Original Study

Survival Outcomes in Patients With *RAS* Wild Type Metastatic Colorectal Cancer Classified According to Köhne Prognostic Category and *BRAF* Mutation Status

Salvatore Siena,[1] Fernando Rivera,[2] Julien Taieb,[3] Marc Peeters,[4] Hans Prenen,[5] Reija Koukakis,[6] Gaston Demonty,[7] Claus-Henning Köhne[8]

Abstract

There is a need to identify patients who may benefit from particular treatments. We investigated prognosis in 915 patients with mCRC from 2 phase III trials of panitumumab plus chemotherapy, based on Köhne category and *BRAF* status. Both Köhne category and *BRAF* status predicted outcomes in terms of PFS and OS, and panitumumab provided benefits over chemotherapy alone.

Background: Köhne prognostic score is used to classify patients with metastatic colorectal cancer (mCRC) as high, intermediate, or low risk. Using data from 2 phase III trials, we analyzed survival in patients categorized according to Köhne prognostic category and virus-induced rapidly accelerated fibrosarcoma murine sarcoma viral oncogene homolog B (*BRAF*) mutation. **Patients and Methods:** PRIME (Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy) (first-line) and 20050181 (second-line) were studies of chemotherapy with or without panitumumab. Progression-free survival (PFS) and overall survival (OS) were analyzed retrospectively in rat sarcoma viral oncogene homolog (*RAS*) wild type (WT) and *RAS* WT+*BRAF* WT mCRC in each Köhne category, and in *BRAF* mutant (MT) mCRC. **Results:** In PRIME (n = 495) and 20050181 (n = 420), 53 (11%) and 44 (10%) patients, respectively, had *BRAF* MT mCRC. Of the *RAS* WT+*BRAF* WT/unknown populations, 85/267/90 and 82/211/83 were categorized as high/medium/low risk, respectively. PFS and OS hazard ratios (HRs), adjusted for Köhne group, for patients with *RAS* WT + *BRAF* WT/unknown mCRC favored panitumumab with chemotherapy versus chemotherapy alone in both studies. In PRIME, the PFS HR was 0.74 (95% confidence interval [CI], 0.61-0.90) and OS HR was 0.78 (95% CI, 0.64-0.95). In 20050181, PFS and OS HRs were 0.80 (95% CI, 0.65-0.99) and 0.78 (95% CI, 0.62-0.99), respectively. Median PFS and OS were lower in patients with *BRAF* MT mCRC than in any of the 3 risk categories for patients with *RAS* WT+*BRAF* WT/unknown mCRC. **Conclusion:** During first- and second-line treatment, Köhne prognostic score allows accurate risk classification in *RAS* WT mCRC. *BRAF* MT mCRC should be classified as high risk regardless of other parameters. Panitumumab with chemotherapy might provide survival benefits versus chemotherapy alone in *RAS* WT and *RAS* WT+*BRAF* WT/unknown mCRC, overall and across risk categories.

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[1]Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, and Dipartimento di Oncologia e Emato-Oncologia, Università degli Studi di Milano, Milan, Italy
[2]Hospital Universitario Marqués de Valdecilla, Santander, Spain
[3]Sorbonne Paris Cité, Paris Descartes University, Georges Pompidou European Hospital, Paris, France
[4]University Hospital Antwerp, Antwerp, Belgium
[5]Digestive Oncology Unit, UZ Leuven, Leuven, Belgium
[6]Biostatistics, Amgen Ltd, Uxbridge, United Kingdom
[7]Medical Development, Amgen (Europe) GmbH, Zug, Switzerland
[8]Klinikum Oldenburg, Oldenburg, Germany

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Address for correspondence: Salvatore Siena, MD, Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Università degli Studi di Milano, Piazza Ospedale Maggiore 3, Milan, I 21062, Italy
Fax: +39 02 6444 2957; e-mail contact: salvatore.siena@ospedaleniguarda.it

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Introduction

Survival outcomes in patients with metastatic colorectal cancer (mCRC) differ widely depending on their disease characteristics at the start of treatment. Furthermore, the choice of first- and second-line treatment is generally made on the basis of patient and disease characteristics, treatment goal (eg, resection or disease control), and rat sarcoma viral oncogene homolog (*RAS*) status.[1] Thus there is a need to define patient subgroups who will derive the most benefit from specific treatments. An analysis of data from 3825 patients with mCRC showed that they can be divided into 3 prognostic categories (high, medium, and low risk) on the basis of 4 baseline clinical parameters[2]: Eastern Cooperative Oncology Group (ECOG) performance status, white blood cell count, alkaline phosphatase levels, and number of metastatic sites. The importance of these parameters has been confirmed in studies of regimens including oxaliplatin and irinotecan combinations.[3,4] More recently, mutations in the virus-induced rapidly accelerated fibrosarcoma murine sarcoma viral oncogene homolog B (*BRAF*) gene have also been identified as a negative prognostic marker in mCRC.[5-9]

Epidermal growth factor receptor (EGFR) inhibitors are an important treatment option for patients with mCRC.[1,10] These agents are licensed only for patients whose tumors have wild type (WT) *RAS* genes (*KRAS* and *NRAS*), because *RAS* mutations result in a lack of response to EGFR inhibitors.[11-15] Several phase III trials have shown the efficacy and tolerability of the EGFR inhibitor panitumumab in patients with *RAS* WT mCRC.[16] For example, results from the first-line PRIME (Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy) study showed that panitumumab significantly improved overall survival (OS) when combined with leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone.[8] In the second-line 20050181 study, panitumumab with leucovorin, 5-fluorouracil, and irinotecan (FOLFIRI) significantly improved progression-free survival (PFS) versus FOLFIRI alone in patients with *RAS* WT mCRC.[17] Using data from the PRIME and 20050181 studies, we retrospectively analyzed survival outcomes in patients with mCRC categorized according to Köhne prognostic category and *BRAF* mutation status.

Patients and Methods

Study Design

The PRIME (ClinicalTrials.gov: NCT00364013) and 20050181 (NCT00339183) were international, open-label phase III studies in which patients were randomized (1:1) to receive FOLFOX4 (PRIME) or FOLFIRI (20050181) with or without panitumumab. Full details of these studies have been published previously.[18,19]

In brief, eligible patients were adults with metastatic adenocarcinoma of the colon or rectum, and an ECOG performance status of 0 to 2. In PRIME, patients were previously untreated, whereas those in 20050181 had previously progressed while receiving, or within 6 months of, 1 previous fluoropyrimidine-based mCRC therapy. In both studies, panitumumab was administered as an intravenous infusion of 6.0 mg/kg on the first day of each 14-day cycle.

The present analysis focused on patients with *RAS* WT mCRC (ie, tumors WT for *KRAS*/*NRAS* exon 2 [codons 12 and 13], exon 3 [codons 59 and 61], and exon 4 [codons 117 and 146]).[8,17] In both

Table 1 Progression-Free Survival and OS in Patients With *RAS* Wild Type mCRC Categorized According to Köhne Prognostic Category in the PRIME and 20050181 Studies

Risk Category	Kaplan–Meier Median PFS, Months (95% CI)		Kaplan–Meier Median OS, Months (95% CI)	
PRIME Study	**Panitumumab and FOLFOX4**	**FOLFOX4**	**Panitumumab and FOLFOX4**	**FOLFOX4**
High	n = 46 6.3 (4.8-12.1)	n = 51 7.6 (4.4-11.4)	n = 46 13.9 (7.4-21.2)	n = 51 15.1 (10.6-17.6)
	HR, 0.89; 95% CI, 0.59-1.35		HR, 0.91; 95% CI, 0.60-1.39	
Medium	n = 146 12.5 (9.7-14.9)	n = 151 8.6 (7.3-9.9)	n = 146 29.8 (23.9-32.8)	n = 151 21.7 (17.4-25.3)
	HR, 0.66; 95% CI, 0.52-0.85		HR, 0.70; 95% CI, 0.55-0.91	
Low	n = 54 10.8 (9.3-17.1)	n = 46 9.5 (7.0-11.1)	n = 54 35.6 (22.5-45.0)	n = 46 26.9 (19.1-40.4)
	HR, 0.79; 95% CI, 0.51-1.20		HR, 0.76; 95% CI, 0.48-1.21	
20050181 Study	**Panitumumab and FOLFIRI**	**FOLFIRI**	**Panitumumab and FOLFIRI**	**FOLFIRI**
High	n = 42 6.1 (4.1-9.3)	n = 50 3.6 (2.5-5.3)	n = 42 11.2 (7.9-16.1)	n = 50 9.2 (5.7-12.8)
	HR, 0.68; 95% CI, 0.44-1.07		HR, 0.76; 95% CI, 0.48-1.21	
Medium	n = 125 6.9 (5.5-8.3)	n = 110 5.5 (3.9-6.8)	n = 125 16.6 (14.3-20.1)	n = 110 13.6 (10.8-19.6)
	HR, 0.91; 95% CI, 0.69-1.21		HR, 0.89; 95% CI, 0.64-1.23	
Low	n = 40 7.5 (5.9-11.2)	n = 52 5.7 (3.7-7.3)	n = 40 23.8 (16.2-28.1)	n = 52 16.6 (14.8-23.7)
	HR, 0.51; 95% CI, 0.31-0.85		HR, 0.63; 95% CI, 0.35-1.12	

