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ORIGINAL REPORT

Randomized, Phase III Trial of Panitumumab With Infusional Fluorouracil, Leucovorin, and Oxaliplatin (FOLFOX4) Versus FOLFOX4 Alone As First-Line Treatment in Patients With Previously Untreated Metastatic Colorectal Cancer: The PRIME Study

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ABSTRACT

Purpose
Panitumumab, a fully human anti–epidermal growth factor receptor (EGFR) monoclonal antibody that improves progression-free survival (PFS), is approved as monotherapy for patients with chemotherapy-refractory metastatic colorectal cancer (mCRC). The Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME) was designed to evaluate the efficacy and safety of panitumumab plus infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as initial treatment for mCRC.

Patients and Methods
In this multicenter, phase III trial, patients with no prior chemotherapy for mCRC, Eastern Cooperative Oncology Group performance status of 0 to 2, and available tissue for biomarker testing were randomly assigned 1:1 to receive panitumumab-FOLFOX4 versus FOLFOX4. The primary end point was PFS; overall survival (OS) was a secondary end point. Results were prospectively analyzed on an intent-to-treat basis by tumor *KRAS* status.

Results
KRAS results were available for 93% of the 1,183 patients randomly assigned. In the wild-type (WT) *KRAS* stratum, panitumumab-FOLFOX4 significantly improved PFS compared with FOLFOX4 (median PFS, 9.6 *v* 8.0 months, respectively; hazard ratio [HR], 0.80; 95% CI, 0.66 to 0.97; $P = .02$). A nonsignificant increase in OS was also observed for panitumumab-FOLFOX4 versus FOLFOX4 (median OS, 23.9 *v* 19.7 months, respectively; HR, 0.83; 95% CI, 0.67 to 1.02; $P = .072$). In the mutant *KRAS* stratum, PFS was significantly reduced in the panitumumab-FOLFOX4 arm versus the FOLFOX4 arm (HR, 1.29; 95% CI, 1.04 to 1.62; $P = .02$), and median OS was 15.5 months versus 19.3 months, respectively (HR, 1.24; 95% CI, 0.98 to 1.57; $P = .068$). Adverse event rates were generally comparable across arms with the exception of toxicities known to be associated with anti-EGFR therapy.

Conclusion
This study demonstrated that panitumumab-FOLFOX4 was well tolerated and significantly improved PFS in patients with WT *KRAS* tumors and underscores the importance of *KRAS* testing for patients with mCRC.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer among men and women in the United States, resulting in approximately 175,000 new cancers yearly.[1] Worldwide, there are more than one million new cases of CRC each year.[2] On the basis of its role in the pathogenesis of CRC, the epidermal growth factor receptor (EGFR) has proven to be a clinically meaningful target for

monoclonal antibodies (mAbs) with efficacy established in all lines of treatment of metastatic CRC (mCRC).[3-9] Panitumumab is a fully human mAb targeting the EGFR.

Retrospectively analyzed studies identified *KRAS* mutation in tumors as a negative predictive factor for panitumumab and cetuximab for improved response rate (RR), progression-free survival (PFS), and overall survival (OS).[10-16] In September 2007, a prospectively defined, retrospective analysis of the pivotal phase III study of panitumumab as monotherapy in the mCRC setting provided evidence that clinical benefit was specific to patients with wild-type (WT) *KRAS* tumors.[17]

The Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME) is an open-label, randomized, multicenter, phase III trial prospectively investigating panitumumab plus infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment for mCRC in patients with WT *KRAS* tumors. Originally designed to compare the treatment effect in all randomly assigned patients, the trial was amended to focus on prospective hypothesis testing in the WT *KRAS* stratum.

PATIENTS AND METHODS

Patients

Eligible patients were ≥ 18 years old, had previously untreated metastatic adenocarcinoma of the colon or rectum, and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2. Fluorouracil-based adjuvant chemotherapy was allowed if disease recurrence occurred 6 months after completion; however, prior oxaliplatin was not allowed. At least one measurable lesion (≥ 20 mm) was required. Paraffin-embedded tumor tissue from the primary tumor or metastasis had to be available for central biomarker analyses. EGFR expression and *KRAS* status were not required at entry. The protocol was approved by the ethics committees at participating sites. All patients signed informed consent before any study-related procedures were performed.

Study Design and Treatment Schedule

This is an open-label, multicenter, phase III trial that compared the efficacy of panitumumab-FOLFOX4 with FOLFOX4 alone in patients with previously untreated mCRC according to tumor *KRAS* status. Patients were randomly assigned 1:1 to receive either panitumumab-FOLFOX4 or FOLFOX4. Random assignment was stratified by geographic region (Western Europe, Canada, and Australia *v* rest of the world) and ECOG PS (0 or 1 *v* 2).

