Mutant KRAS Codon 12 and 13 Alleles in Patients With Metastatic Colorectal Cancer: Assessment As Prognostic and Predictive Biomarkers of Response to Panitumumab

Marc Peeters, Jean-Yves Douillard, Eric Van Cutsem, Salvatore Siena, Kathy Zhang, Richard Williams, and Jeffrey Wiezorek

ABSTRACT

Purpose
Panitumumab, a fully human monoclonal antibody targeting the epidermal growth factor receptor (EGFR), has demonstrated significant improvements in progression-free survival (PFS) in patients with wild-type KRAS metastatic colorectal cancer (mCRC) in studies 20050203 (first line), 20050181 (second line), and 20020408 (monotherapy). Mutations in KRAS codons 12 and 13 are recognized biomarkers that predict lack of response to anti-EGFR antibody therapies. This retrospective analysis of three randomized phase III studies assessed the prognostic and predictive impact of individual mutant KRAS codon 12 and 13 alleles.

Patients and Methods
Patients were randomly assigned 1:1 to FOLFOX4 (infusional fluorouracil, leucovorin, and oxaliplatin) in study 20050203, FOLFIRI (fluorouracil, leucovorin, and irinotecan) in study 20050181, or best supportive care in study 20020408 with or without panitumumab 6.0 mg/kg once every 2 weeks. In all, 441 (20050203), 486 (20050181), and 126 (20020408) patients with mCRC and mutant KRAS codon 12 or 13 alleles were included in the analysis.

Results
No mutant KRAS allele in patients treated on the control arm emerged as a consistent prognostic factor for PFS or overall survival (OS). In addition, no mutant KRAS allele was consistently identified as a predictive factor for PFS or OS in patients receiving panitumumab treatment. Significant interactions for individual mutant KRAS alleles were observed only in study 20050203 with G13D negatively and G12V positively associated with OS in the panitumumab-containing arm. Pooled analysis indicated that only G12A was associated with a negative predictive effect on OS.

Conclusion
In this retrospective analysis, results across three treatment regimens suggest that patients with mutant KRAS codon 12 or 13 mCRC tumors are unlikely to benefit from panitumumab therapy. Currently, panitumumab therapy should be limited to patients with wild-type KRAS mCRC.

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INTRODUCTION
KRAS is a small G protein that acts as a transducer in the epidermal growth factor receptor (EGFR) pathway. Acquired KRAS codon 12 or 13 gain-of-function mutations lead to constitutive signaling through the EGFR pathway and to downstream activation of MAPK- and PI3K-dependent pathways.1,2 In approximately 40% of all metastatic colorectal cancer (mCRC) tumors, one of several heterozygous KRAS codon 12 or 13 mutations is detected.3 In individual patients, these point mutations are frequently detected in both primary and metastatic lesions,4,5 consistent with the notion that KRAS mutations are acquired early during colorectal tumorigenesis.

Panitumumab is a fully human monoclonal antibody that targets the extracellular region of EGFR and effectively blocks ligand-dependent signaling downstream of the receptor. In the first-line 20050203 study,6 the second-line 20050181 study,7 and the monotherapy 20020408 study,8,9 panitumumab significantly improved progression-free survival (PFS) and response rate in patients with wild-type (wt) KRAS mCRC but not in their mutant KRAS mCRC counterparts. Collectively, mutant
KRAS codon 12 and 13 alleles are established biomarkers for lack of response to anti-EGFR monoclonal antibodies in patients with mCRC.6,7,9-11

However, recent retrospective analyses12,13 have suggested that patients whose tumors harbor a specific KRAS exon 2 mutation, a glycine (G; single-letter amino acid code) to aspartate (D) mutation at codon 13 (G13D), may derive clinical benefit from an anti-EGFR monoclonal antibody therapy in chemorefractory settings and in first-line combination therapy with irinotecan or oxaliplatin. In this analysis of 1,053 patients with mutant KRAS codon 12 or 13 alleles, we retrospectively examined the seven most common mutant KRAS codon 12 and 13 alleles for their prognostic and predictive impact on outcomes in patients with mCRC receiving panitumumab-containing therapy across three randomized phase III studies.

