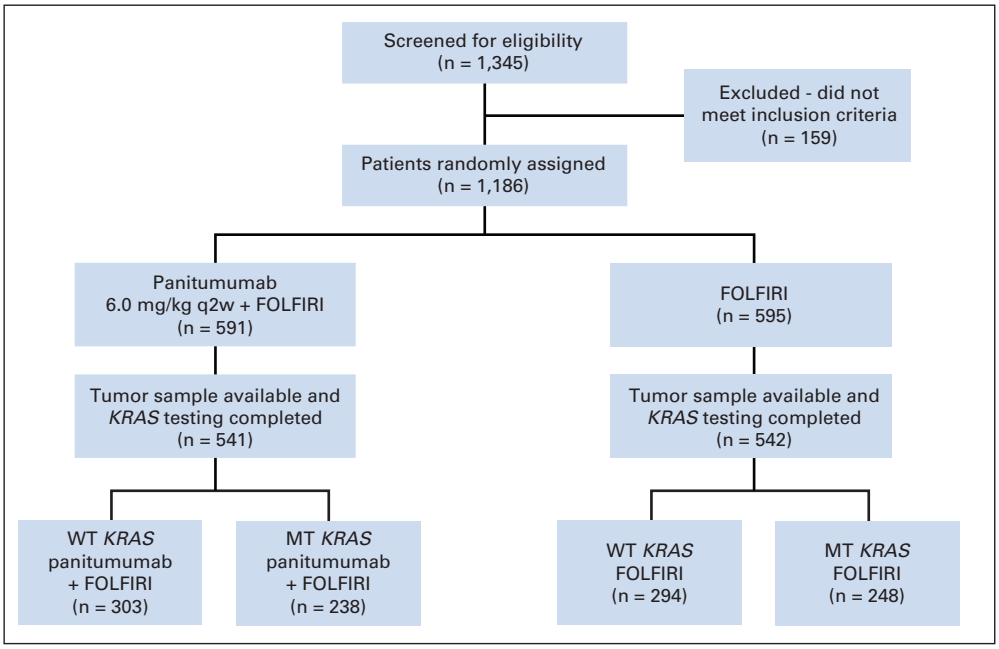

Fig 1. CONSORT diagram. q2w, every 2 weeks; FOLFIRI, fluorouracil, leucovorin, and irinotecan; WT, wild type; MT, mutant.

for specific skin and nail toxicities.[21] AEs of interest included those known to be associated with an EGFR inhibitor and/or FOLFIRI.

An independent data monitoring committee oversaw the planned interim analyses of safety and the planned interim analysis of OS.

Statistical Analysis

The objective of this study was to evaluate the treatment effect of the addition of panitumumab to FOLFIRI on PFS (based on blinded central radiology review) and OS as second-line therapy for mCRC in patients with WT *KRAS* tumors and also in patients with MT *KRAS* tumors. Other key end points included objective response rate, duration of response, safety (including incidence of AEs and significant laboratory changes), and patient-reported outcomes (reported separately).

The study was initially estimated to require 1,100 patients unselected for *KRAS* tumor status. Based on emerging *KRAS* data from other panitumumab studies showing that monotherapy clinical benefit was isolated to patients with WT *KRAS*, the protocol was amended after completion of enrollment, and the primary objective was changed to incorporate patient stratification for *KRAS* status.[14,16] An overall 5% significance level was used to compare treatments with respect to both OS and PFS in the WT and MT *KRAS* subpopulations. A 1% significance level test for a treatment effect on PFS in the MT *KRAS* subpopulation was performed conditional on a 1% level significant PFS result in the WT *KRAS* subpopulation. A total of 380 PFS events (where events are either radiologic progression per modified RECIST determined by blinded central review or death) were required to achieve 90% power for a 1% significance level test if the PFS hazard ratio (HR; panitumumab-FOLFIRI: FOLFIRI) was 0.67 in the WT *KRAS* subpopulation. A 4% significance level test for a treatment effect on OS in the MT *KRAS* subpopulation was performed conditional on a 4% level significant OS result in the WT *KRAS* subpopulation. A total of 380 OS events were required to achieve 85% power for a 4% significance level test assuming an OS HR of 0.724 that compensates for an expected 20% incidence of subsequent anti-EGFR therapy in the control arm.[22] One planned interim OS analysis in the WT *KRAS* subpopulation was conducted with 285 OS events using the O'Brien-Fleming stopping boundary. The primary analysis of PFS was planned to coincide with the earlier of a positive interim OS analysis or the primary OS analysis.