Panitumumab was administered intravenously (IV) over 1 hour at 6 mg/kg every 2 weeks on day 1 before FOLFOX4 chemotherapy. If tolerated, subsequent infusions could be administered over 30 minutes. FOLFOX4 was administered every 2 weeks as oxaliplatin 85 mg/m^2 IV infusion on day 1 and leucovorin 200 mg/m^2 (or equivalent) IV infusion followed by fluorouracil 400 mg/m^2 IV bolus and 600 mg/m^2 22-hour continuous infusion on days 1 and 2. Treatment was administered until progression or unacceptable toxicity (Fig 1A).

Objective tumor response was evaluated by blinded central radiology review using modified Response Evaluation Criteria in Solid Tumors (RECIST)[18] in all patients with baseline measurable disease per central review. Patients were evaluated every 8 weeks until progression. Responses were confirmed at least 4 weeks later. Resections of metastases were reported as being either complete or partial; the status of the surgical margins was not specifically captured. Patients were observed for safety 30 days after the last study drug administration and for survival every 3 months. Adverse events (AEs) were graded using the Common Terminology Criteria for Adverse Events (version 3.0) with modifications for specific skin- and nail-related toxicities. Safety results were summarized for patients who received at least one dose of protocol therapy. Patient-reported outcomes were measured and will be reported separately. An independent data monitoring committee reviewed interim analyses of safety and one descriptive interim analysis of PFS.

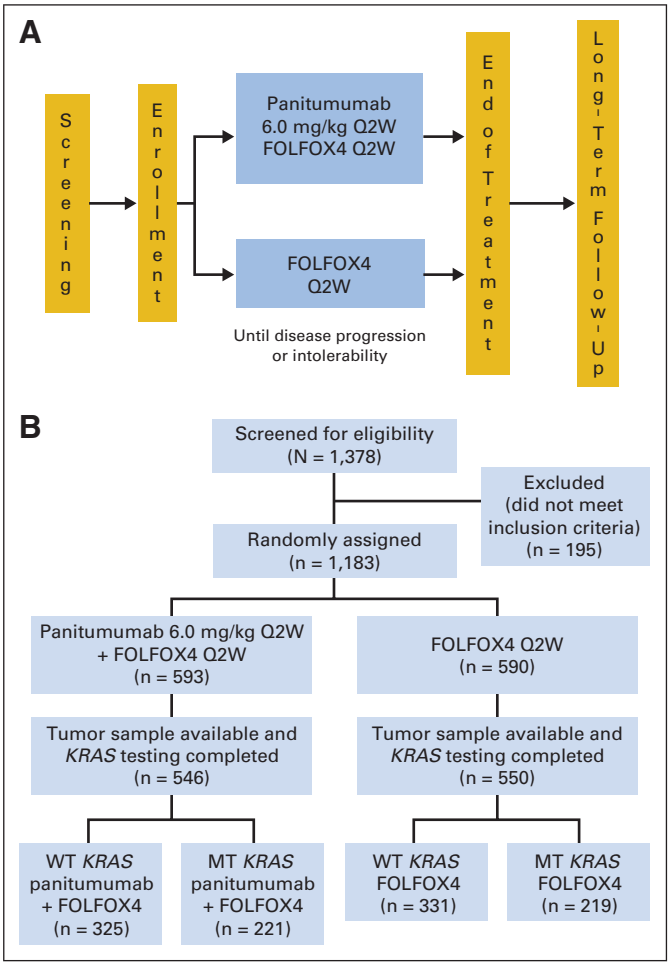

Fig 1. (A) Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME) study schema. (B) Treatment assignment by *KRAS* status. Q2W, every 2 weeks; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin; WT, wild type; MT, mutant.

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.[17] Testing was initiated after the study population was enrolled and was completed 3 months before the primary analysis (Appendix Fig A1, online only). Serum antipanitumumab antibodies were analyzed as previously described.[19]

Statistical Analysis

The primary objective of this study was to assess the treatment effect of the addition of panitumumab to FOLFOX4 on PFS (blinded central radiology review) as initial therapy for mCRC in patients with WT *KRAS* tumors and also in patients with mutant (MT) *KRAS* tumors. Originally designed to test the treatment effect in all randomly assigned patients (N = 900), the study was amended to compare PFS (primary end point) and OS (secondary end point) according to *KRAS* status before any efficacy analyses. The sample size was increased to 1,150 to ensure adequate power to test PFS in the WT *KRAS* population. No multiplicity adjustments were made for end points other than

PFS and OS. There was no planned interim analysis by *KRAS* status after the amendment, because *KRAS* status was not expected to be available until approximately the time of the primary analysis. A treatment comparison of OS in the WT *KRAS* stratum and of PFS in the MT *KRAS* stratum was conditional on first demonstrating a significant difference in PFS ($P < .05$) in the WT *KRAS* stratum. A treatment comparison of OS in the MT *KRAS* stratum was conditional on a significant difference in PFS in the same stratum. The primary OS analysis was planned when at least 50% of patients in both treatment arms had died in the WT *KRAS* stratum, and a significance level of $P = .0499$ was used to account for a planned interim OS analysis.