Abbreviations: FOLFIRI = leukovorin, 5-fluorouracil, and irinotecan; FOLFOX4 = leukovorin, 5-fluorouracil, and oxaliplatin; HR = hazard ratio; mCRC = metastatic colorectal cancer; OS = overall survival; PFS = progression-free survival; PRIME = Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy.

Table 2 Progression-Free Survival and OS in *BRAF* Wild Type/Unknown mCRC Categorized According to Köhne Prognostic Category, and *BRAF* Mutant mCRC in the PRIME and 20050181 Studies

Risk Category	Kaplan–Meier Median PFS, Months (95% CI)		Kaplan–Meier Median OS, Months (95% CI)	
PRIME Study	**Panitumumab and FOLFOX4**	**FOLFOX4**	**Panitumumab and FOLFOX4**	**FOLFOX4**
***BRAF* Wild Type/Unknown**				
High	n = 38 8.3 (5.8-13.8)	n = 47 7.8 (5.3-11.4)	n = 38 16.7 (10.5-21.9)	n = 47 15.1 (10.6-20.2)
	HR, 0.79; 95% CI, 0.50-1.24		HR, 0.83; 95% CI, 0.53-1.30	
Medium	n = 136 12.6 (9.7-15.4)	n = 131 9.3 (7.7-11.0)	n = 136 30.4 (25.4-36.1)	n = 131 23.6 (18.4-27.7)
	HR, 0.70; 95% CI, 0.54-0.90		HR, 0.71; 95% CI, 0.54-0.93	
Low	n = 49 10.9 (9.4-17.7)	n = 41 9.9 (7.2-12.9)	n = 49 40.0 (22.5-47.4)	n = 41 35.2 (23.1-46.8)
	HR, 0.81; 95% CI, 0.52-1.28		HR, 0.79; 95% CI, 0.48-1.29	
***BRAF* Mutant**				
Overall	n = 24 6.0 (3.5-10.7)	n = 29 5.4 (3.3-6.2)	n = 24 10.4 (5.6-18.9)	n = 29 9.2 (7.5-15.7)
	HR, 0.74; 95% CI, 0.42-1.29		HR, 0.97; 95% CI, 0.55-1.69	
20050181 Study	**Panitumumab and FOLFIRI**	**FOLFIRI**	**Panitumumab and FOLFIRI**	**FOLFIRI**
***BRAF* Wild Type**				
High	n = 38 7.4 (5.2-9.4)	n = 44 3.7 (2.8-5.6)	n = 38 13.3 (8.1-19.0)	n = 44 11.1 (5.7-14.5)
	HR, 0.68; 95% CI, 0.42-1.09		HR, 0.78; 95% CI, 0.47-1.28	
Medium	n = 111 7.4 (6.1-8.7)	n = 100 5.6 (3.9-6.9)	n = 111 18.7 (15.2-21.5)	n = 100 15.9 (12.1-22.9)
	HR, 0.87; 95% CI, 0.65-1.18		HR, 0.89; 95% CI, 0.63-1.26	
Low	n = 37 7.5 (5.9-11.2)	n = 46 5.9 (4.6-7.5)	n = 37 23.8 (16.5-28.1)	n = 46 18.4 (15.1-23.8)
	HR, 0.53; 95% CI, 0.31-0.90		HR, 0.67; 95% CI, 0.36-1.23	
***BRAF* Mutant**				
Overall	n = 21 2.6 (1.7-3.7)	n = 23 1.9 (1.8-3.7)	n = 21 4.8 (2.8-9.8)	n = 23 5.7 (3.2-7.3)
	HR, 1.04; 95% CI, 0.56-1.94		HR, 0.74; 95% CI, 0.39-1.39	

Abbreviations: FOLFIRI = leukovorin, 5-fluorouracil, and irinotecan; FOLFOX4 = leukovorin, 5-fluorouracil, and oxaliplatin; HR = hazard ratio; mCRC = metastatic colorectal cancer; OS = overall survival; PFS = progression-free survival; PRIME = Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy.

studies, *KRAS* exon 2 testing was performed in a blinded central laboratory using allele-specific polymerase chain reaction (DxS Ltd, Manchester, United Kingdom).[18,19] *RAS* mutations beyond *KRAS* exon 2 were detected using bidirectional Sanger sequencing (both studies) and using WAVE-based Surveyor Scan Kits (Transgenomic Inc, Omaha, NB; PRIME only) in WT *KRAS* exon 2 tumor specimens.[8,17] Patients were characterized as having *RAS* mutations if any predefined activating mutation in *KRAS* or *NRAS* was detected.

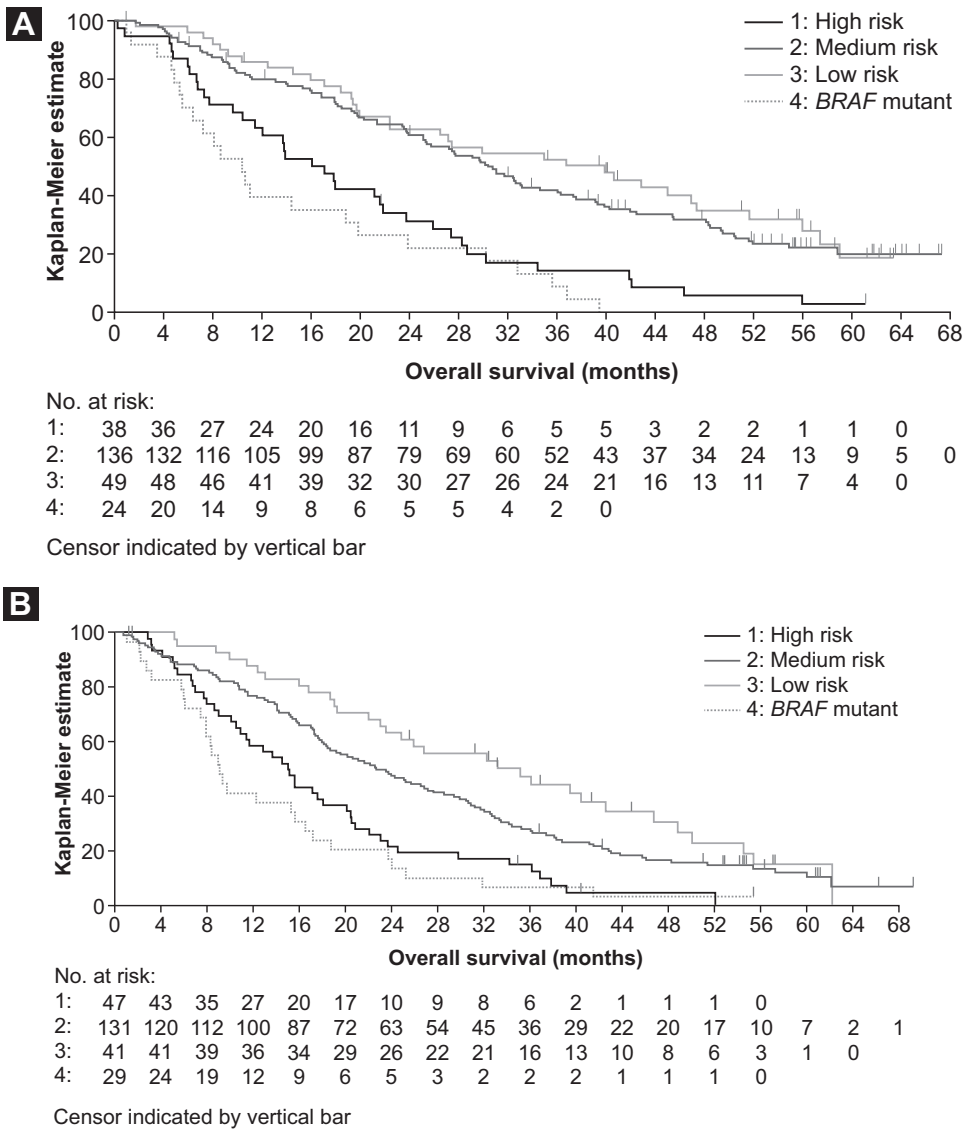
Patients were also categorized on the basis of *BRAF* mutation status (exon 15 [V600E]), assessed using bidirectional Sanger sequencing in WT *KRAS* exon 2 tumor specimens (both studies) and using WAVE-based SURVEYOR Scan Kits (Transgenomic Inc; PRIME only).[8,17]