PFS and OS were analyzed based on the Kaplan-Meier method using all randomly assigned patients within each *KRAS* subpopulation. A log-rank test stratified by randomization factors was used to compare the treatment effect for PFS and OS.

KRAS and Antibody Testing

KRAS testing was performed in a blinded central laboratory using allele-specific polymerase chain reaction (DxS, Manchester, United Kingdom) as previously described.[14] Testing was performed after completion of accrual and just before the interim OS analysis. Reasons for no *KRAS* test result included no tumor available for testing (no specimen submitted or no tumor present) or inadequate quantity or quality of extracted DNA.

Antipanitumumab antibodies were analyzed from available patient serum samples by enzyme-linked immunosorbent assay and Biacore (Biacore Life Sciences, Piscataway, NJ) methods as previously described.[23,24]

RESULTS

Patients

From June 2006 to March 2008, 1,186 patients were randomly assigned, 591 (50%) to panitumumab-FOLFIRI and 595 (50%) to FOLFIRI alone (Fig 1). Of these, 1,083 patients (91%) had available *KRAS* tumor status results: 597 patients (55%) with WT *KRAS* tumors and 486 patients (45%) with MT *KRAS* tumors.

Baseline demographics and disease characteristics were balanced between treatment arms within *KRAS* subpopulations, including patients with liver-only disease, prior oxaliplatin therapy, and prior bevacizumab therapy (Table 1). Median follow-up time was 13.3 months (range, 0.2 to 31.7 months) in the WT *KRAS* panitumumab-FOLFIRI arm, 10.2 months (range, 0.5 to 32.9 months) in the WT *KRAS* FOLFIRI arm, 10.5 months (range, 0.2 to 30.1 months) in the MT *KRAS* panitumumab-FOLFIRI arm, and 9.5 months (range, 0 to 31.7 months) in the MT *KRAS* FOLFIRI arm.

Table 1. Demographics and Disease Characteristics

Characteristic	WT *KRAS*				MT *KRAS*			
	Panitumumab-FOLFIRI (n = 303)		FOLFIRI (n = 294)		Panitumumab-FOLFIRI (n = 238)		FOLFIRI (n = 248)	
	No.	%	No.	%	No.	%	No.	%
Sex, male	188	62	191	65	133	56	148	60
Age, years								
Median	60		61		61		64	
Minimum	28		29		29		29	
Maximum	84		86		83		86	
Race, white	294	97	278	95	226	95	238	96
ECOG performance status								
0-1	288	95	273	93	224	94	233	94
2	15	5	21*	7	14	6	15	6
Primary tumor type								
Colon	187	62	189	64	156	66	164	66
Rectal	116	38	105	36	82	34	84	34
Sites of metastatic disease								
Liver only	51	17	59	20	37	16	35	14
Liver + other	205	68	189	64	166	70	172	69
Other only	47	16	44	15	34	14	39	16
Missing or unknown	0	0	2	< 1	1	< 1	2	< 1
Prior therapy								
Oxaliplatin	204	67	191	65	164	69	169	68
Bevacizumab	55	18	60	20	45	19	43	17

Abbreviations: WT, wild-type; FOLFIRI, fluorouracil, leucovorin, and irinotecan; MT, mutant; ECOG, Eastern Cooperative Oncology Group.
*Includes one patient with ECOG performance status of 3.