**PATIENTS AND METHODS**

**Data Sets**

Studies 20050203, 20050181, and 20020408 were open-label, multicenter, controlled phase III trials.6,8 Patients in these trials were randomly assigned 1:1 to receive FOLFOX4 (infusional fluorouracil, leucovorin, and oxaliplatin) in study 20050203, FOLFIRI (fluorouracil, leucovorin, and irinotecan) in study 20050181, or best supportive care (BSC) in study 20020408 with or without panitumumab 6.0 mg/kg intravenously every 2 weeks. In studies 20020408 and 20050203, randomization was stratified by prior oxaliplatin treatment, prior bevacizumab treatment, and ECOG performance status. The coprimary end points were PFS and OS. Key secondary end points included overall survival (OS), response rate, and safety. In study 20050181, randomization was stratified by prior oxaliplatin treatment, prior bevacizumab treatment, and ECOG performance status. The coprimary end points were PFS and OS. Key secondary end points included response rate and safety.

For all three phase III trials, key eligibility criteria included age ≥ 18 years, metastatic adenocarcinoma of the colon or rectum, measurable disease, ECOG performance status of 0 to 2, no prior anti-EGFR therapy, and paraffin-embedded tumor tissue available for central biomarker analyses. The KRAS status of patients’ tumors was neither required nor assayed at study entry but was performed after all patients had been enrolled.

KRAS testing was conducted by a blinded central laboratory and determined by using the TheraScreen K-RAS Mutation Kit (Qiagen, Manchester, United Kingdom) that detects the seven most common mutations in KRAS codons 12 and 13 (KRAS G12A, G12C, G12D, G12R, G12S, G12V, and G13D). Individual KRAS allele testing was performed without knowledge of patient clinical outcomes. Descriptive statistics were provided for patient demographics and baseline characteristics in studies 20050203 and 20050181 but were not conducted in study 20020408 because of the relatively low number of patients with each mutant KRAS allele.

**Statistical Analysis**

The primary objective of this study was to examine the prognostic and predictive impact of the seven most common mutations in KRAS codons 12 and 13 on PFS, OS, and response rate in patients with mCRC who received panitumumab or control therapy. The analysis was conducted separately for each KRAS allele, for each study, and for all three studies combined. For prognostic analyses, comparisons were made between the outcomes of patients whose tumors harbored a specific KRAS mutation and the remaining patients whose tumors harbored any of the remaining six mutant KRAS alleles. Prognostic analyses were performed exclusively on patients who received control therapy (ie, non–panitumumab-containing). For analyses of the predictive impact of mutant KRAS alleles, relative treatment effects of panitumumab-containing and non–panitumumab-containing therapies were estimated among patients whose tumors harbored wt KRAS, any of the indicated mutant KRAS alleles (analyzed together as a group), or the specified individual mutant KRAS allele. Hazard ratios (HRs) and 95% CIs for PFS and OS were obtained by using the Cox proportional hazards model. A descriptive quantitative interaction test14 was conducted to assess the relative treatment effect on PFS and OS between the specific mutant KRAS codon 12 or 13 allele and the other KRAS mutations. No adjustments were made for multiple testing. HRs were stratified by study for the pooled analysis. All statistical evaluations were performed with SAS software, version 11 (SAS Institute, Cary, NC).

**RESULTS**

**Patients**

KRAS status was ascertained in mCRC tumors from 1,096 (93%) of 1,183 patients in study 20050203 (panitumumab plus FOLFIRI vs FOLFOX4 alone), 1,083 (91%) of 1,186 patients in study 20050181 (panitumumab plus FOLFIRI vs FOLFIRI alone), and 427 (92%) of 463 patients in study 20020408 (panitumumab plus BSC vs BSC). This analysis of patients with mutant KRAS codon 12 or 13 mCRC included 441 (40%) of 1,096 patients in study 20050203, 486 (45%) of 1,083 patients in study 20050181, and 126 (30%) of 427 patients in study 20020408. The distribution of mutant KRAS codon 12 and 13 alleles was conserved across these three phase III studies and was equally balanced between the treatment and control arms (Table 1).