Survival Analysis

Progression-free survival and OS were analyzed retrospectively for the overall *RAS* WT population for each Köhne prognostic category, established on the basis of data from before the previous first-line therapy was started. In a second analysis, patients with *BRAF* mutant (MT) mCRC were analyzed separately, with the remaining patients then analyzed according to Köhne prognostic category (see Supplemental Figure 1 in the online version). For the purposes of this analysis, patients from PRIME with unknown *BRAF* status were grouped together with patients who had *BRAF* WT tumors, although a separate analysis was conducted in which patients with unknown *BRAF* status were excluded.

For PRIME, the analysis was conducted when 80% of patients enrolled in the study had died. For 20050181, the primary analysis data cutoff (380 PFS events) was used. Survival was analyzed using the Kaplan–Meier method and presented as median (95% confidence interval [CI]) values. Hazard ratios (HRs) for PFS and OS in the panitumumab with FOLFOX4 arm versus the FOLFOX4-alone arm, and the panitumumab with FOLFIRI arm versus the FOLFIRI-alone arm, were calculated using a Cox proportional hazards model. All of the analyses were exploratory and descriptive in nature.

Figure 1 Kaplan–Meier Curves for Overall Survival in Patients in the PRIME (Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy) Study With *BRAF* Wild Type/Unknown Metastatic Colorectal Cancer (mCRC) Categorized According to Köhne Prognostic Group, and for Patients With *BRAF* Mutant mCRC Overall, in the (A) Panitumumab With FOLFOX4, and (B) FOLFOX4-Alone Arms



Abbreviation: FOLFOX4 = leukovorin, 5-fluorouracil, and oxaliplatin.

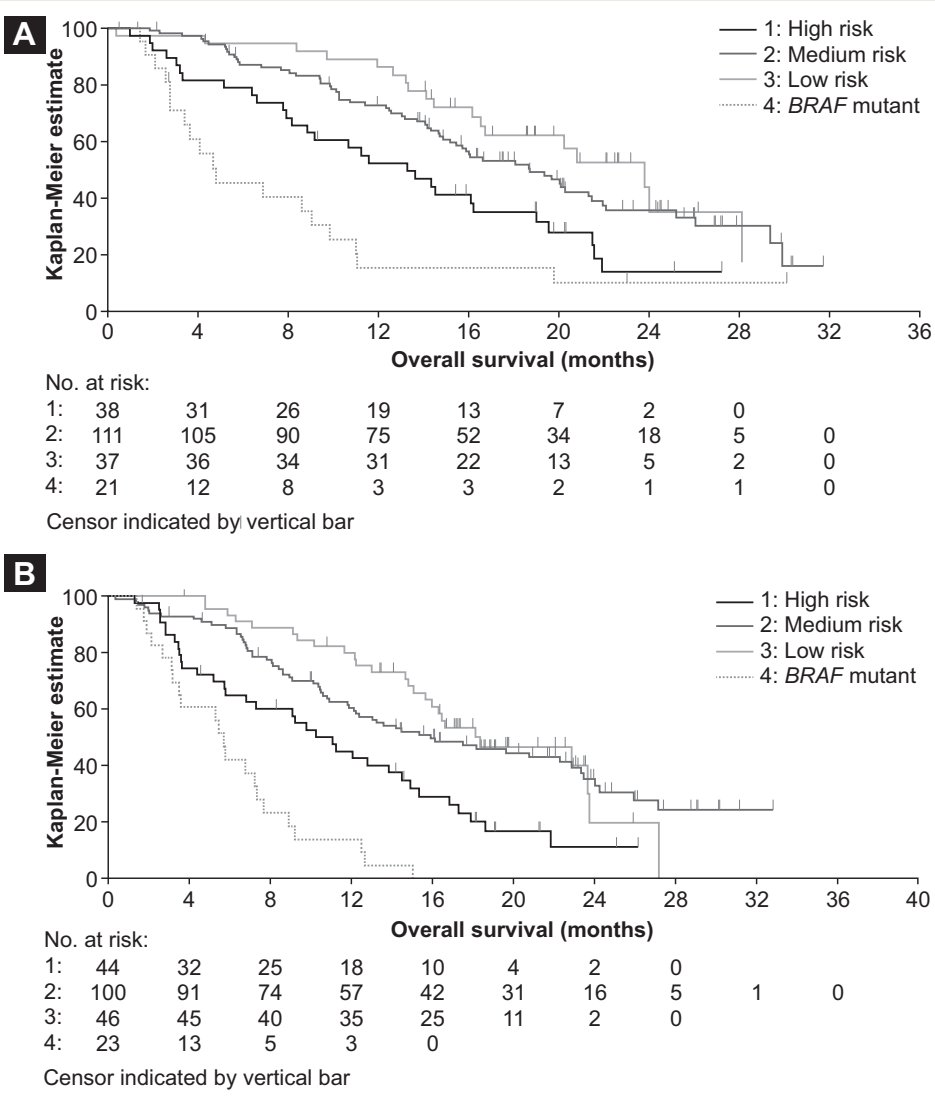
Results

Patients

Of 1183 patients enrolled in PRIME, 505 (43%) had *RAS* WT mCRC, of whom 494 (98%) had sufficient data for a Köhne prognostic category to be established, with 97, 297, and 100 patients categorized as high, medium, and low risk, respectively. Of 1186 patients enrolled in the 20050181 study, 421 had *RAS* WT mCRC, of whom 419 (>99%) had sufficient data for a Köhne prognostic category to be established, with 92 high-risk, 235 medium-risk, and 92 low-risk patients.

Of the 505 patients in PRIME with *RAS* WT mCRC, tumors from 53 patients (11%) were categorized as *BRAF* MT (see Supplemental Figure 2 in the online version). *BRAF* status was unknown in 13 patients (3%); these were grouped alongside patients with *BRAF* WT status for the purposes of the analysis. The remaining *RAS* WT+*BRAF* WT/unknown analysis included 85, 267, and 90 patients categorized as high, medium, and low risk, respectively. In the 20050181 study, *BRAF* status was known for all patients, and tumors from 44 (10%) of the 421 patients with *RAS* WT mCRC were categorized as *BRAF* MT, including 1 patient who

Figure 2 Kaplan–Meier Curves for Overall Survival in Patients in the 20050181 Study With *BRAF* Wild Type Metastatic Colorectal Cancer (mCRC) Categorized According to Köhne Prognostic Group, and for Patients With *BRAF* Mutant mCRC Overall, in the (A) Panitumumab With FOLFIRI, and (B) FOLFIRI-Alone Arms



Abbreviation: FOLFIRI = leukovorin, 5-fluorouracil, and oxaliplatin.

was excluded from the overall *RAS* WT analysis because a Köhne prognostic category could not be established. Of the remaining *RAS* WT/*BRAF* WT patients, 82, 211, and 83 were categorized as high, medium, and low risk, respectively. In each of the 2 studies, baseline demographic and disease characteristics were similar between the treatment arms (see Supplemental Table 1 in the online version).

Overall RAS *WT Analysis*

For PRIME, data were fully mature for OS analysis (median follow-up, 80 weeks), with 80 (94%), 212 (81%), and 65 (75%) patients in the high, medium, and low risk categories, respectively, having died at the time of analysis. At the time of analysis in the 20050181 study (median follow-up, 48 weeks), the number of deaths was 73 (79%), 147 (63%), and 51 (55%), respectively.