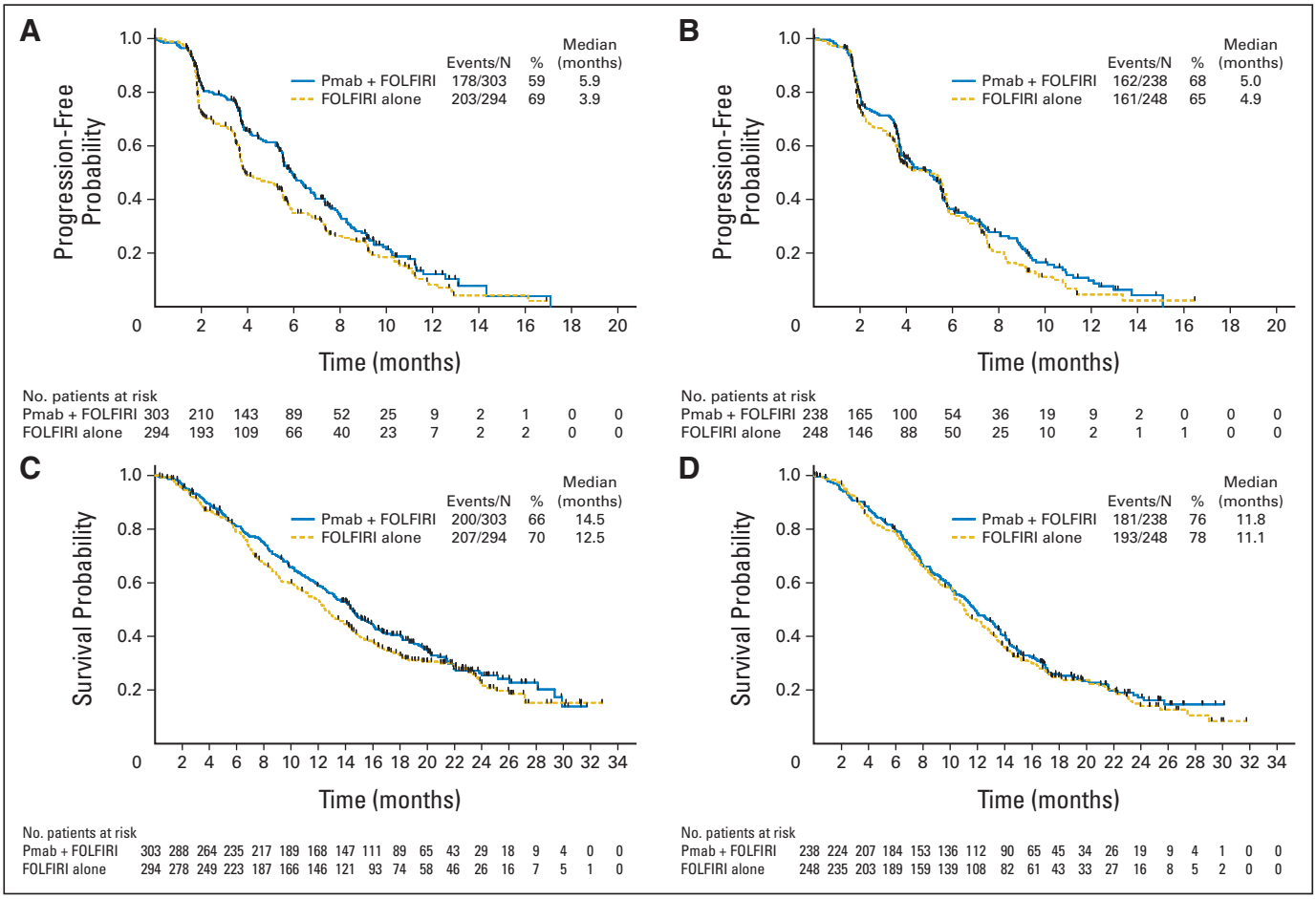

Fig 2. Progression-free survival (central review) by (A) wild-type (WT) *KRAS* and (B) mutant (MT) *KRAS*. Overall survival by (C) WT *KRAS* and (D) MT *KRAS*. Pmab, panitumumab; FOLFIRI, fluorouracil, leucovorin, and irinotecan.

Efficacy

Progression-free survival. For the primary analysis of PFS in the WT *KRAS* subpopulation, there were 381 progression or death events: 178 patients (59%) in the panitumumab-FOLFIRI arm and 203 patients (69%) in the FOLFIRI arm. A statistically significant improvement in PFS with panitumumab-FOLFIRI versus FOLFIRI was demonstrated (HR = 0.73; 95% CI, 0.59 to 0.90; $P = .004$, stratified log-rank; Fig 2A). Median PFS was 5.9 months (95% CI, 5.5 to 6.7 months) for panitumumab-FOLFIRI and 3.9 months (95% CI, 3.7 to 5.3 months) for FOLFIRI alone.