A log-rank test stratified by random assignment factors was used to compare PFS and OS. In the WT *KRAS* stratum, a hazard ratio (HR) of 0.714 was hypothesized (panitumumab-FOLFOX4 to FOLFOX4). To achieve 90% power for a two-sided, $P = .05$ significance level in the WT *KRAS* stratum, a total of 380 PFS events (radiologic progression per modified RECIST by blinded central review or death) and a sample size of 1,150 patients independent of *KRAS* status were required. Treatment effects on PFS and OS were estimated using stratified Cox proportional hazards models and the Kaplan-Meier method. An exact 95% CI was estimated for a stratified odds ratio for objective RR. The random assignment factors were used for analysis stratification. Descriptive analyses of treatment effects were planned in prospectively identified subsets. After protocol amendment, an interim PFS analysis after 258 events in all randomly assigned patients (because tumor *KRAS* results were not yet available) was retained to stop for inferior results given an estimated HR $\geq$ 1.28. At the time of the primary PFS analysis, a $P = .001$ nominal significance level was used to compare OS in an interim analysis in the WT and MT *KRAS* strata. The interim OS results were reported along with the primary PFS results (after the cutoff date for the primary OS analysis).[20] A prespecified final analysis, which will include OS, is planned after a 2.5-year minimum follow-up period.

RESULTS

Patients

Between August 2006 and February 2008, 1,183 patients were randomly assigned from among 133 institutions in 19 countries; 593 patients (50%) were randomly assigned to receive panitumumab-FOLFOX4, and 590 patients (50%) were randomly assigned to receive FOLFOX4 (Fig 1B). Of these patients, 1,096 patients (93%) had available tumor *KRAS* status results; 656 patients (60%) had WT *KRAS* tumors, and 440 patients (40%) had MT *KRAS* tumors.

Baseline demographics and disease characteristics were generally balanced within each treatment arm and *KRAS* stratum (Table 1), with the exception that there were more patients with three or more disease sites, elevated baseline carcinoembryonic antigen, and elevated lactate dehydrogenase in the panitumumab-FOLFOX4 arm than in the FOLFOX4 arm in the MT *KRAS* stratum. For the primary PFS analysis, median follow-up time from random assignment to data cutoff in the WT *KRAS* stratum was 13.2 months (range, 0 to 25.2 months) for patients who received panitumumab-FOLFOX4 and 12.5 months (range, 0 to 24.7 months) for patients who received FOLFOX4. Median follow-up time was 10.8 months (range, 0.7 to

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	WT *KRAS*				MT *KRAS*			
	Panitumumab-FOLFOX4 (n = 325)		FOLFOX4 (n = 331)		Panitumumab-FOLFOX4 (n = 221)		FOLFOX4 (n = 219)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Male	217	67	204	62	145	66	128	58
Age, years								
Median	62		61		63		61	
Range	27-85		24-82		33-83		27-82	
White race	296	91	307	93	196	89	196	89
ECOG performance status*								
0-1	305	94	312	94	213	96	209	95
$\geq$ 2	20	6	18	5	8	4	10	5
Region: Western Europe, Canada, Australia	194	60	187	56	119	54	122	56
Primary tumor type								
Colon	214	66	216	65	151	68	160	73
Rectal	111	34	115	35	70	32	59	27
Site of metastatic disease								
Liver only	60	18	56	17	32	14	36	16
Liver + other	223	69	227	69	156	71	159	73
Other only	40	12	47	14	31	14	23	11
Missing or unknown	2	1	1	< 1	2	1	1	< 1
No. of sites of disease								
1	68	21	67	20	39	18	43	20
2	112	34	116	35	70	32	80	37
$\geq$ 3	143	44	147	44	110	50	95	43
CEA > ULN	255	78	255	77	188	85	170	78
LDH $\geq$ 1.5× ULN	92	28	96	29	73	33	59	27
Prior adjuvant chemotherapy	53	16	55	17	35	16	26	12

Abbreviations: WT, wild type; MT, mutant; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin; ECOG, Eastern Cooperative Oncology Group; CEA, carcinoembryonic antigen; ULN, upper limit of normal; LDH, lactate dehydrogenase.
*One patient had an unknown ECOG performance status at baseline.