In the *RAS* WT population, the PFS and OS HRs adjusted for Köhne prognostic group favored panitumumab with chemotherapy versus chemotherapy alone in both studies (Table 1). In PRIME, the PFS HR was 0.74 (95% CI, 0.62-0.90) and the OS HR was 0.76 (95% CI, 0.63-0.93). In the 20050181 study, the PFS and OS HRs were 0.78 (95% CI, 0.63-0.96) and 0.82 (95% CI, 0.64-1.04), respectively.

Outcome in Patients With RAS *WT*+BRAF *WT/Unknown mCRC*

As in the *RAS* WT population, the PFS and OS HRs adjusted for Köhne prognostic group for patients with *RAS* WT+*BRAF* WT/unknown mCRC favored panitumumab with chemotherapy versus chemotherapy alone in both studies (Table 2; Figures 1 and 2; see Supplemental Figures 3-6 in the online version). In PRIME, the

PFS HR was 0.74 (95% CI, 0.62-0.90) and the OS HR was 0.78 (95% CI, 0.64-0.95), whereas in the 20050181 study the PFS and OS HRs were 0.80 (95% CI, 0.65-0.99) and 0.78 (95% CI, 0.61-0.99), respectively. Median PFS and OS were numerically lower in patients with *BRAF* MT mCRC than in any of the 3 risk categories for patients with *RAS* WT+*BRAF* WT/unknown mCRC (Table 2). Results were similar when the 13 patients with unknown *BRAF* status were excluded from the PRIME analysis (see Supplemental Table 2 in the online version).

Discussion

The results of our analysis of PRIME study data confirm that, in patients with previously untreated mCRC, the prognostic scoring system developed by Köhne and colleagues[2] allows accurate risk classification in *RAS* WT and *RAS* WT +*BRAF* WT/unknown mCRC. On the basis of data from the 20050181 study, we have shown for the first time that the Köhne score also allows risk classification in patients with *RAS* WT mCRC undergoing second-line treatment. In both studies, Köhne categorization was particularly successful for prediction of OS.

As previously reported,[5-9] the presence of *BRAF* mutations was a strong negative prognostic marker for outcome in both studies, and such patients should be classified as high risk regardless of other clinical parameters. Notably, the prevalence of *BRAF* mutations varies between studies. In the triplet plus bevacizumab (TRIBE) study, for example, 6% of patients had *BRAF* mutations,[20] compared with 11% and 12%, respectively, in the present analyses of the PRIME and 20050181 studies. In contrast, 21% of tumors in a Scandinavian registry had *BRAF* mutations.[21] It should also be noted that only 1 specific *BRAF* mutation (V600E) was evaluated in our study, and it is possible that other *BRAF* mutations would have different effects on outcomes.[22,23]

The overall efficacy results of the PRIME and 20050181 studies showed that PFS was improved by the additional use of panitumumab with chemotherapy.[8,17] OS was also improved by the additional use of panitumumab with FOLFOX4 in the PRIME study.[12] In the 20050181 study, OS was numerically longer with panitumumab with FOLFIRI than with FOLFIRI alone.[24] Consistent with this, the HRs in these retrospective, exploratory analyses suggest that panitumumab with chemotherapy might provide PFS and OS benefits versus chemotherapy alone in patients with *RAS* WT and *RAS* WT+*BRAF* WT/unknown mCRC, overall and across Köhne risk categories. Furthermore, a pilot study of first-line panitumumab monotherapy has shown the activity and tolerability of treatment in frail elderly patients with gastrointestinal cancer classified as Köhne intermediate or high risk.[25]

The treatment guidelines issued by the European Society of Medical Oncology in 2016 recommend that the aim of treatment should be considered in management decisions for patients with mCRC.[1] The guidelines broadly define 2 patient categories: those with potentially resectable disease or who need a rapid reduction in tumor symptoms, for whom cytoreduction is the primary aim of treatment, and those for whom the aim is disease control and aggressive treatment is not necessary. The results of our analysis suggest that panitumumab improves outcomes for both of these patient subgroups: aggressive Köhne high-risk mCRC and nonaggressive Köhne low-risk mCRC.

One of the strengths of the present work is that it is on the basis of data from phase III, randomized, controlled trials, although these were retrospective, post hoc analyses, and thus only descriptive data are reported. The present work was also limited by the small patient numbers in some subgroups. Further analysis using other prognostic scores, such as the Groupe Coopérateur Multidisciplinaire en Oncologie model[26] or the neutrophil/lymphocyte ratio,[27] might be of interest. More recently, side of disease of the primary tumor (left vs. right colon) has emerged as a predictive and prognostic variable,[28-31] which might be driven by *BRAF* and other unfavorable mutations. Indeed, the percentage of patients with right-sided disease in the present analysis was higher in the *BRAF* MT group than in any of the 3 Köhne prognostic groups, which each had a similar percentage of patients with right-sided disease. As a result of the small number of patients with right-sided disease in the present study, however, we did not conduct any further analysis of the prognostic effect of primary tumor location. In the era of molecular subtyping—for example using mutational profile,[32] gene expression,[33] or protein levels—it will be interesting to correlate clinical subgroups to the underlying molecular alterations. Finally, it has been suggested that the prognostic ability of the Köhne model could be improved by incorporating baseline serum lactate dehydrogenase levels and quality of life measures of pain and mobility.[34]

Conclusion

In patients with untreated mCRC, Köhne prognostic score allows accurate risk classification in *RAS* WT and *RAS* WT+*BRAF* WT/unknown mCRC, particularly with regard to OS. Thus, Köhne score can be used as a stratification factor in future clinical trials even when targeted agents are used. Although the Köhne prognostic score was developed for use in the first-line mCRC setting, we show for the first time that it also allows risk classification in patients with *RAS* WT and *RAS* WT/*BRAF* WT mCRC undergoing second-line treatment. *BRAF* mutations are also strongly negatively prognostic for outcome, and patients with *BRAF* MT mCRC should be classified as high risk regardless of other clinical parameters. The HRs in this retrospective, exploratory analysis suggest that panitumumab with chemotherapy might provide PFS and OS benefits versus chemotherapy alone in patients with *RAS* WT and *RAS* WT+*BRAF* WT/unknown mCRC, overall and across risk categories. Further research is necessary to investigate the relationship between Köhne prognostic category and other known risk factors, such as primary tumor location.

Clinical Practice Points

- Survival outcomes in patients with metastatic colorectal cancer (mCRC) differ widely depending on their disease characteristics at the start of treatment.
- Choice of treatment is generally made on the basis of patient and disease characteristics, treatment goal (e.g., resection or disease control), and *RAS* status.
- Patients with mCRC can be divided into 3 Köhne prognostic categories (high, medium and low risk) based on 4 baseline clinical parameters.
- Mutations in the *BRAF* gene have been identified as a negative prognostic marker in mCRC.
- Several phase III trials have demonstrated the efficacy and tolerability of the EGFR inhibitor panitumumab in patients with *RAS* WT mCRC.

- In patients with previously untreated mCRC, Köhne prognostic scoring allows accurate risk classification in *RAS* WT and *RAS* WT+*BRAF* WT/unknown mCRC.
- The Köhne score also allows risk classification in patients with *RAS* WT mCRC undergoing second-line treatment.
- Köhne categorisation was particularly successful for prediction of OS.
- The presence of *BRAF* mutations was a strong negative prognostic marker for outcome in both studies.
- Köhne score can be used as a stratification factor in future clinical trials even when targeted agents are used.
- Patients with *BRAF* MT mCRC should be classified as high risk regardless of other clinical parameters.
- Panitumumab with chemotherapy may provide PFS and OS benefits versus chemotherapy alone in patients with *RAS* WT and *RAS* WT+*BRAF* WT/unknown mCRC, overall and across risk categories.