In the MT *KRAS* subpopulation, there were 323 progression or death events: 162 patients (68%) in the panitumumab-FOLFIRI arm and 161 patients (65%) in the FOLFIRI arm. There was no statistically significant difference in PFS (HR = 0.85; 95% CI, 0.68 to 1.06; $P = .14$, stratified log-rank; Fig 2B). Median PFS was 5.0 months (95% CI, 3.8 to 5.6 months) for panitumumab-FOLFIRI and 4.9 months (95% CI, 3.6 to 5.6 months) for FOLFIRI alone.

From planned subgroup analyses for PFS in the WT *KRAS* subpopulation, all subsets favored panitumumab, including ECOG, age, sex, and prior treatment with bevacizumab or oxaliplatin (Fig 3A).

Overall survival. For the primary analysis of OS in the WT *KRAS* subpopulation, there were 407 deaths: 200 patients (66%) in the panitumumab-FOLFIRI arm and 207 patients (70%) in the FOLFIRI arm. There was no statistically significant difference in OS (HR = 0.85; 95% CI, 0.70 to 1.04; $P = .12$, stratified log-rank; Fig 2C). Median OS was 14.5 months (95% CI, 13.0 to 16.0 months) for panitumumab-FOLFIRI and 12.5 months (95% CI, 11.2 to 14.2 months) for FOLFIRI alone. Subgroup analyses are shown in Figure 3B.

In the MT *KRAS* subpopulation, there were 374 deaths: 181 patients (76%) in the panitumumab-FOLFIRI arm and 193 patients (78%) in the FOLFIRI arm. According to the statistical analysis plan, the precondition to formally test OS in the MT *KRAS* subpopulation was not met (HR = 0.94; 95% CI, 0.76 to 1.15; Fig 2D). Median OS was 11.8 months (95% CI, 10.4 to 13.3 months) for panitumumab-FOLFIRI and 11.1 months (95% CI, 10.3 to 12.4 months) for FOLFIRI alone.

In the WT *KRAS* subpopulation, subsequent use of EGFR mAbs was reported in 10% of patients in the panitumumab-FOLFIRI arm versus 31% of patients in the FOLFIRI arm, with a median time to use of 11.8 and 7.6 months, respectively. Use of any subsequent chemotherapy (specifically oxaliplatin, irinotecan, and/or FU) was balanced overall (47% and 48% for the panitumumab-FOLFIRI and FOLFIRI arms, respectively) and included oxaliplatin in 18% and 16% of patients, respectively. Subsequent irinotecan use was less common in the panitumumab-FOLFIRI arm (18%) than in the