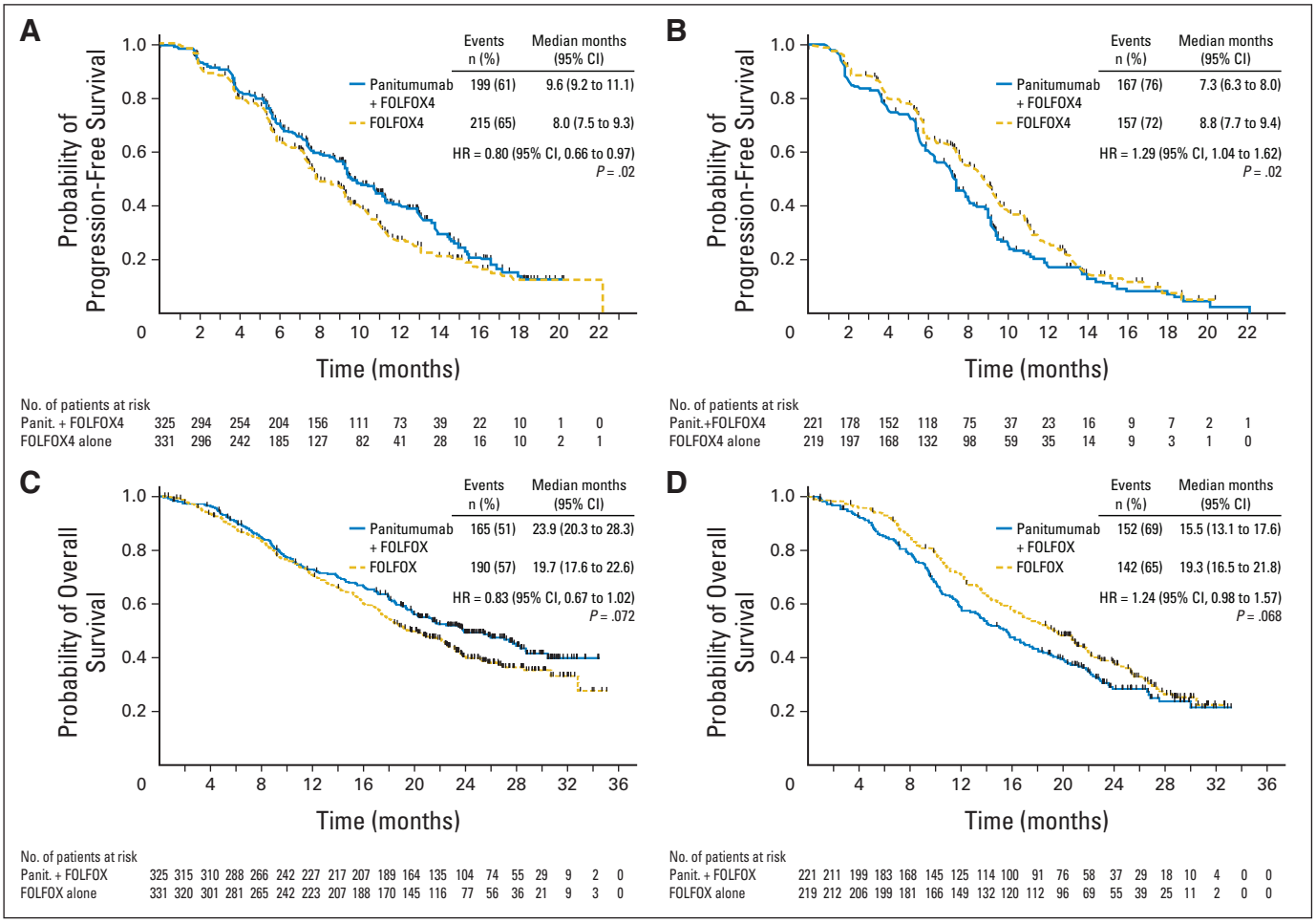

Fig 2. Progression-free survival in patients with (A) wild-type (WT) *KRAS* and (B) mutant (MT) *KRAS*. Overall survival in patients with (C) WT *KRAS* and (D) MT *KRAS*. FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin; Panit., panitumumab; HR, hazard ratio.

22.4 months) for patients with MT *KRAS* status who received panitumumab-FOLFOX4 and 12 months (range, 0.2 to 23.1 months) for patients who received FOLFOX4.