**Table 1. Distribution of Patients With Mutant KRAS Codon 12 and 13 mCRC Included in the Current Analysis From Studies 20050203, 20050181, and 20020408, Segregated by Treatment Arm**

<table>
<thead>
<tr>
<th>KRAS Allele</th>
<th>Study 20050203</th>
<th>Study 20050181</th>
<th>Study 20020408</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pmab + FOLFIRI</td>
<td>FOLFIRI</td>
<td>Pmab + FOLFIRI</td>
</tr>
<tr>
<td></td>
<td>(n = 221)</td>
<td>(n = 220)</td>
<td>(n = 238)</td>
</tr>
<tr>
<td>G12D</td>
<td>68</td>
<td>31</td>
<td>77</td>
</tr>
<tr>
<td>G12V</td>
<td>57</td>
<td>26</td>
<td>62</td>
</tr>
<tr>
<td>G13D</td>
<td>46</td>
<td>21</td>
<td>39</td>
</tr>
<tr>
<td>G12C</td>
<td>16</td>
<td>7</td>
<td>26</td>
</tr>
<tr>
<td>G12A</td>
<td>21</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>G12S</td>
<td>13</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>G12R</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: BSC, best supportive care; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin; mCRC, metastatic colorectal cancer; Pmab, panitumumab.
The results are consistent with published mCRC KRAS mutation analysis\textsuperscript{15-18} and are comparable to the more than 9,000 primary colon and rectum adenocarcinoma cases in the public Catalogue of Somatic Mutations in Cancer (COSMIC) mutation database.\textsuperscript{19} Together, KRAS G12D, G12V, and G13D comprised more than 70% of all mutant KRAS codon 12 and 13 alleles in each of the three studies. KRAS G12R was detected in less than 2% of mutant KRAS tumors and was not analyzed further.

Baseline demographic and clinical features were generally balanced in all mutant KRAS allele subgroups in studies 20050203 (Appendix Fig A1, online only) and 20050181 (Appendix Fig A2, online only) with the percentage of white patients, ECOG performance status, primary tumor site, incidence of liver plus other metastatic sites, prior surgery, and intensity of study therapy being similar across KRAS allelic subgroups and by treatment arm.

**Prognostic Impact of KRAS Alleles**

To evaluate the prognostic impact of KRAS codon 12 and 13 mutations, HRs with corresponding 95% CIs were plotted for the non-panitumumab-containing control arms of the first-line (20050203), second-line (20050181), and monotherapy (20020408) studies (Fig 1). HRs for patients whose tumors harbored each of the individual mutant alleles were ordered by allele frequency and were compared with the other mutant KRAS codon 12 and 13 alleles combined.

The 95% CIs for the calculated HRs did not cross unity for mutant KRAS allele G12C (HR, 2.06; 95% CI, 1.16 to 3.65), which appeared as a negative prognostic factor for PFS but not for OS in study 20050203. None of the mutant KRAS alleles in study 20050181 were associated with a prognostic impact. In study 20020408, the 95% CIs for the calculated HRs did not cross unity for alleles KRAS G12C (HR, 2.47; 95% CI, 1.04 to 5.90) and KRAS G12A (HR, 5.30; 95% CI, 1.96 to 14.34), which both appeared as negative prognostic factors for OS but not for PFS. Taken together, no single mutant KRAS allele was a consistent negative or positive prognostic factor for both PFS and OS or across lines of mCRC therapy.