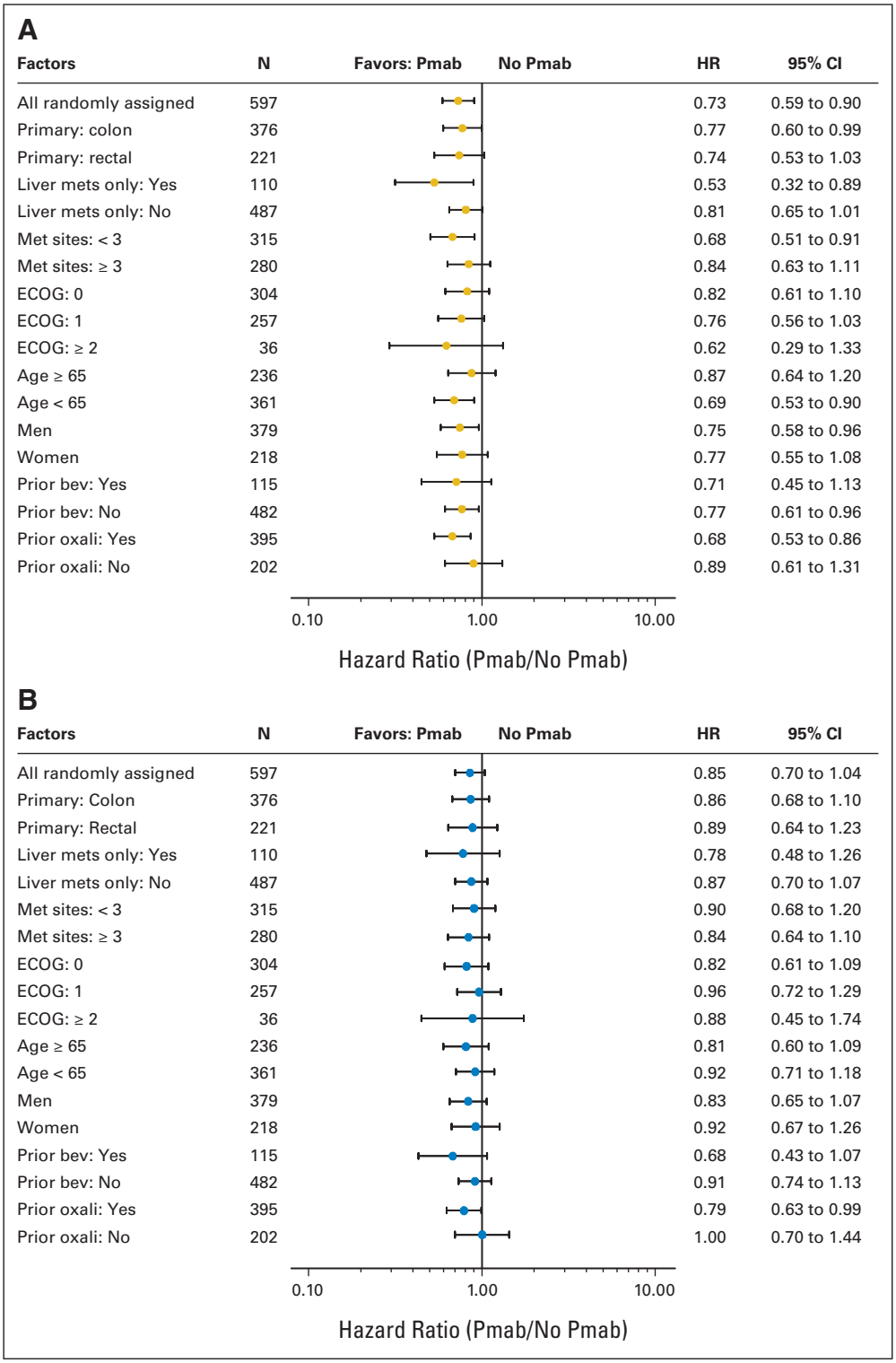

Fig 3. Wild-type *KRAS* subgroup analyses for (A) progression-free survival and (B) overall survival. Pmab, panitumumab; HR, hazard ratio; mets, metastases; met, metastatic; ECOG, Eastern Cooperative Oncology Group; bev, bevacizumab; oxali, oxaliplatin.

FOLFIRI arm (32%), and fewer patients in the panitumumab-FOLFIRI arm received both irinotecan and an EGFR inhibitor (9%), as compared with the FOLFIRI arm (24%). Subsequent bevacizumab use was reported in 8% of patients in the panitumumab-FOLFIRI arm and in 11% of patients in the FOLFIRI arm.

Objective response. Objective response was assessed by blinded central radiology review for all patients with baseline measurable disease per central review. In patients with WT *KRAS*, the objective response rate by central review was 35% (95% CI, 30% to 41%) in the panitumumab-FOLFIRI arm versus 10% (95% CI, 7% to 14%) in the FOLFIRI arm (descriptive $P < .001$; Table 2). In patients with MT *KRAS*, the objective response rate was 13% (95% CI, 9% to 18%) in the panitumumab-FOLFIRI arm versus 14% (95% CI, 10% to 19%) in the FOLFIRI arm.

Table 2. Efficacy: WT and MT *KRAS*

Response Category	WT *KRAS*		MT *KRAS*	
	Panitumumab-FOLFIRI (n = 303)	FOLFIRI (n = 294)	Panitumumab-FOLFIRI (n = 238)	FOLFIRI (n = 248)
PFS*				
PFS event				
No.	178	203	162	161
%	59	69	68	65
Median PFS				
Months	5.9	3.9	5.0	4.9
95% CI	5.5 to 6.7	3.7 to 5.3	3.8 to 5.6	3.6 to 5.6
P	.004		.14	
OS				
Deaths				
No.	200	207	181	193
%	66	70	76	78
Median OS				
Months	14.5	12.5	11.8	11.1
95% CI	13.0 to 16.0	11.2 to 14.2	10.4 to 13.3	10.3 to 12.4
P	.12		ND†	
Response*‡				
No. of patients	297	285	232	237
Objective response rate				
%	35	10	13	14
95% CI	30 to 41	7 to 14	9 to 18	10 to 19
P	< .0001		1.0	
Complete response, %	0	0	0	0
Partial response, %	35	10	13	14
Stable disease, %	39	55	55	49

Abbreviations: WT, wild-type; MT, mutant; FOLFIRI, fluorouracil, leucovorin, and irinotecan; PFS, progression-free survival; OS, overall survival; ND, not done.
*By central radiology review.
†Not done because the precondition to formally test for OS in the MT *KRAS* subpopulation was not met.
‡Included only patients with baseline measurable disease per central review.