Efficacy

PFS. In the WT *KRAS* stratum, there were 414 progression or death events—199 (61%) in the panitumumab-FOLFOX4 arm and 215 (65%) in the FOLFOX4 arm. A statistically significant improvement in PFS was observed with panitumumab-FOLFOX4 compared with FOLFOX4 (HR = 0.80; 95% CI, 0.66 to 0.97; $P = .02$, stratified log-rank test; Fig 2A). Median PFS was 9.6 months (95% CI, 9.2 to 11.1 months) for panitumumab-FOLFOX4 and 8.0 months (95% CI, 7.5 to 9.3 months) for FOLFOX4. From the planned subgroup analyses for PFS in the WT *KRAS* stratum, the HR for all subsets was less than 1 (panitumumab-FOLFOX4 *v* FOLFOX4), with the exception of patients ≥ 65 years old, women, and patients with ECOG PS of 2 (Fig 3A).

In the MT *KRAS* stratum, there were 324 progression or death events—167 (76%) in the panitumumab-FOLFOX4 arm and 157 (72%) in the FOLFOX4 arm. PFS was inferior in patients receiving panitumumab-FOLFOX4 versus FOLFOX4 (HR = 1.29; 95% CI, 1.04 to 1.62; $P = .02$, stratified log-rank test; Fig 2B). Median PFS was 7.3 months (95% CI, 6.3 to 8.0 months) for panitumumab-FOLFOX4 and 8.8 months (95% CI, 7.7 to 9.4 months) for FOLFOX4.

OS. In the WT *KRAS* stratum, at the time of the analysis, 355 deaths had occurred—165 (51%) in the panitumumab-FOLFOX4 arm and 190 (57%) in the FOLFOX4 arm. Median OS was 23.9 months (95% CI, 20.3 to 28.3 months) for panitumumab-FOLFOX4 and 19.7 months (95% CI, 17.6 to 22.6 months) for FOLFOX4 arm, resulting in an absolute difference of 4.2 months. The HR was 0.83 (95% CI, 0.67 to 1.02; $P = .072$) favoring the panitumumab-FOLFOX4 arm (Fig 2C). From planned subgroup analyses for OS, the HR for all subsets was less than 1, with the exception of the small subsets with no liver metastases and ECOG PS ≥ 2 (Fig 3B).

Subsequent to study treatment, 8% of patients in the panitumumab-FOLFOX4 arm and 18% of patients in the FOLFOX4 arm received anti-EGFR mAb therapy. Median time to anti-EGFR therapy from random assignment was 18 months in the panitumumab-FOLFOX4 arm and 11 months in the FOLFOX4 arm. Subsequent chemotherapy (including oxaliplatin, irinotecan, and/or fluoropyrimidine) was received by 62% of patients in the FOLFOX4 arm and 53% of patients in the panitumumab-FOLFOX4 arm and included bevacizumab in 12% and 15% of patients, respectively.

In the MT *KRAS* stratum, 294 deaths occurred—152 (69%) in the panitumumab-FOLFOX4 arm and 142 (65%) in the FOLFOX4 arm. Median OS was 15.5 months (95% CI, 13.1 to 17.6 months) for panitumumab-FOLFOX4 and 19.3 months (95% CI, 16.5 to 21.8