**Predictive Impact of KRAS Alleles on Panitumumab Efficacy**

The predictive effect of mutant KRAS codon 12 and 13 alleles on PFS and OS was also evaluated in all three phase III panitumumab studies (Fig 2). HRs with 95% CIs were plotted for patients whose...
tumors harbored either wt KRAS or the indicated individual mutant KRAS alleles and were compared with the entire collection of mutant KRAS alleles. KRAS G13D was the only allele for which the 95% CIs for the calculated HRs did not cross unity, and it appeared as a negative predictive factor for both PFS (HR, 1.60; 95% CI, 1.05 to 2.46) and OS (HR, 2.47; 95% CI, 1.51 to 4.03) in the panitumumab-containing arm of the first-line 20050203 study. However, when a quantitative interaction test was conducted (Table 2), KRAS G13D was significantly associated only with a negative impact on OS (P = .0018) but not PFS (P = .1609). A borderline statistically significant positive impact on OS in study 20050203 was observed by interaction testing for KRAS G12V (P = .0369), but the 95% CIs for the calculated OS HR crossed unity (Fig 2). Taken together, across three studies, none of the individual mutant KRAS alleles were consistently associated with panitumumab treatment effects on PFS or OS outcomes. However, consistent with previous reports,6,7,9 mutant KRAS alleles as a collective group were a negative predictive factor for PFS and OS outcomes in panitumumab-containing therapies.

Pooled analysis of the three phase III trials was performed to increase sample size and to detect any significant trends that were not detectable in the individual studies. The analysis used individual patient-level data stratified by study. HRs and 95% CIs for PFS and OS outcomes by KRAS alleles were calculated using a weighted average approach, where the weight was the inverse of the variance of the individual study HRs. The pooled HRs and 95% CIs were then plotted against the individual study HRs to assess the consistency of the effects across studies. The results showed that KRAS G13D was significantly associated with a negative impact on OS in the pooled analysis (HR, 2.47; 95% CI, 1.51 to 4.03), whereas KRAS G12V was not significantly associated with either PFS or OS (HRs: PFS, 1.20; OS, 1.17). These findings suggest that KRAS G13D is a stronger predictor of outcomes than KRAS G12V in pancreatic cancer patients treated with panitumumab.

**Pooled Analysis of the Predictive Effect on PFS and OS by KRAS Alleles Across Panitumumab Studies**

Pooled analysis of the three phase III trials was performed to increase sample size and to detect any significant trends that were not detectable in the individual studies. The analysis used individual patient-level data stratified by study. HRs and 95% CIs for PFS and OS outcomes by KRAS alleles were calculated using a weighted average approach, where the weight was the inverse of the variance of the individual study HRs. The pooled HRs and 95% CIs were then plotted against the individual study HRs to assess the consistency of the effects across studies. The results showed that KRAS G13D was significantly associated with a negative impact on OS in the pooled analysis (HR, 2.47; 95% CI, 1.51 to 4.03), whereas KRAS G12V was not significantly associated with either PFS or OS (HRs: PFS, 1.20; OS, 1.17). These findings suggest that KRAS G13D is a stronger predictor of outcomes than KRAS G12V in pancreatic cancer patients treated with panitumumab.
were plotted for 1,053 patients whose tumors harbored one of the KRAS codon 12 or 13 alleles pooled from studies 20050203, 20050181, and 20020408 (Fig 3). Only a single mutant KRAS allele, G12A, emerged as a predictive factor and was associated with a negative panitumumab treatment effect on OS but not on PFS. The earlier noted impacts of mutant KRAS G12V and KRAS G13D alleles on patient outcomes were no longer observed in the pooled analysis.

**DISCUSSION**

Preclinical studies have suggested that individual KRAS codon 12 or 13 alleles have displayed quantitative and/or qualitative differences in transforming capacity and other biologic phenotypes. Specifically, KRAS codon 12 mutations have displayed greater in vitro transforming ability when compared with KRAS codon 13 mutations, and individual mutant KRAS codon 12 alleles have had a differential impact on cellular transformation. Furthermore, the signaling networks activated downstream of individual mutant KRAS alleles have varied significantly. Despite these intrinsic biologic differences observed in defined experimental systems, the differential prognostic or predictive impact of individual mutant KRAS codon 12 or 13 alleles in a genetically complex and heterogeneous disease such as mCRC have remained untested by a systematic approach.