Safety

Grade 3 and 4 AEs of interest, including events that occurred with a greater than 5% difference between treatment arms, are shown in Table 3. The incidence of AEs in the WT *KRAS* subpopulation in the panitumumab-FOLFIRI and FOLFIRI arms were, respectively, 68% versus 43% for worst grade 3 or 4 treatment-related (as assessed by the investigator), 41% versus 31% for serious, and 4% versus 6% for fatal, some of which included cases

Table 3. Grade 3 and 4 Adverse Events of Interest*

Adverse Event by MedDRA Term	WT *KRAS* (n = 596)				MT *KRAS* (n = 483)			
	Panitumumab-FOLFIRI (n = 302)		FOLFIRI (n = 294)		Panitumumab-FOLFIRI (n = 237)		FOLFIRI (n = 246)	
	No.	%	No.	%	No.	%	No.	%
Patients with any event	219	73	152	52	151	64	123	50
Skin toxicity	111	37	7	2	75	32	2	1
Neutropenia	59	20	68	23	32	14	43	17
Diarrhea	41	14	27	9	32	14	26	11
Mucositis†	23	8	8	3	22	9	9	4
Hypokalemia	20	7	3	1	9	4	2	1
Pulmonary embolism	15	5	7	2	7	3	5	2
Dehydration	10	3	5	2	8	3	4	2
Hypomagnesemia	9	3	1	< 1	11	5	0	0
Paronychia	9	3	1	< 1	6	3	0	0
Febrile neutropenia	6	2	9	3	3	1	7	3
Infusion-related reaction (panitumumab)	2	< 1	—	—	0	0	—	—

Abbreviations: WT, wild-type; MT, mutant; FOLFIRI, fluorouracil, leucovorin, and irinotecan; MedDRA, Medical Dictionary for Regulatory Activities.
*Included all events, regardless of relatedness.
†Includes events of stomatitis, oral mucositis, and oral inflammation.

where the primary cause of death was disease progression. There were six fatal AEs that were treatment-related, two (ileus and diarrhea) in the panitumumab-FOLFIRI arm and four (two sepsis, one acute cardiac failure, and one general physical health deterioration) in the FOLFIRI arm.

The incidence of AEs in the MT *KRAS* subpopulation in the panitumumab-FOLFIRI and FOLFIRI arms were, respectively, 62% versus 40% for worst grade 3 to 4 treatment-related, 37% versus 30% for serious, and 7% versus 5% for fatal, some of which included cases where the primary cause of death was disease progression. There was one fatal AE reported to be treatment-related in each arm: acute cardiac failure in the panitumumab-FOLFIRI arm and cerebrovascular accident in the FOLFIRI arm.

Grade 3 to 4 panitumumab-related infusion reactions occurred in two patients (<1%; both grade 4); these patients did not receive further panitumumab.

Treatment Exposure

The relative dose-intensity for irinotecan was 87% in the panitumumab-FOLFIRI arm versus 90% in the FOLFIRI arm for both *KRAS* subpopulations (Appendix Table A1, online only). The relative dose-intensity for FU (bolus and infusional) was 84% to 85% in the panitumumab-FOLFIRI arm versus 89% to 90% in the FOLFIRI arm for both *KRAS* subpopulations. In the WT *KRAS* subpopulation, the median number of cycles of chemotherapy received was higher for patients randomly assigned to the panitumumab-FOLFIRI arm, and the median cumulative dose delivered was correlated with the number of cycles received. The most common reason for FOLFIRI discontinuation was disease progression, which occurred in 59% of patients with WT *KRAS* tumor status and 66% of patients with MT *KRAS* tumor status. Other reasons for FOLFIRI discontinuation included patient request and AEs and were balanced between treatment arms and *KRAS* subpopulations.