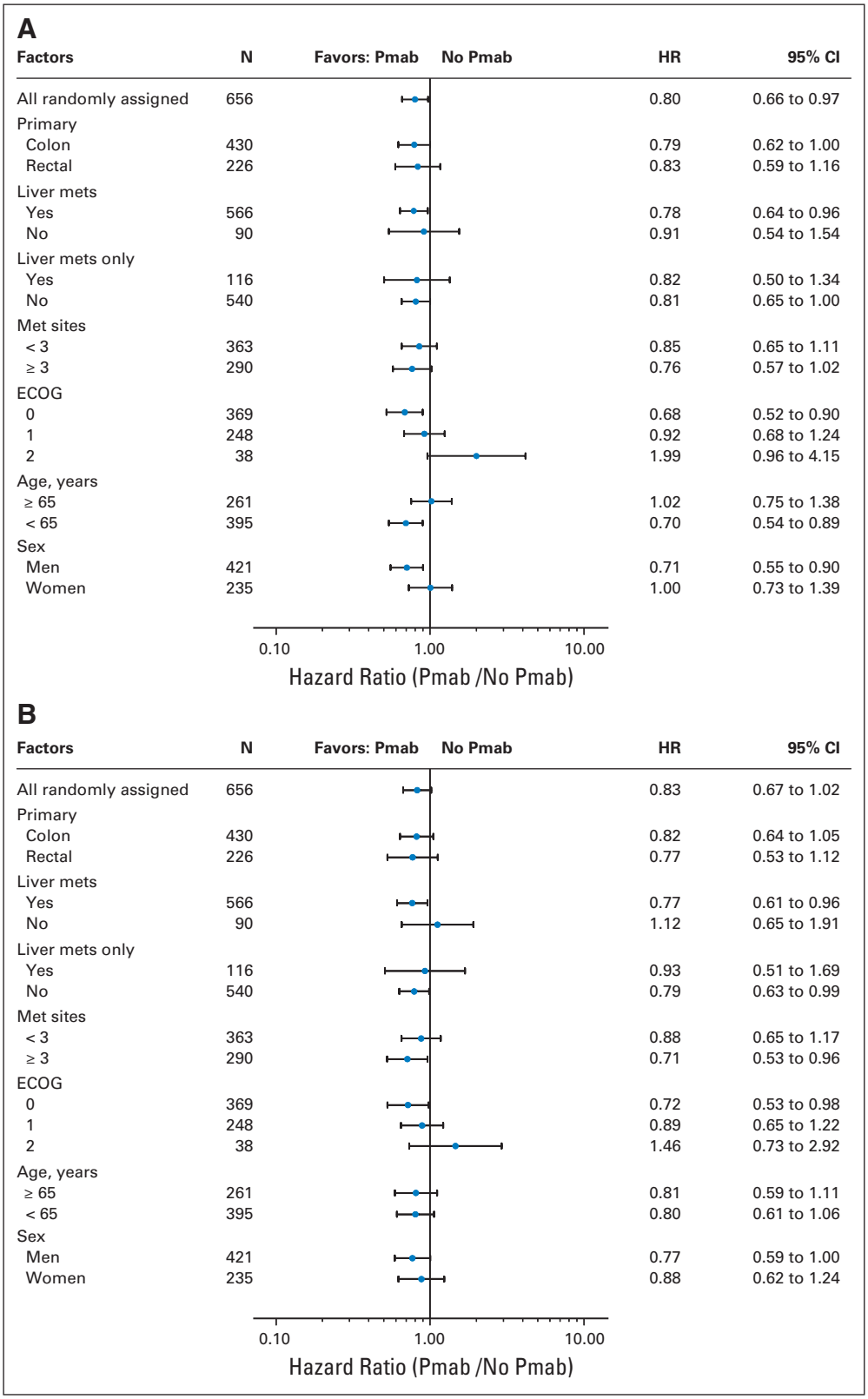

Fig 3. Wild-type (WT) *KRAS* by subgroup analyses. (A) Subset analyses of progression-free survival by WT *KRAS* (panitumumab [Pmab] -FOLFOX4 *v* FOLFOX4). (B) Subset analyses of overall survival by WT *KRAS* (Pmab-FOLFOX4 *v* FOLFOX4). HR, hazard ratio; met, metastasis; ECOG, Eastern Cooperative Oncology Group.

months) for FOLFOX4 (HR = 1.24; 95% CI, 0.98 to 1.57; $P = .068$, stratified log-rank test; Fig 2D).

Within the panitumumab-FOLFOX4 arm, the HR for OS for the WT stratum versus MT stratum was 0.57 (95% CI, 0.46 to 0.71; $P < .001$). In the FOLFOX4 arm, the HR for OS for the WT stratum versus MT stratum was 0.87 (95% CI, 0.70 to 1.08; $P = .21$).

Objective response. In the WT *KRAS* stratum, the RR was 55% for panitumumab-FOLFOX4 and 48% for FOLFOX4 (stratified odds

Table 2. Grade 3 and 4 Adverse Events of Interest

Adverse Event by MedDRA Term	WT *KRAS* (n = 649)				MT *KRAS* (n = 435)			
	Panitumumab-FOLFOX4 (n = 322)		FOLFOX4 (n = 327)		Panitumumab-FOLFOX4 (n = 217)		FOLFOX4 (n = 218)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Patients with any event	270	84	227	69	173	80	159	73
Neutropenia	136	42	134	41	81	37	103	47
Skin toxicity	116	36	7	2	66	30	3	1
Diarrhea	59	18	29	9	43	20	21	10
Neurologic toxicities	52	16	51	16	36	17	37	17
Hypokalemia	32	10	15	5	19	9	8	4
Fatigue	30	9	10	3	16	7	11	5
Mucositis*†	28	9	2	< 1	12	6	6	3
Hypomagnesemia	20	6	1	< 1	13	6	1	< 1
Paronychia†	11	3	0	0	4	2	0	0
Pulmonary embolism	9	3	5	2	7	3	8	4
Febrile neutropenia	8	2	7	2	7	3	7	3
Infusion-related reaction (panitumumab)†	2	< 1	—	—	0	0	—	—

NOTE. All events are included, regardless of relatedness to therapy.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; WT, wild type; MT, mutant; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin.
*Results are based on the following prespecified list of preferred terms: stomatitis, mucosal inflammation, aphthous stomatitis, mouth ulceration, mucosal dryness, and mucosal ulceration.
†No grade 4 events.

ratio, 1.35; $P = .068$). In the MT *KRAS* stratum, the RR was 40% in each arm.