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Disclosure

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Supplemental Data

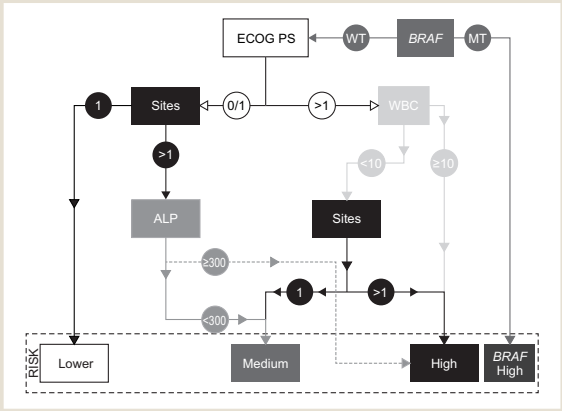
Supplemental figures and tables accompanying this article can be found in the online version https://doi.org/10.1016/j.clcc.2017.09.006.

References

1. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016; 27: 1386-422.
2. Köhne CH, Cunningham D, Di CF, et al. Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. *Ann Oncol* 2002; 13:308-17.
3. Van Belle S, Swieboda-Sadlej A, Karanikiotis C, et al. A final analysis from the CHOICE study examining darbepoetin alfa use for chemotherapy-induced anaemia in current European clinical practice. *Curr Med Res Opin* 2012; 28: 1079-87.
4. Vansteenkiste J, Hedenus M, Gascon P, et al. Darbepoetin alfa for treating chemotherapy-induced anemia in patients with a baseline hemoglobin level < 10 g/dL versus > or = 10 g/dL: an exploratory analysis from a randomized, double-blind, active-controlled trial. *BMC Cancer* 2009; 9:311.
5. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. *J Clin Oncol* 2008; 26:5705-12.
6. Phipps AI, Buchanan DD, Makar KW, et al. BRAF mutation status and survival after colorectal cancer diagnosis according to patient and tumor characteristics. *Cancer Epidemiol Biomarkers Prev* 2012; 21:1792-8.
7. Morris V, Overman MJ, Jiang ZQ, et al. Progression-free survival remains poor over sequential lines of systemic therapy in patients with BRAF-mutated colorectal cancer. *Clin Colorectal Cancer* 2014; 13:164-71.
8. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med* 2013; 369:1023-34.
9. Taieb J, Zaanan A, Le MK, et al. Prognostic effect of BRAF and KRAS mutations in patients with stage III colon cancer treated with leucovorin, fluorouracil, and oxaliplatin with or without cetuximab: a post hoc analysis of the PETACC-8 trial. *JAMA Oncol* 2016; 2:643-53.
10. Sartore-Bianchi A, Loupakis F, Argiles G, Prager GW. Challenging chemoresistant metastatic colorectal cancer: therapeutic strategies from the clinic and from the laboratory. *Ann Oncol* 2016; 27:1456-66.
11. Lièvre A, Artru P, Guiu M, et al. The KRAS mutation detection within the initial management of patients with metastatic colorectal cancer: a status report in France in 2011. *Eur J Cancer* 2013; 49:2126-33.
12. Douillard JY, Rong A, Sidhu R. RAS mutations in colorectal cancer. *N Engl J Med* 2013; 369:2159-60.
13. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; 15:1065-75.
14. Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. *J Clin Oncol* 2014; 32:2240-7.
15. Bardelli A, Siena S. Molecular mechanisms of resistance to cetuximab and panitumumab in colorectal cancer. *J Clin Oncol* 2010; 28:1254-61.
16. Peeters M, Karthaus M, Rivera F, Terwey JH, Douillard JY. Panitumumab in metastatic colorectal cancer: the importance of tumour *RAS* status. *Drugs* 2015; 75:731-48.
17. Peeters M, Oliner KS, Price TJ, et al. Analysis of KRAS/NRAS mutations in a phase III study of panitumumab with FOLFIRI compared with FOLFIRI alone as second-line treatment for metastatic colorectal cancer. *Clin Cancer Res* 2015; 21: 5469-79.
18. Douillard JY, Siena S, Cassidy J, et al. 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. *J Clin Oncol* 2010; 28:4697-705.
19. Peeters M, Price TJ, Cervantes A, et al. 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. *J Clin Oncol* 2010; 28:4706-13.
20. Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol* 2015; 16:1306-15.
21. Sorbye H, Dragomir A, Sundstrom M, et al. High BRAF mutation frequency and marked survival differences in subgroups according to KRAS/BRAF mutation status and tumor tissue availability in a prospective population-based metastatic colorectal cancer cohort. *PLoS One* 2015; 10:e0131046.
22. Cremolini C, Di Bartolomeo M, Amatu A, et al. BRAF codons 594 and 596 mutations identify a new molecular subtype of metastatic colorectal cancer at favorable prognosis. *Ann Oncol* 2015; 26:2092-7.
23. Oddo D, Sennott EM, Barault L, et al. Molecular landscape of acquired resistance to targeted therapy combinations in BRAF-mutant colorectal cancer. *Cancer Res* 2016; 76:4504-15.
24. Peeters M, Oliner KS, Price TJ, et al. Analysis of KRAS/NRAS mutations in phase 3 study 20050181 of panitumumab (pmab) plus FOLFIRI versus FOLFIRI for second-line treatment (tx) of metastatic colorectal cancer (mCRC) (abstract LBA387). *J Clin Oncol* 2014; 32(suppl 3), Abstract LBA387.
25. Sastre J, Massuti B, Pulido G, et al. First-line single-agent panitumumab in frail elderly patients with wild-type KRAS metastatic colorectal cancer and poor prognostic factors: a phase II study of the Spanish Cooperative Group for the Treatment of Digestive Tumours. *Eur J Cancer* 2015; 51:1371-80.
26. Chibaudel B, Bonnetain F, Tournigand C, et al. Simplified prognostic model in patients with oxaliplatin-based or irinotecan-based first-line chemotherapy for metastatic colorectal cancer: a GERCOR study. *Oncologist* 2011; 16:1228-38.
27. Chua W, Charles KA, Baracos VE, Clarke SJ. Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. *Br J Cancer* 2011; 104:1288-95.
28. Yahagi M, Okabayashi K, Hasegawa H, Tsuruta M, Kitagawa Y. The worse prognosis of right-sided compared with left-sided colon cancers: a systematic review and meta-analysis. *J Gastrointest Surg* 2016; 20:648-55.

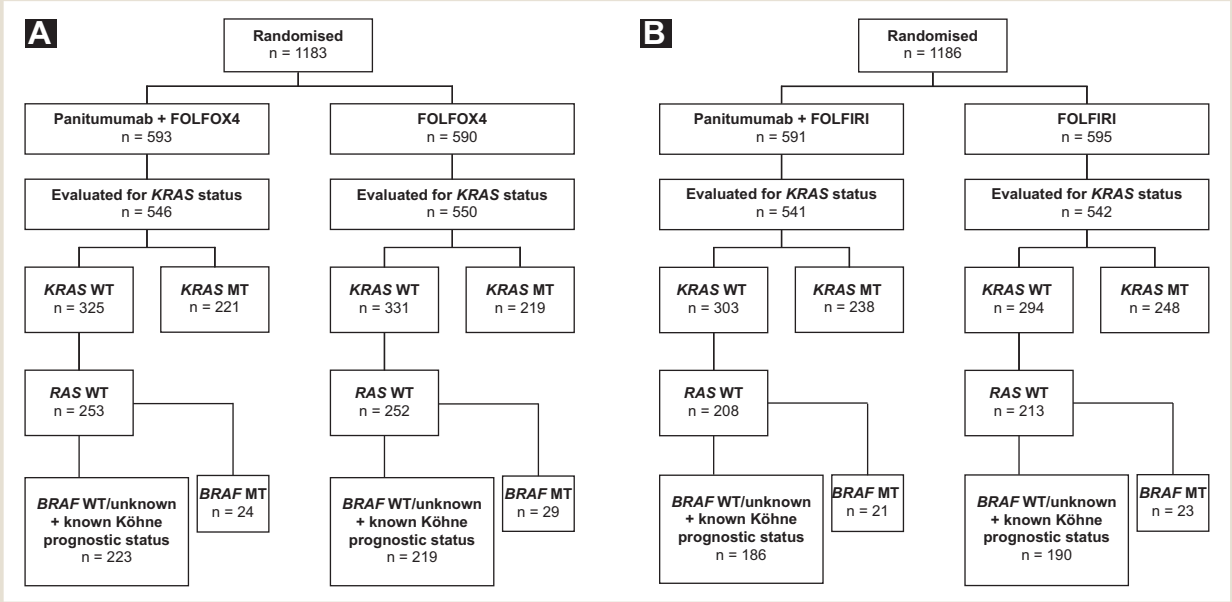
29. Tejpar S, Stintzing S, Ciardiello F, et al. Prognostic and predictive relevance of primary tumor location in patients with *RAS* wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. *JAMA Oncol* 2017; 3: 194-201.
30. Boeckx N, Koukakis R, Op de Beeck K, et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies. *Ann Oncol* 2017; 28:1862-8.
31. Arnold D, Lueza B, Douillard JY, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. *Ann Oncol* 2017; 28:1713-29.
32. Akkad J, Bochum S, Martens UM. Personalized treatment for colorectal cancer: novel developments and putative therapeutic strategies. *Langenbecks Arch Surg* 2015; 400:129-43.
33. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. *Nat Med* 2015; 21:1350-6.
34. Diouf M, Chibaudel B, Filleron T, et al. Could baseline health-related quality of life (QoL) predict overall survival in metastatic colorectal cancer? The results of the GERCOR OPTIMOX 1 study. *Health Qual Life Outcomes* 2014; 12:69.