Antibodies

Antibodies to panitumumab that developed after treatment were detected in less than 1% of patients (four of 501), none of which were neutralizing.

DISCUSSION

This is the first study to prospectively analyze the treatment effect of an anti-EGFR mAb according to tumor *KRAS* status in patients with previously treated mCRC. A total of 1,186 patients were randomly assigned; consistent with the high quality of study conduct in this trial, *KRAS* results were available from more than 90% of these patients.

The addition of panitumumab to FOLFIRI resulted in a significant 27% reduction ($P = .004$) in the risk of progression or death (in the absence of progression) in the WT *KRAS* subpopulation. An absolute difference in median PFS of 2.0 months (5.9 months for panitumumab-FOLFIRI *v* 3.9 months for FOLFIRI alone) was observed, and this treatment effect on PFS was consistently seen across all predefined subsets. These results are comparable to the results of a previous second-line study that evaluated the value of adding cetuximab to irinotecan (350 mg/m^2).[15,25] In this cetuximab trial, a median PFS difference from 2.8 to 4.0 months ($P = .095$) was observed in the WT *KRAS* subpopulation; no significant difference in OS was detected.[25] Important differences between this study and our study include that in our study, oxaliplatin resistance was not required for study entry, and FOLFIRI, which may be considered a preferred regimen to single-agent irinotecan,[26] was used.

OS was an independently tested coprimary end point. Although an absolute increase of 2.0 months in median OS was observed (12.5 *v* 14.5 months) in favor of panitumumab in the WT *KRAS* subpopulation, the effect on OS was not statistically significant. The imbalance in subsequent EGFR inhibitor use may have attenuated the estimated treatment effect of panitumumab on OS.

The response rate (35%) in the WT *KRAS* subpopulation that received panitumumab-FOLFIRI in this study is the highest reported in a randomized, phase III, second-line study. Response rates for irinotecan-based regimens in second-line therapy are generally between 4% and 16% in *KRAS* unselected populations.[9,15] In our study, similar response rates were observed in the FOLFIRI alone arm (10% and 14% in the WT and MT *KRAS* subpopulation, respectively), indicating that the patient population was similar to those studied previously. The high response rate seen with panitumumab-FOLFIRI may be of particular value in patients who experience disease progression during first-line therapy with borderline resectable metastases or symptomatic disease. In patients with MT *KRAS* tumors, there was no evidence of a benefit when panitumumab was added to FOLFIRI, and in contrast to what was observed in other studies with panitumumab or cetuximab in combination with oxaliplatin-based chemotherapy, there was no evidence of a detrimental effect in the MT *KRAS* subpopulation that received panitumumab with FOLFIRI.[27,28]

Panitumumab plus FOLFIRI appeared to have an acceptable safety profile. The AEs reported in the panitumumab-FOLFIRI arm comprised previously recognized AEs associated with FOLFIRI regimen and anti-EGFR mAb therapy. As expected, there were differences in the incidence of skin toxicity and hypomagnesemia between the panitumumab and the control arm. Due to potential overlapping toxicities between an EGFR inhibitor and an irinotecan regimen, guidance for diarrhea management was provided to investigators, resulting in only a 4% increase in grade 3 to 4 events. The incidence of panitumumab-related infusion-related reactions was low (grade 3 to 4 rate is < 1%) and is comparable to rates reported in the monotherapy setting.[23] Panitumumab is administered every 2 weeks, which synchronizes with the most frequently used regimens in mCRC.

This large phase III trial demonstrated the efficacy of panitumumab when added to FOLFIRI in patients with previously treated WT *KRAS* mCRC. Based on the *KRAS* results, which were available for 91% of enrolled patients, this study demonstrated a statistically significant improvement in PFS in patients with WT *KRAS* tumors and confirms tumor *KRAS* status as a predictive biomarker in this setting. In conclusion, panitumumab is effective when combined with FOLFIRI, a frequently used chemotherapy regimen for patients with previously treated mCRC. This regimen provides a convenient administration schedule with a manageable toxicity profile and represents an important new treatment option in patients with WT *KRAS* tumors. Further analyses to characterize the effect of other biomarkers on treatment outcomes, as well as analyses of patient-reported outcomes, are ongoing.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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