Resection rate. Metastasectomy of any site was attempted in 10.5% of patients treated with panitumumab-FOLFOX4 and 9.4% of patients treated with FOLFOX4 with WT *KRAS* status; complete resections were achieved in 8.3% and 7.0% of patients, respectively.

Safety

Grade 3 and 4 AEs of interest are listed in Table 2. The incidence of skin toxicity was 96% for patients receiving panitumumab-FOLFOX4 and 31% for patients receiving FOLFOX4. In the WT *KRAS* stratum, the rates of AEs in the panitumumab-FOLFOX4 and FOLFOX4 arms were 82% and 63%, respectively, for worst grade 3 or 4 treatment-related AEs (considered by the investigator to be related to chemotherapy and/or panitumumab treatment) and 40% and 36%, respectively, for serious AEs. Fatal AEs were reported in 16 patients (5%) in the panitumumab-FOLFOX4 arm and in 20 patients (6%) in the FOLFOX4 arm and included cases where the primary cause of death was disease progression. In each arm, there were four fatal treatment-related AEs including two that were panitumumab related, pneumonitis (no infectious etiology identified) and pneumonia.

In the MT *KRAS* stratum, the AE rates in the panitumumab-FOLFOX4 and FOLFOX4 arms were 79% and 69%, respectively, for worst grade 3 or 4 treatment-related AEs and 47% and 29%, respectively, for serious AEs. Fatal AEs were reported in 17 patients (8%) in the panitumumab-FOLFOX4 arm and in seven patients (3%) in the FOLFOX4 arm; fatal events included cases where the primary cause of death was disease progression. There were three treatment-related fatal AEs, none of which were reported as related to panitumumab (one septic shock in each arm and one febrile neutropenia in the panitumumab-FOLFOX4 arm). Grade 3 panitumumab-related infusion reactions occurred in two patients (0.3%); both patients received additional panitumumab treatment after premedication.

Treatment Exposure

The median number of cycles of panitumumab and chemotherapy and the relative dose-intensity were similar between treatment arms in both the WT and MT *KRAS* strata (Table 3). The most common reason for chemotherapy discontinuation was disease progression, which occurred in 51% of patients with WT *KRAS* tumor status and 61% of patients with MT *KRAS* tumor status. Other reasons for discontinuation included patient request and AEs and were balanced between treatment arms and *KRAS* strata.

Antibody

Treatment-emergent binding antipanitumumab antibodies were detected in 14 (3.0%) of 470 patients who received panitumumab. Neutralizing antibodies were detected in postdose samples from two (0.4%) of 470 patients.

DISCUSSION

PRIME is the first study, to our knowledge, to evaluate the impact of the addition of panitumumab to FOLFOX4 for the initial treatment of patients with WT *KRAS* mCRC. Importantly, the results were prospectively analyzed by *KRAS* status, and the study achieved the primary objective by demonstrating a significant improvement in the probability of being alive without disease progression when panitumumab is added to chemotherapy for patients with WT *KRAS* tumors. The difference in median OS for patients with WT *KRAS* status, although not statistically significant, was also favorable, with a 4.2-month improvement in the panitumumab-FOLFOX4 arm compared with the FOLFOX4 arm. There was a statistically significant interaction between the treatment effect and *KRAS* tumor status for PFS (Appendix Table A1, online only). The goal of the primary OS analysis was to obtain median estimates, and only 51% of patients had an event

Table 3. Treatment Exposure

Treatment Measure	WT *KRAS*		MT *KRAS*	
	Panitumumab-FOLFOX4 (n = 322)	FOLFOX4 (n = 327)	Panitumumab-FOLFOX4 (n = 217)	FOLFOX4 (n = 218)
Median No. of cycles received				
Panitumumab	11	—	10	—
Oxaliplatin	11	11	11	11
FU (bolus)	12	12	12	12
FU (continuous infusion)	12	12	12	12
Median relative dose-intensity, %				
Panitumumab	81	—	83	—
Oxaliplatin	77	79	80	80
FU (bolus)	77	81	80	81
FU (continuous infusion)	78	81	81	81
Median cumulative total dose				
Panitumumab, mg/kg	62	—	57	—
Oxaliplatin, mg/m^2	859	865	824	856
FU (bolus), mg/m^2	8,627	8,618	8,294	8,711
FU (continuous infusion), mg/m^2	13,483	13,229	12,878	13,109

Abbreviations: WT, wild type; MT, mutant; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin; FU, fluorouracil.

in the panitumumab-treated WT *KRAS* population at the time of this analysis. Responses were more frequent in the panitumumab-FOLFOX4 arm versus the FOLFOX4 arm (Appendix Table A2, online only); however, resection rates were similar.

A total of 87 patients were excluded from analysis who were unevaluable for *KRAS*, which may have introduced ascertainment bias; however, various prospective and post hoc intent-to-diagnosis sensitivity analyses provided results consistent with the primary analysis for each *KRAS* stratum. Details are included in Appendix Table A3, online only.

All planned subsets consistently demonstrated favorable effects of panitumumab on PFS, with the exception of patients $\geq$ 65 years old, women, and the small subset of patients with ECOG PS of 2 (Fig 3A). Importantly, however, a favorable OS effect was observed in women and older patients receiving panitumumab (Fig 3B). In addition, absolute differences in RR were similar between men and women (data not shown).

Safety was as expected when an anti-EGFR mAb is added to chemotherapy and included increased skin toxicity in panitumumab-treated patients. There is evidence that skin toxicity associated with EGFR inhibition can be effectively managed.[21] As reported in other studies,[3,5,8] an association between skin toxicity and efficacy was observed in PRIME (data not shown). Additional analyses are underway to determine the importance of skin toxicity as a predictive factor after adjusting for other prognostic characteristics. Although diarrhea and hypomagnesemia were increased, these toxicities were clinically manageable based on the infrequency with which they lead to treatment discontinuation (Amgen, data on file). Infusion reactions were rare. Two patients (0.3%) experienced a grade 3 panitumumab-related infusion reaction; both received additional panitumumab treatment.

The positive results in the WT *KRAS* population in PRIME are consistent with the findings of a recently reported trial in which panitumumab was added to fluorouracil, leucovorin, and irinotecan chemotherapy in previously treated patients with mCRC.[22] The effect observed in PRIME is also generally consistent with that seen in two other first-line mCRC studies with cetuximab and chemotherapy, although *KRAS* status was analyzed retrospectively in those studies.[8,9] The 4.2-month benefit in median OS observed in PRIME, although not statistically significant, is comparable to the median OS improvement of 3.5 months reported for the WT *KRAS* population in the phase III CRYSTAL (Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) study with cetuximab and fluorouracil, leucovorin, and irinotecan based on an updated retrospective efficacy analysis.[23] In contrast, there was no improvement in either OS or PFS when cetuximab was added to oxaliplatin-based chemotherapy in the recently reported Medical Research Council COIN (Continuous Chemotherapy Versus Intermittent Chemotherapy) trial, which, similar to PRIME, was prospectively analyzed according to tumor *KRAS* status.[24] Efficacy results in the WT *KRAS* population in PRIME also compared favorably with those reported for the subset of all patients who received FOLFOX4 chemotherapy when bevacizumab was added to treatment.[25]

Although data from the PRIME trial demonstrate that *KRAS* is not a prognostic biomarker in this treatment setting (the outcomes of patients with MT *KRAS* receiving FOLFOX4 were generally similar to those of patients with WT *KRAS* with respect to RR, PFS, and OS), this trial does confirm the importance of *KRAS* as a predictive biomarker of efficacy for anti-EGFR mAb therapy. As opposed to the positive effects seen in the WT *KRAS* strata, in the MT *KRAS* strata, the addition of panitumumab resulted in a significant detrimental effect on PFS. A similar detrimental effect was also observed in patients with MT *KRAS* tumors when cetuximab was used in combination with oxaliplatin.[9] There were no appreciable differences in chemotherapy exposure or AEs to explain this finding, and the mechanism is still unknown. These results emphasize the importance of incorporating early *KRAS* testing into treatment algorithms for patients with mCRC.

Consistent with findings from studies of panitumumab in patients with previously treated mCRC,[3,22] panitumumab, when added to FOLFOX4, significantly improved PFS for patients with previously untreated WT *KRAS* mCRC. Other clinically meaningful attributes of panitumumab include that severe panitumumab-related infusion reactions are rare and a standard 2-week dosing regimen allows for synchronization with chemotherapy dosing and minimizes the number of required clinic visits. In conclusion, panitumumab is well tolerated and effective when added to FOLFOX4. This combination

represents a relevant and new therapeutic option for the treatment of patients with WT *KRAS* mCRC. Efforts are underway to identify additional predictive biomarkers for anti-EGFR therapy within the WT *KRAS* population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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