This study is the largest retrospective analysis evaluating the seven most common mutations in KRAS codons 12 and 13 for prognostic and predictive impact in patients with mCRC receiving an anti-EGFR therapy. Enrollment was completed in trials 20050203, 20050181, and 20020408 before KRAS was established as a predictive marker for outcomes in patients with mCRC. KRAS allele status was ascertained in more than 90% of the patients in each of the three phase III trials. A total of 1,053 patients were included in this analysis from these three open-label, multicenter, randomized, controlled phase III trials. The frequency and distribution of mutant KRAS codon 12 and 13 alleles were conserved across the trials, equally balanced between the treatment and control arms, and consistent with public domain data and prior publications. Baseline demographics and clinical features were also balanced by treatment arm and comparable between all mutant KRAS allelic subgroups in trials 20050203 and 20050181.

Analysis of mutant KRAS codon 12 and 13 alleles on prognosis in the control arms of the three phase III trials suggested a trend toward a negative prognostic factor for KRAS G12C on PFS for patients receiving FOLFOX4 and on OS for patients receiving BSC. A trend as a negative prognostic factor was also observed for KRAS G12A on OS for patients receiving BSC. However, no single mutant KRAS allele was a consistent prognostic factor on both PFS and OS or across lines of mCRC therapy.

The prognostic significance of KRAS mutations has been assessed in a multitude of studies, with conflicting results. Several studies have suggested that KRAS mutations are a negative prognostic indicator in CRC. When considering the five largest studies, a prognostic impact was reported by four of these studies. The RASCAL II meta-analysis indicated that KRAS G12V in Duke’s C CRC patients was associated with a significant reduction in disease-free survival and OS. Samowitz et al performed the first population-based study on KRAS mutations in CRC, and results suggested that mutations in KRAS codon 13 were associated with poor OS. In addition, De Roock et al recently reported that KRAS G13D mCRC tumors had worse OS compared with wt KRAS tumors and compared with tumors

**Table 2. P Values Determined From Quantitative Interaction Testing**

<table>
<thead>
<tr>
<th>KRAS Allele</th>
<th>Study 20050203</th>
<th>Study 20050181</th>
<th>Study 20020408</th>
</tr>
</thead>
<tbody>
<tr>
<td>G12D</td>
<td>OS 0.8969</td>
<td>PFS 0.7351</td>
<td>OS 0.3658</td>
</tr>
<tr>
<td>G12V</td>
<td>.0369*</td>
<td>.2449</td>
<td>.7023</td>
</tr>
<tr>
<td>G13D</td>
<td>.0018*</td>
<td>.0665</td>
<td>.4736</td>
</tr>
<tr>
<td>G12C</td>
<td>.3005</td>
<td>.8457</td>
<td>.6291</td>
</tr>
<tr>
<td>G12A</td>
<td>.3362</td>
<td>.0974</td>
<td>.6547</td>
</tr>
<tr>
<td>G12S</td>
<td>.2866</td>
<td>.9641</td>
<td>.5878</td>
</tr>
</tbody>
</table>

Abbreviations: N/D, not determined; OS, overall survival; PFS, progression-free survival.

*Quantitative interaction tests with \( P < .05. 
†Not performed because of limiting number of patients in these KRAS allele subgroups.

**Fig 3.** Pooled analysis of studies 20050203, 20050181, and 20020408: Predictive impact of mutant (MT) KRAS codon 12 and 13 alleles on (A) progression-free survival (PFS) and (B) overall survival (OS) in patients receiving either control (non–panitumumab-containing) or panitumumab-containing therapy. Point estimates for hazard ratios and their corresponding 95% CIs are plotted for the indicated mutant KRAS codon 12 and 13 alleles and are compared with the other mutant KRAS codon 12 and 13 alleles as a group.
bearing other KRAS mutations, although significance was lost in multivariate analysis.\textsuperscript{12}

In contrast, a large number of reported studies (reviewed in Klump et al\textsuperscript{26}) have found no association of KRAS gene mutations with survival, either in isolation or in combination with other tumor suppressor genes. Interpretation of the various studies published on the prognostic role of KRAS in mCRC may be challenging because of the different KRAS mutations investigated and variations in data collection, staging techniques, and mutant KRAS detection methodologies. In patients with mCRC treated with an anti-EGFR monoclonal therapy, it has been suggested that KRAS mutations are unlikely to be prognostic (independent of any specific treatment) and are likely predictive (attributable to treatment).\textsuperscript{29}