Supplemental Figure 1 Updated Algorithm for Determining Köhne Prognostic Score



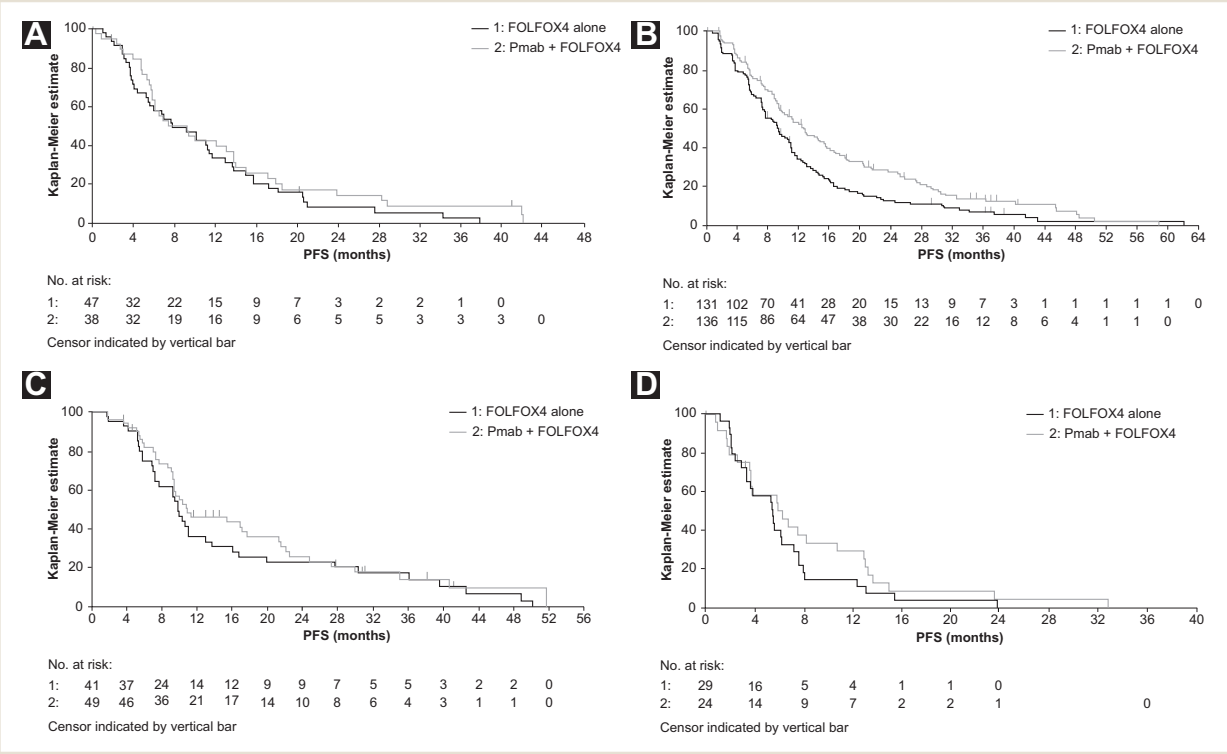
Abbreviations: ALP = alkaline phosphatase (U/L); ECOG PS = Eastern Cooperative Oncology Group performance status; MT = mutant; WBC = white blood cells (10×10^9/L); WT = wild type.

Supplemental Figure 2 Flow Charts of Patient *RAS* Analysis in the (A) PRIME and (B) 20050181 Studies



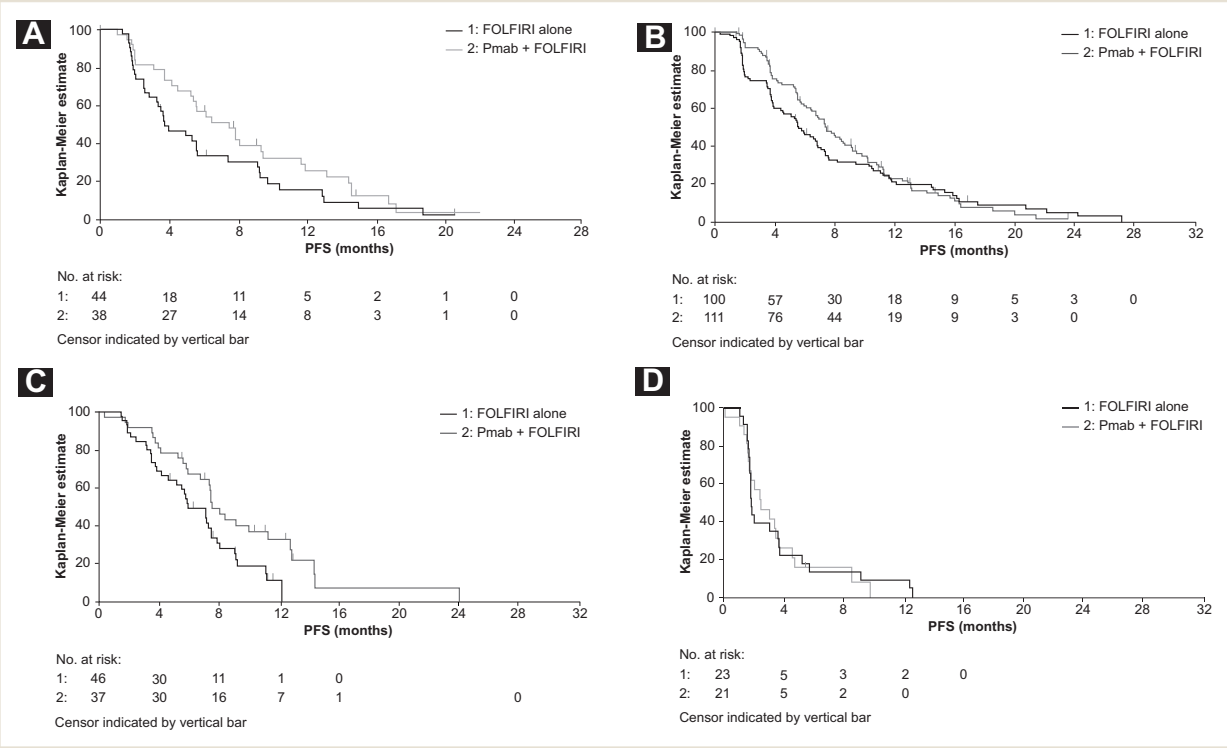
Abbreviations: FOLFIRI = leukovorin, 5-fluorouracil, and irinotecan; FOLFOX4 = leukovorin, 5-fluorouracil, and oxaliplatin; MT = mutant; PRIME = Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy; WT = wild type.

Supplemental Figure 3 **Kaplan–Meier Curves for Progression-Free Survival (PFS) in Patients in the PRIME Study With *BRAF* Wild Type/Unknown Metastatic Colorectal Cancer (mCRC) Categorized as Köhne (A) High Risk, (B) Medium Risk, or (C) Low Risk, and (D) for Patients With *BRAF* Mutant mCRC Overall in the Panitumumab With FOLFOX4 and FOLFOX4-Alone Arms**



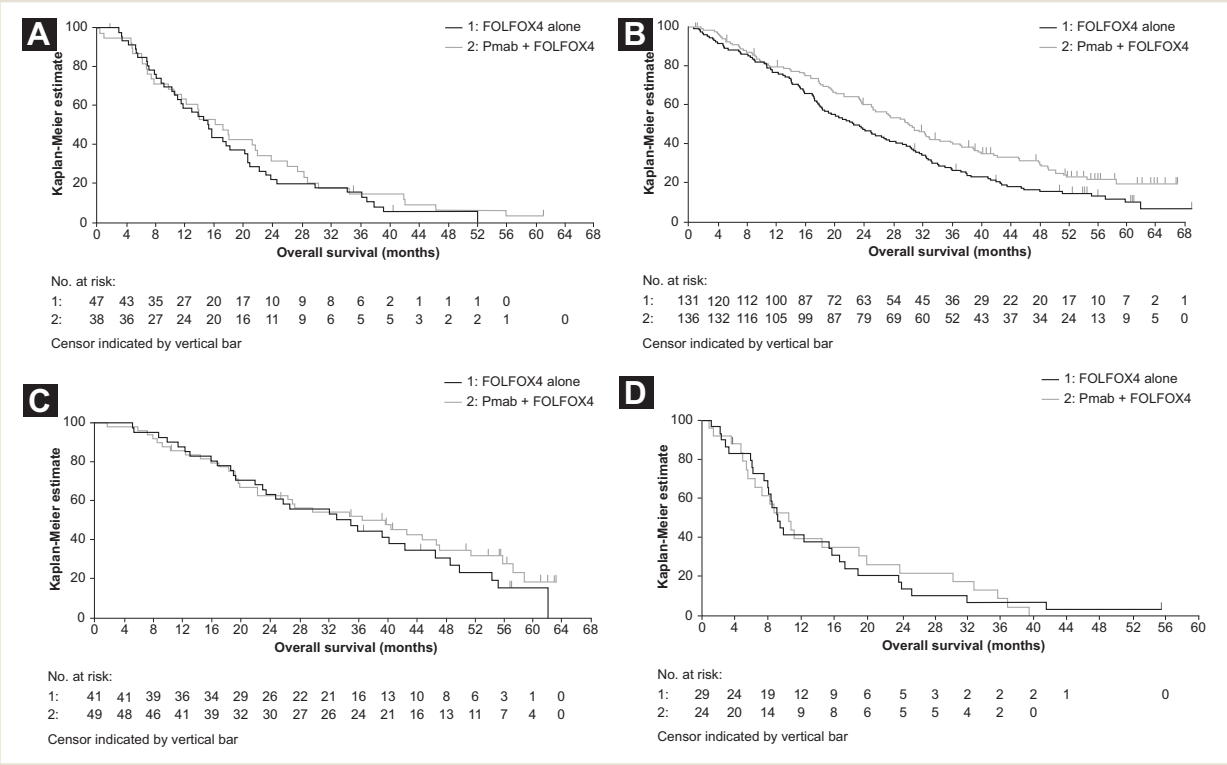
Abbreviations: FFXFOLFOX4 = leukovorin, 5-fluorouracil, and oxaliplatin; Pmab = panitumumab; PRIME = Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy.

Supplemental Figure 4 Kaplan–Meier Curves for Progression-Free Survival (PFS) in Patients in the 20050181 Study With *BRAF* Wild Type/Unknown Metastatic Colorectal Cancer (mCRC) Categorized as Köhne (A) High Risk, (B) Medium Risk, or (C) Low Risk, and (D) for Patients With *BRAF* Mutant mCRC Overall in the Panitumumab and FOLFIRI and FOLFIRI-Alone Arms



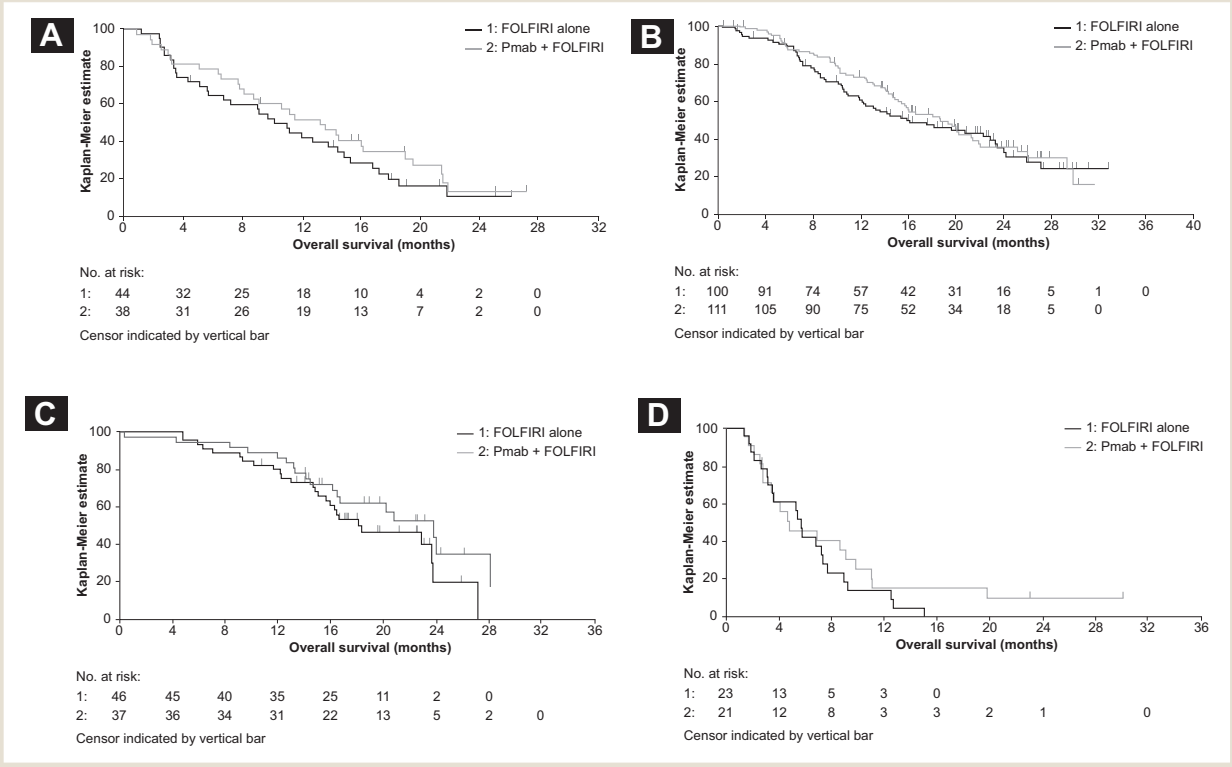
Abbreviations: FOLFIRI = leukovorin, 5-fluorouracil, and irinotecan; Pmab = panitumumab.

Supplemental Figure 5 Kaplan–Meier Curves for Overall Survival in Patients in the PRIME Study With *BRAF* Wild Type/Unknown Metastatic Colorectal Cancer (mCRC) Categorized as Köhne (A) High Risk, (B) Medium Risk, or (C) Low Risk, and (D) for Patients With *BRAF* Mutant mCRC Overall in the Panitumumab and FOLFOX4 and FOLFOX4-Alone arms



Abbreviations: FOLFOX4 = leukovorin, 5-fluorouracil, and oxaliplatin; Pmab = panitumumab; PRIME = Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy.

Supplemental Figure 6 Kaplan–Meier Curves for Overall Survival in Patients in the 20050181 Study With *BRAF* Wild Type/Unknown Metastatic Colorectal Cancer (mCRC) Categorized as Köhne (A) High Risk, (B) Medium Risk, or (C) Low Risk, and (D) for Patients With *BRAF* Mutant mCRC Overall in the Panitumumab and FOLFIRI and FOLFIRI-Alone Arms



Abbreviations: FOLFIRI =leukovorin, 5-fluorouracil, and irinotecan; Pmab = panitumumab.