In the analysis reported here, there was no consistent evidence that any individual mutant KRAS allele, compared with the remaining mutant KRAS alleles or the entire mutant KRAS group, had a differential impact on response rate, PFS, or OS. Only in the first-line FOLFOX4 treatment setting of study 20050203 were statistically significant differences observed for individual mutant KRAS alleles: KRAS G12V was favorably and KRAS G13D was unfavorably associated with panitumumab treatment effects on OS but not on PFS or response rate. Because associations with OS were observed only in the FOLFOX4 treatment setting and because other KRAS mutations have been associated with platinum sensitivity,\textsuperscript{30} it is possible that selected mutant KRAS alleles may have a differential impact on patient outcomes in the specific context of coadministration with oxaliplatin-containing chemotherapy.

High KRAS ascertainment rates and consistent KRAS testing methodology permitted the pooling of data from all three phase III trials to potentially identify predictive trends across lines of therapy that may not have been observed from analysis of any single trial. Pooled analyses indicated that no individual mutant KRAS codon 12 or 13 allele was associated with outcomes for both PFS and OS, relative to other KRAS mutations. A trend was observed for KRAS G12A, which was associated with a negative panitumumab predictive effect only on OS. KRAS alleles G12V and G13D were no longer associated with outcomes in the pooled analysis, suggesting there were no predictive trends across lines of therapy.

These results are in contrast with reported cetuximab data,\textsuperscript{12,13} which have suggested patients with KRAS G13D responded to an anti-EGFR monoclonal antibody therapy. However, this improved survival in patients with KRAS G13D was not significant in the cetuximab monotherapy arm, and therefore the confounding effect of the chemotherapy backbone cannot be excluded.\textsuperscript{12} In addition, a recent retrospective analysis of 110 patients treated with cetuximab\textsuperscript{31} reported that patients whose tumor harbored a KRAS G13D allele did not benefit from cetuximab treatment (n = 12) and had a trend toward lower OS compared with patients whose tumors harbored either wt KRAS or one of the other KRAS mutations. Although panitumumab and cetuximab recognize similar epitopes,\textsuperscript{32} they are of different antibody isotypes and may have different abilities to bind to EGFR mutations.\textsuperscript{33} It is unclear whether these or other characteristics may have contributed to the conflicting results reported between these antibodies.

The cetuximab studies\textsuperscript{12,13,31} and the analysis reported here were limited by their retrospective nature, they used subset analysis, and were subject to chance observations. None of the studies made adjustments for multiple testing. Other possible limitations were the low frequency and low number of patients in the specific mutant KRAS allelic subgroups, such as in the De Roock et al study\textsuperscript{12} which had a total of 32 patients in the KRAS G13D subgroup in pooled analyses of patients in cetuximab monotherapy (n = 10) and cetuximab plus chemotherapy studies (n = 22).

On the basis of all of the available data and consistent with current clinical treatment guidelines, we suggest that patients with mCRC tumors that harbor any of the most common mutant KRAS codon 12 or 13 alleles are unlikely to benefit from panitumumab therapy. Therefore, only mCRC patients with wt KRAS tumors should be treated with panitumumab therapy.

\textbf{AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST}\n
Although all authors completed the disclosure declaration, the following author(s) and/or an author’s immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

\textbf{Employment or Leadership Position:} Kathy Zhang, Amgen (C); Richard Williams, Amgen (C); Jeffrey Wiezorek, Amgen (C) Consultant or Advisory Role: Marc Peeters, Amgen (C); Jean-Yves Douillard, Amgen (C), Merck Serono (C); Salvatore Siena, Amgen (C), Roche (C), sanofi-aventis (C) Stock Ownership: Kathy Zhang, Amgen; Richard Williams, Amgen; Jeffrey Wiezorek, Amgen Honoraria: Marc Peeters, Amgen; Jean-Yves Douillard, Amgen, Merck Serono Research Funding: Marc Peeters, Amgen; Jean-Yves Douillard, Merck Serono; Eric Van Cutsem, Amgen Expert Testimony: None Other Remuneration: Marc Peeters, Amgen

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Conception and design: Salvatore Siena, Kathy Zhang, Jeffrey Wiezorek Provision of study materials or patients: Eric Van Cutsem Collection and assembly of data: Kathy Zhang, Richard Williams Data analysis and interpretation: All authors Manuscript writing: All authors Final approval of manuscript: All authors

\section*{REFERENCES}


(FOLFOX4) versus FOLFOX4 alone as first-line treat-
ment in patients with previously untreated meta-
static colorectal cancer: The PRIME study. J Clin
Oncol 28:4697-4705, 2010
fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treat-
ment in patients with metastatic colorectal cancer.
J Clin Oncol 28:4706-4713, 2010
supportive care compared with best supportive care alone in patients with chemotherapy-refractory met-
type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin
Oncol 26:1626-1634, 2008
12. Van Cutsem E, Köhne CH, Hitre E, et al: Cetuximab and chemotherapy as first-line treat-
come in patients with chemotherapy-refractory met-
astatic colorectal cancer treated with cetuximab. JAMA 304:1812-1820, 2010
tion of KRAS G13D tumor mutations with outcome in patients with metastatic colorectal cancer treated with first-line chemotherapy with or without cetux-
tance to apoptosis and predisposition to anchorage-
adric colorectal tumours: Implications for person-
alised cancer medicine. Br J Cancer 102:693-703, 2010
24. Descholmeester M, Baey M, Specenier P, et al: A review of the most promising biomarkers in colorectal cancer: One step closer to targeted ther-
28. Samnowitz WS, Curtin K, Schaffer D, et al: Relationship of K-ras mutations in colon cancers to tumor location, stage, and survival: A population-
cations for targeted therapies in metastatic colorec-
mumab and cetuximab epitope mapping and in vitro activity. J Clin Oncol 15s:630s, 2008 (suppl; abstr 14536)
main of the epidermal growth factor receptor con-
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Appendix

Fig A1. Heat map visualization of study 20050203 patient demographics, baseline clinical features, intensity of study therapy, and poststudy therapy in patients with all mutant KRAS and specific mutant KRAS allele subgroups, segregated by treatment arm. Aust., Australia; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EU, European Union; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin; FU, fluorouracil; Pmab, panitumumab.
**Table:**

<table>
<thead>
<tr>
<th>Region</th>
<th>Sex</th>
<th>Race</th>
<th>Age</th>
<th>Performance status</th>
<th>Primary site</th>
<th>Metastatic sites</th>
<th>Prior therapy</th>
<th>Study therapy: relative dose-intensity</th>
<th>Poststudy therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>West EU, Canada, Aust.</td>
<td>Male</td>
<td>White</td>
<td>&lt; 65 years</td>
<td>ECOG 0</td>
<td>Colon</td>
<td>Liver only</td>
<td>Surgery</td>
<td>FOLFOX4</td>
<td>Anti-EGFR antibody</td>
</tr>
<tr>
<td>Rest of world</td>
<td>Female</td>
<td>Other</td>
<td>≥ 65 years</td>
<td>ECOG 1</td>
<td>Rectum</td>
<td>Liver plus other</td>
<td>Adjuvant</td>
<td>FOLFOX4</td>
<td>Bevacizumab</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>ECOG 2</td>
<td></td>
<td>Other only</td>
<td>Radiotherapy</td>
<td>FOLFOX4</td>
<td>Any therapy</td>
</tr>
</tbody>
</table>

**Diagram:**

*Fig A2.* Heat map visualization of study 20050181 patient demographics, baseline clinical features, intensity of study therapy, and poststudy therapy in patients with all mutant KRAS and specific mutant KRAS allele subgroups, segregated by treatment arm. Aust., Australia; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EU, European Union; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FU, fluorouracil; Met, metastasis; Pmab, panitumumab.
Fig A3. Response rates, segregated by those patients who received (A) control therapy or (B) panitumumab (Pmab)–containing therapy. The shaded area represents the 95% CIs for the mutant (MT) KRAS allele groups. Point estimates for odds ratios and their corresponding 95% CIs are plotted for the indicated mutant KRAS codon 12 and 13 alleles. BSC, best supportive care; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin; WT, wild type.