Supplemental Table 1 Baseline Demographic and Disease Characteristics in the PRIME and 20050181 Studies

Characteristic	Panitumumab and FOLFOX4 (n = 247)					FOLFOX4 (n = 248)				
		Risk Category					Risk category			
PRIME Study	Total (n = 247)	*BRAF* Mutant (n = 24)	High (n = 38)	Medium (n = 136)	Low (n = 49)	Total (n = 248)	*BRAF* Mutant (n = 29)	High (n = 47)	Medium (n = 131)	Low (n = 41)
Sex, n (%)										
Female	82 (33)	10 (42)	13 (34)	39 (29)	20 (41)	92 (37)	14 (48)	24 (51)	37 (28)	17 (41)
Male	165 (67)	14 (58)	25 (66)	97 (71)	29 (59)	156 (63)	15 (52)	23 (49)	94 (72)	24 (59)
Median Age (Range), Years	61 (27-81)	62 (44-80)	61 (37-78)	62 (30-81)	59 (27-77)	61 (24-82)	66 (37-76)	59 (31-79)	62 (24-80)	58 (27-82)
ECOG Performance Score, n (%)										
0	146 (59)	10 (42)	20 (53)	81 (60)	35 (71)	135 (54)	17 (59)	12 (26)	78 (60)	28 (68)
1	87 (35)	11 (46)	8 (21)	54 (40)	14 (29)	97 (39)	11 (38)	23 (49)	50 (38)	13 (32)
2	14 (6)	3 (13)	10 (26)	1 (1)	0 (0)	16 (6)	1 (3)	12 (26)	3 (2)	0 (0)
Primary Tumor Diagnosis, n (%)										
Colon	159 (64)	20 (83)	22 (58)	80 (59)	37 (76)	161 (65)	27 (93)	30 (64)	81 (62)	23 (56)
Rectum	88 (36)	4 (17)	16 (42)	56 (41)	12 (24)	87 (35)	2 (7)	17 (36)	50 (38)	18 (44)
Tumor Side, n (%)										
Left	167 (68)	7 (29)	27 (71)	98 (72)	35 (71)	158 (64)	8 (28)	34 (72)	85 (65)	31 (76)
Right	38 (15)	13 (54)	2 (5)	17 (13)	6 (12)	49 (20)	16 (55)	3 (6)	26 (20)	4 (10)
Unknown	42 (17)	4 (17)	9 (24)	21 (15)	8 (16)	41 (17)	5 (17)	10 (21)	20 (15)	6 (15)
Sites of Metastases, n (%)										
Liver and other	164 (66)	18 (75)	34 (89)	112 (82)	0 (0)	170 (69)	19 (66)	42 (89)	109 (83)	0 (0)
Liver only	48 (19)	1 (4)	1 (3)	1 (1)	45 (92)	41 (17)	4 (14)	0 (0)	1 (1)	36 (88)
Other only	35 (14)	5 (21)	3 (8)	23 (17)	4 (8)	37 (15)	6 (21)	5 (11)	21 (16)	5 (12)
Previous Adjuvant Chemotherapy, n (%)										
Yes	205 (83)	20 (83)	33 (87)	107 (79)	45 (92)	211 (85)	23 (79)	44 (94)	107 (82)	37 (90)
No	42 (17)	4 (17)	5 (13)	29 (21)	4 (8)	37 (15)	6 (21)	3 (6)	24 (18)	4 (10)

Supplemental Table 1 Continued

Characteristic	Panitumumab and FOLFIRI					FOLFIRI				
		Risk Category					Risk Category			
20050181 Study	Total (n = 207)	*BRAF* Mutant (n = 21)	High (n = 38)	Medium (n = 111)	Low (n = 37)	Total (n = 213)	*BRAF* Mutant (n = 23)	High (n = 44)	Medium (n = 100)	Low (n = 46)
Sex, n (%)										
Female	72 (35)	8 (38)	15 (39)	42 (38)	7 (19)	73 (34)	10 (43)	19 (43)	29 (29)	15 (33)
Male	135 (65)	13 (62)	23 (61)	69 (62)	30 (81)	140 (66)	13 (57)	25 (57)	71 (71)	31 (67)
Median Age (Range), Years	60 (28-81)	61 (42-76)	58 (37-78)	60 (36-81)	65 (28-79)	60 (33-85)	62 (40-72)	60 (33-85)	61 (41-82)	60 (35-79)
ECOG Performance Score, n (%)										
0	102 (49)	5 (24)	13 (34)	61 (55)	23 (62)	104 (49)	7 (30)	17 (39)	58 (58)	22 (48)
1	94 (45)	14 (67)	16 (42)	50 (45)	14 (38)	94 (44)	13 (57)	18 (41)	39 (39)	24 (52)
2	11 (5)	2 (10)	9 (24)	0 (0)	0 (0)	15 (7)	3 (13)	9 (20)	3 (3)	0 (0)
Primary Tumor Diagnosis, n (%)										
Colon	118 (57)	13 (62)	23 (61)	61 (55)	21 (57)	148 (69)	21 (91)	30 (68)	70 (70)	27 (59)
Rectum	89 (43)	8 (38)	15 (39)	50 (45)	16 (43)	65 (31)	2 (9)	14 (32)	30 (30)	19 (41)
Tumor Side, n (%)										
Left	150 (72)	7 (33)	28 (74)	86 (77)	29 (78)	148 (69)	4 (17)	31 (70)	74 (74)	39 (85)
Right	31 (15)	9 (43)	3 (8)	17 (15)	2 (5)	39 (18)	13 (57)	7 (16)	16 (16)	3 (7)
Unknown	26 (13)	5 (24)	7 (18)	8 (7)	6 (16)	26 (12)	6 (26)	6 (14)	10 (10)	4 (9)
Sites of Metastases, n (%)										
Liver and other	140 (68)	17 (81)	31 (82)	92 (83)	0 (0)	134 (63)	14 (61)	40 (91)	80 (80)	0 (0)
Liver only	37 (18)	3 (14)	2 (5)	0 (0)	32 (86)	49 (23)	4 (17)	0 (0)	3 (3)	42 (91)
Other only	30 (14)	1 (5)	5 (13)	19 (17)	5 (14)	30 (14)	5 (22)	4 (9)	17 (17)	4 (9)
Previous Adjuvant Chemotherapy, n (%)										
Yes	157 (76)	15 (71)	31 (82)	83 (75)	28 (76)	181 (85)	19 (83)	43 (98)	78 (78)	41 (89)
No	45 (22)	5 (24)	5 (13)	27 (24)	8 (22)	31 (15)	3 (13)	1 (2)	22 (22)	5 (11)
Missing	5 (2)	1 (5)	2 (5)	1 (<1)	1 (3)	1 (<1)	1 (4)	0 (0)	0 (0)	0 (0)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; FOLFIRI = leukovorin, 5-fluorouracil, and irinotecan; FOLFOX4 = leukovorin, 5-fluorouracil, and oxaliplatin; PRIME = Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy.

Supplemental Table 2 Progression-Free Survival and OS in *BRAF* Wild Type mCRC Categorized According to Köhne Prognostic Category, and *BRAF* Mutant mCRC in the PRIME Study

Risk Category	Kaplan–Meier Median PFS, Months (95% CI)		Kaplan-Meier Median OS, Months (95% CI)	
	Panitumumab With FOLFOX4	FOLFOX4	Panitumumab With FOLFOX4	FOLFOX4
***BRAF* Wild Type**				
High	n = 36 7.1 (5.7-13.8)	n = 47 7.8 (5.3-11.4)	n = 36 15.0 (9.7-21.7)	n = 47 15.1 (10.6-20.2)
	HR, 0.82; 95% CI, 0.52-1.30		HR, 0.89; 95% CI, 0.56-1.40	
Medium	n = 134 12.6 (9.7-15.4)	n = 125 9.2 (7.3-10.6)	n = 134 30.8 (25.4-36.3)	n = 125 22.6 (17.8-27.2)
	HR, 0.63; 95% CI, 0.48-0.82		HR, 0.67; 95% CI, 0.51-0.88	
Low	n = 46 10.9 (9.4-21.3)	n = 41 9.9 (7.2-12.9)	n = 46 40.7 (26.6-51.7)	n = 41 35.2 (23.1-46.8)
	HR, 0.78; 95% CI, 0.49-1.24		HR, 0.72; 95% CI, 0.44-1.19	
***BRAF* Mutant**				
Overall	n = 24 6.0 (3.5-10.7)	n = 29 5.4 (3.3-6.2)	n = 24 10.4 (5.6-18.9)	n = 29 9.2 (7.5-15.7)
	HR, 0.74; 95% CI, 0.42-1.29		HR, 0.97; 95% CI, 0.55-1.69	

Abbreviations: FOLFOX4 = leukovorin, 5-fluorouracil, and oxaliplatin; HR = hazard ratio; mCRC = metastatic colorectal cancer; OS = overall survival; PFS = progression-free survival; PRIME = Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy.