This item is the archived peer-reviewed author-version of:

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

Reference:

Peeters Marc, Oliner Kelly S., Price Timothy J., 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

Clinical cancer research - ISSN 1078-0432 - 21:24(2015), p. 5469-5479

Full text (Publishers DOI): <http://dx.doi.org/doi:10.1158/1078-0432.CCR-15-0526>

To cite this reference: <http://hdl.handle.net/10067/1311020151162165141>

Analysis of *KRAS/NRAS* Mutations in a Phase 3 Study of Panitumumab With FOLFIRI Compared With FOLFIRI Alone as Second-Line Treatment for Metastatic Colorectal Cancer

M. Peeters,¹ K. S. Oliner,² T. J. Price,³ A. Cervantes,⁴ A. F. Sobrero,⁵ M. Ducreux,⁶ Y. Hotko,⁷ T. André,⁸ E. Chan,⁹ F. Lordick,¹⁰ C. J. A. Punt,¹¹ A. H. Strickland,¹² G. Wilson,¹³ T. E. Ciuleanu,¹⁴ L. Roman,¹⁵ E. Van Cutsem,¹⁶ P. He,² H. Yu,² R. Koukakis,¹⁷ J.-H. Terwey,¹⁷ A. S. Jung,² R. Sidhu,² S. D. Patterson^{2*}

¹Antwerp University Hospital and University of Antwerp, Edegem, Belgium; ²Amgen Inc., Thousand Oaks, CA, USA; ³Queen Elizabeth Hospital and University of Adelaide, Woodville, Australia; ⁴Biomedical Research Institute INCLIVA, University of Valencia, Spain; ⁵Ospedale San Martino, Genova, Italy; ⁶Institut Gustave Roussy, Villejuif, and Paris-Sud University, Le Kremlin Bicetre; ⁷Uzhgorod National University, Uzhgorod, Ukraine; ⁸Hôpital Saint Antoine and Université Pierre et Marie Curie (UMPC; Paris VI), Paris, France; ⁹Vanderbilt University Medical Center, Nashville, TN, USA; ¹⁰University Cancer Center, Leipzig, Germany; ¹¹Academic Medical Center, Amsterdam, Netherlands; ¹²Monash Medical Center, East Bentleigh, Australia; ¹³Christie Hospital, Manchester, UK; ¹⁴Institutul Oncologic Ion Chiricuta and University of Medicine and Pharmacy Iuliu Hatieganu, Cluj Napoca, Romania; ¹⁵Leningrad Regional Oncology Dispensary, Saint Petersburg, Russia; ¹⁶University Hospitals and KU Leuven, Leuven, Belgium; ¹⁷Amgen (Europe) GmbH, Zug, Switzerland

†Currently at Gilead Sciences, Foster City, CA

Address correspondence to: Marc Peeters, MD, PhD
 Department of Oncology
 Antwerp University Hospital
 Wilrijkstraat 10
 B-2650 Edegem
 Belgium
 Phone: +32 3 821 39 54
 Fax: +32 3 825 05 64
 Email: Marc.Peeters@uza.be

Trial registration: ClinicalTrials.gov, NCT00339183

Running head: Panitumumab plus FOLFIRI and *RAS* mutations in colorectal cancer

Previous presentation: The results of this study have been presented in part at the 2014 ASCO Gastrointestinal Cancers Symposium (January 16–18, 2014; San Francisco, CA) and at the 2014 ASCO Annual Meeting (May 29–June 2, 2015; Chicago, IL)

Funding: Amgen Inc.

Keywords: Gastrointestinal cancers: colorectal; Phase I-III
 Trials_Gastrointestinal cancers: colorectal

Conflicts of Interest: MP has received honoraria, consulting fees, travel fees, and research funding from Amgen Inc, Merck, and Serono and has served on speakers' bureaus for Amgen Inc. JP has received consulting fees from Amgen Inc and Merck. AC has received consulting fees and served on speakers' bureaus for Amgen Inc, Merck, and Serono. AC has received consulting fees, served on speakers' bureaus, and satellite symposia for Amgen Inc, Bayer, Merck, Roche, and Sanofi. MD has received honoraria from Amgen Inc, Bayer, Biocompatibles, Merck, Pfizer, and Roche, has received consulting fees from Roche, and has received research funding from Pfizer and Roche. AT has received honoraria from Amgen Inc, Roche, Novartis Pharmaceuticals, Bayer, and Sanofi, has received consulting fees from Amgen Inc and Roche, and has received research funding from Amgen Inc, Roche, and Celgene. ES has received consulting fees from Amgen Inc, Lilly, Merrimack, and Castle Biosciences, and has received research funding from Amgen Inc, Bristol Myers Squibb, Lilly, Millenium, Dekkun, Aduro, Halozyme, Novartis, and Boehringer Ingelheim. FL has received consulting fees from Eli Lilly, Roche, Taiho, and Celgene, has received research funding from GlaxoSmithKline, Fresenius Biotech, and Merck, and has received travel fees from Roche, Merck, and Amgen Inc. CJAP has received consulting fees from Roche, Amgen Inc, and Bayer. TEC has received consulting fees from Amgen Inc. LR and EVC have received research funding from Amgen Inc. HY was an employee and stockholder in Amgen Inc at the time this rearch was conducted. RK is an employee,

stockholder, and has received travel feeds from Amgen Inc. KSO, PH, JHT, AJS, RS and SP are employees of and stockholders in Amgen Inc. YH, AHS, and GW have no conflicting interests to disclose.

STATEMENT OF TRANSLATIONAL RELEVANCE

In preclinical studies, identification of mutations in *RAS* enzymes that resulted in constitutive activation suggested that presence of these mutations may preclude response to anti-epidermal growth factor receptor (EGFR) therapy. Although studies have already demonstrated that commonly occurring *KRAS* exon 2 mutations in patients with metastatic colorectal cancer (mCRC) were associated with lack of response to anti-EGFR therapy, a large, prospective-retrospective analysis of a phase 3 study of panitumumab plus FOLFOX as first-line treatment in mCRC found that evaluation of a broader panel of *RAS* mutations (including mutations in *KRAS* exons 3 and 4, and *NRAS* exons 2, 3, and 4) better predicted patient outcomes. In this study, we found an improved benefit-risk profile (compared with *KRAS* exon 2 wild-type patients) for panitumumab plus FOLFIRI versus FOLFIRI alone among *RAS* wild-type patients and provide further support for *RAS* testing for patients with mCRC.

ABSTRACT

Purpose: We evaluated the influence of *RAS* mutation status on the treatment effect of panitumumab in a prospective-retrospective analysis of a randomized, multicenter phase 3 study of panitumumab plus fluorouracil, leucovorin, and irinotecan (FOLFIRI) versus FOLFIRI alone as second-line therapy in patients with metastatic colorectal cancer (mCRC; ClinicalTrials.gov, NCT0039183).

Experimental Design: Outcomes were from the study's primary analysis. *RAS* mutations beyond *KRAS* exon 2 (*KRAS* exons 3, 4; *NRAS* exons 2, 3, 4; *BRAF* exon 15) were detected by bidirectional Sanger sequencing in wild-type *KRAS* exon 2 tumor specimens. Progression-free survival (PFS) and overall survival (OS) were coprimary endpoints.

Results: The *RAS* ascertainment rate was 85%; 18% of wild-type *KRAS* exon 2 tumors harbored other *RAS* mutations. For PFS and OS, the hazard ratio for panitumumab plus FOLFIRI versus FOLFIRI alone more strongly favored panitumumab in the wild-type *RAS* population than in the wild-type *KRAS* exon 2 population (PFS HR, 0.70 [95%CI=0.54–0.91]; *P*=0.007 versus 0.73 [95%CI=0.59–0.90]; *P*=0.004; OS HR, 0.81 [95%CI=0.63–1.03]; *P*=0.08 versus 0.85 [95%CI=0.70–1.04]; *P*=0.12). Patients with *RAS* mutations were unlikely to benefit from panitumumab. Among *RAS* wild-type patients, the objective response rate was 41% in the panitumumab-FOLFIRI group versus 10% in the FOLFIRI group.

Conclusions: Patients with *RAS* mutations were unlikely to benefit from panitumumab-FOLFIRI and the benefit-risk of panitumumab-FOLFIRI was improved in the wild-type *RAS* population compared to the wild-type *KRAS* exon 2 population. These findings support *RAS* testing for patients with mCRC.

Word count: 234 (limit, 250)

1 INTRODUCTION

2 The epidermal growth factor receptor (EGFR) is overexpressed in colorectal cancer (1), and
 3 plays an important role in cellular proliferation and metastasis in metastatic colorectal cancer
 4 (mCRC) (2). The *RAS* family of small GTPases plays a central role in signaling downstream
 5 from the EGFR (3). Activating mutations in *RAS* can result in persistent signaling in the
 6 absence of ligand binding to the EGFR, and resistance to therapy with the anti-EGFR
 7 monoclonal antibodies panitumumab and cetuximab (3,4). *KRAS* and *NRAS* activation result in
 8 different patterns of intracellular signaling, and mutations in *KRAS* and *NRAS* arise in different
 9 cellular contexts and are not functionally redundant (5). *KRAS* exon 2 mutations are an
 10 established predictive biomarker of lack of response to anti-EGFR therapy in mCRC patients (6-
 11 10). These initial studies evaluated the most commonly occurring mutations in codons 12 and
 12 13 of *KRAS*; predictive value of *KRAS* mutations beyond exon 2 and mutations in other *RAS*
 13 enzymes (such as *NRAS*) were not assessed (6-9). Based on large retrospective analyses (11)
 14 and results from hypothesis-generating studies employing next-generation sequencing
 15 techniques (12,13), analyses of studies evaluating anti-EGFR therapies as first-line therapy for
 16 mCRC demonstrated that additional activating mutations in *KRAS* exons 3, and 4 and *NRAS*
 17 exons 2, 3, and 4 predicted lack of response to panitumumab plus FOLFOX as first-line
 18 treatment (14,15). However, there is limited data evaluating panitumumab in combination with
 19 irinotecan-based therapy by *RAS* status.

20 The primary analysis from the phase 3, randomized, controlled 20050181 study demonstrated a
 21 significant improvement in median progression-free survival (PFS) and a trend toward
 22 improvement in overall survival (OS) with panitumumab plus fluorouracil, leucovorin, and
 23 irinotecan (FOLFIRI) compared with FOLFIRI alone in patients with *KRAS* exon 2 wild-type
 24 mCRC (PFS hazard ratio [HR]=0.73, 95% CI=0.59–0.90; *P*=0.004; OS HR=0.85;
 25 95%CI=0.70–1.04; *P*=0.12) but not in patients with mutated *KRAS* exon 2 mCRC (PFS

Panitumumab-FOLFIRI and *RAS* mutations

1 HR=0.85; 95%CI=0.68–1.06; OS HR=0.94; 95%CI=0.76–1.15) (8). This prospective-
2 retrospective analysis demonstrated an improved benefit-risk profile of panitumumab plus
3 FOLFIRI versus FOLFIRI alone among *RAS* wild-type patients enrolled in the 20050181 study.

4

METHODS

Study Design and Eligibility

This prospective-retrospective analysis used data from an open-label, randomized, multicenter, phase 3 study comparing the efficacy of panitumumab plus FOLFIRI with FOLFIRI alone in patients with previously treated mCRC (ClinicalTrials.gov, NCT0039183). The primary analysis has been described previously (8). PFS and OS in the primary analysis population were the study's coprimary endpoints. Objective response rate (ORR) was a key secondary endpoint.

Tumor Specimens

For patients identified as wild-type *KRAS* exon 2 by an investigational-use-only assay in the primary study (Therascreen® *KRAS* Mutation Kit, Qiagen, Germantown, MD; LightCycler®, Roche Diagnostics, Indianapolis, IN), DNA for *RAS* analysis was extracted from banked formalin-fixed paraffin-embedded patient tumor specimens (DNA Extraction Mini Kit, Qiagen, Germantown, MD). Specimens containing <50% tumor area were macrodissected.

Extended *RAS* Analysis

Analysis of *KRAS* exon 3 (codons 59/61) and exon 4 (codons 117/146); *NRAS* exon 2 (codons 12/13), exon 3 (codons 59/61), and exon 4 (codons 117/146); and *BRAF* exon 15 (codon 600) was performed using gold-standard bidirectional Sanger sequencing and WAVE-based SURVEYOR® Scan Kits (Transgenomic, Omaha, NE) was performed as previously described (14). Mutations and analysis methods were prespecified based on previous findings (14,16-19). The central testing laboratory was blinded to treatment assignment and patient outcome.

Assessments

Radiographic imaging (computed tomography/magnetic resonance imaging) was performed every 8 weeks throughout the study. Survival was monitored at 3-month intervals during long-

term follow-up. Adverse events (AEs) occurring during the treatment phase and up to 30 days following the final dose of study drug were recorded and graded according to the NCI-CTCAE v3.0 with modifications for specified skin and nail toxicities (20). An independent data monitoring committee oversaw the safety analysis.

Statistical Analysis

The statistical analysis plan for this *RAS* analysis was developed after the *KRAS* exon 2 analysis was unblinded but before the *RAS* and *BRAF* mutational analysis was done. Clinical outcomes were from the primary analysis.

The primary objective was to evaluate by *RAS* and *BRAF* status the treatment effect of panitumumab plus FOLFIRI versus FOLFIRI alone on PFS and OS in the primary analysis population. For the purposes of this analysis, patients were characterized as having *RAS* mutations if analysis identified any predefined activating mutation in *KRAS* or *NRAS*. Similarly, patients were characterized as having *RAS* or *BRAF* mutations if any predefined *RAS* or *BRAF* mutation was detected.

Hypothesis testing was exploratory and similar to that employed in extended *RAS* analysis of the PRIME study (14). A sequential testing scheme evaluated the treatment effect of panitumumab plus FOLFIRI versus FOLFIRI alone on progression free survival followed by a test of the treatment effects on OS among patients with wild-type *RAS* and wild-type *RAS* and *BRAF* (5% significance level). Effects of panitumumab on PFS and OS within each biomarker group were evaluated using log-rank tests stratified by the randomization factors. The magnitude of the panitumumab treatment effect on OS and PFS was calculated using Cox proportional hazards models stratified by the randomization factors. All randomized patients within each biomarker subgroup were included. Tumor response was evaluated per RECIST by blinded independent central radiology review for patients with ≥ 1 unidimensionally measurable

1 lesion (21). Responses were confirmed ≥ 28 days after the criteria for response were first met.
2 Analyses of early tumor response only included those patients with available baseline and week
3 8 measurements. Differences in early tumor response between groups were evaluated using a
4 Fisher exact test. For patients with reductions from baseline in tumor size, median depth of
5 response was calculated as percentage change from baseline to nadir. For patients with tumor
6 growth or no change in tumor dimensions (ie, with no recorded tumor shrinkage), depth of
7 response was defined as percentage change from baseline to progression or as missing if the
8 patient did not have progression. Differences in depth of response were evaluated using a
9 Wilcoxon test.

10

RESULTS

Patients

Among the 1186 patients randomized, *RAS* status was ascertained in 1014 (85%) patients (**Figure S1; Table S1**). Among these patients, 421 (42%) had wild-type *RAS* tumors (panitumumab + FOLFIRI, n=208; FOLFIRI alone, n=213) and 593 (58%) had mutated *RAS* tumors (panitumumab + FOLFIRI, n=299; FOLFIRI alone, n=294). Among the 597 patients evaluated as having wild-type *KRAS* exon 2 tumors in the primary analysis, 107 (18%; panitumumab + FOLFIRI, n=61; FOLFIRI alone, n=46) were found to have other *RAS* mutations (*KRAS* exons 3/4 or *NRAS*) in this study. Among patients with wild-type *RAS*, 376/421 (89%) had wild-type *BRAF* and 45/421 (11%) had mutant *BRAF*. Of the 1186 randomized patients, 638 (54%) had mutant *RAS* or mutant *BRAF*.

Baseline clinical/demographic characteristics were similar between treatment arms and between patients with wild-type and mutated *RAS*, and were similar to the baseline demographics in the wild-type *KRAS* exon 2 population as previously reported (**Table 1**) (8).

Efficacy Outcomes by Tumor *RAS* Mutation Status

For PFS, the HR for panitumumab plus FOLFIRI versus FOLFIRI alone was 0.73 (95%CI=0.59–0.90; *P*=0.004; **Figure 1A**) in patients with wild-type *KRAS* exon 2 compared with 0.70 (95%CI=0.54–0.91; *P*=0.007; **Figure 1B**) in patients with wild-type *RAS*. Estimated median PFS was longest in the *RAS* wild-type panitumumab plus FOLFIRI group. For OS, the HR for panitumumab plus FOLFIRI versus FOLFIRI alone more strongly favored panitumumab in the extended wild-type *RAS* population than in the wild-type *KRAS* exon 2 population (HR=0.81 [95%CI=0.63–1.03]; *P*=0.08 versus HR=0.85 [95%CI=0.70–1.04]; *P*=0.12; **Figures 1C,1D**). Again, estimated median OS was longest in the *RAS* wild-type panitumumab plus FOLFIRI

group. Sensitivity analyses using Branson & Whitehead models (22) and Law methods (23), did not provide evidence of an influence of post-progression anti-EGFR therapy on OS time.

Patients with *RAS* mutations did not derive clinical benefit from panitumumab plus FOLFIRI and there was no evidence that outcomes were worse or of a negative interaction between the administered agents. Among patients with wild-type *KRAS* exon 2 but with other *RAS* mutations, the HR for PFS for panitumumab plus FOLFIRI versus FOLFIRI alone was 0.89 (95%CI=0.56–1.42; $P=0.63$; **Figure 2A**). Among patients with any *RAS* mutation, the HR for PFS for panitumumab plus FOLFIRI versus FOLFIRI alone was 0.86 (95%CI=0.71–1.05; $P=0.14$; **Figure 2B**). Findings were similar for OS (**Figures 2C,D**) in patients with any *RAS* mutation. Among patients with mutated *KRAS* exon 2, the HR for PFS for panitumumab plus FOLFIRI versus FOLFIRI was 0.85 (95%CI=0.68–1.06); for OS the HR was 0.94 (95%CI=0.76–1.15; **Figure 3A**).

Quantitative interaction tests for the negative predictive value of *RAS* mutations beyond those in *KRAS* exon 2 on panitumumab treatment effect were not statistically significant (PFS, $P=0.37$; OS, $P=0.93$).

Efficacy Outcomes by Tumor *BRAF* Mutation Status

BRAF mutation status was not predictive of benefit with panitumumab. Among patients with wild-type *RAS* and wild-type *BRAF* ($n=376$), the HR for panitumumab plus FOLFIRI versus FOLFIRI alone was 0.68 (95%CI=0.51–0.90; 6.9 versus 5.5 months; $P=0.006$); similarly, in patients with wild-type *RAS* and mutated *BRAF* ($n=45$), the HR for panitumumab plus FOLFIRI versus FOLFIRI alone was 0.69 (95%CI=0.32–1.49; 2.5 versus 1.8 months; $P=0.34$; **Figure 3A**). Similar results were observed for OS: the HR among patients with wild-type *RAS* and wild-type *BRAF* was 0.83 (95%CI=0.64–1.07; 18.7 versus 15.4 months; $P=0.15$) and the HR among patients with wild-type *RAS* and mutated *BRAF* was 0.64 (95%CI=0.32–1.28; 4.7 versus 5.7

months; $P=0.20$). Irrespective of assigned treatment, the HR for PFS favored patients with wild-type *BRAF* versus those with mutated *BRAF* (HR=0.28; 95%CI=0.20–0.40; $n=421$). For OS, the HR was 0.25 (95%CI=0.18–0.36). The presence of a *BRAF* mutation was associated with poorer prognosis (**Figure 3B**).

Tumor Response

In *KRAS* exon 2 wild-type patients, the ORR was 35% in the panitumumab plus FOLFIRI group versus 10% in the FOLFIRI alone group, whereas in patients with wild-type *RAS*, the ORR was 41% in the panitumumab plus FOLFIRI group and 10% in the FOLFIRI alone group (**Figure 4; Table S2**). ORR was similar for panitumumab plus FOLFIRI and FOLFIRI alone among patients with any *RAS* mutation (15% versus 13%; **Table S1**) and for patients with mutated *KRAS* exon 2 (13% versus 14%, respectively). Median duration of response was 9.3 months for panitumumab plus FOLFIRI versus 7.7 months for FOLFIRI alone (**Figure 4**).

Exploratory response assessments were performed to describe the timing and magnitude of response. For patients with wild-type *RAS*, mean percentage change from baseline in the sum of longest diameter of target lesions was markedly greater among patients who received panitumumab (**Figure 4**). Depth of response (assessed by median percentage tumor shrinkage) was greater with panitumumab plus FOLFIRI versus FOLFIRI alone (37% versus 10%; $P<0.0001$; **Figure 4**). Similarly, a greater proportion of wild-type *RAS* patients receiving panitumumab plus FOLFIRI had a $\geq 30\%$ change in sum of longest diameter of target lesions within the first 8 weeks of treatment compared with those receiving FOLFIRI alone (37% versus 7%; $P<0.0001$). Early tumor response and depth of response outcomes were more favorable in panitumumab-treated wild-type *RAS* patients than panitumumab-treated wild-type *KRAS* exon 2 patients (**Table S3**).

Adverse Events

The types, incidence rates, and severity of AEs were similar in patients with wild-type *RAS* and mutated *RAS* in the panitumumab plus FOLFIRI arm (**Table 2**). Additionally, the nature and frequency of incidence of AEs was similar to that previously reported for the wild-type *KRAS* exon 2 population.(8) The most frequently occurring AEs reported among all patients were diarrhea, fatigue, and neutropenia. The incidence of hypomagnesemia and skin toxicities were higher with panitumumab plus FOLFIRI compared with FOLFIRI alone (**Table 2**). In patients with wild-type *RAS*, 25% in the panitumumab plus FOLFIRI group and 12% in the FOLFIRI alone group had AEs leading to discontinuation.

DISCUSSION

Routine *KRAS* exon 2 mutation testing has allowed for identification of mCRC patients more likely to derive benefit from panitumumab. However, a substantial proportion of patients with wild-type *KRAS* exon 2 mCRC do not respond to panitumumab therapy, and there is potential for further refinement of patient selection. Results from this prospective-retrospective analysis provide support for use of this regimen in patients with *RAS* wild-type mCRC. We found improvements in the treatment effect for panitumumab plus FOLFIRI versus FOLFIRI alone for both PFS and OS in the wild-type *RAS* mCRC group compared with the wild-type *KRAS* exon 2 mCRC group. Conversely, patients with *RAS* mutations beyond *KRAS* exon 2 or with any *RAS* mutation were unlikely to benefit from addition of panitumumab to FOLFIRI. Although there was a trend toward longer OS among wild-type *KRAS* exon 2/mutated other *RAS* patients (11.3 versus 9.2 months), PFS was similar (3.7 months in both groups), and exclusion of wild-type *RAS* patients did not alter ORR. Importantly, there was no evidence of worsening of OS or PFS with panitumumab treatment in the mutated *RAS* group. High *RAS* ascertainment (85%) was a strength of the study, ensuring the *RAS*-evaluable population was likely representative of the overall population and allowing for a robust estimate of the proportion (18%) of patients with wild-type *KRAS* exon 2 tumors harboring other *RAS* mutations.

The totality of available evidence supports routine use of *RAS* analysis. For panitumumab, our results in the second-line setting are consistent with those from a previous prospective-retrospective *RAS* analysis of the PRIME study (which evaluated panitumumab plus FOLFOX4 versus FOLFOX4 as first-line therapy) (14), a prospective *RAS* analysis of the PEAK study (which evaluated panitumumab or bevacizumab plus FOLFOX as first-line therapy) (15), and the original hypothesis-generating analysis of the 408 study (which evaluated panitumumab monotherapy in patients with chemotherapy-refractory disease) (12,13). The results are also

consistent with analysis of two smaller studies that showed improvements in response rate with *RAS* analysis among patients with chemotherapy-refractory disease receiving panitumumab plus irinotecan (24) or liver-limited disease receiving neoadjuvant panitumumab plus FOLFOX/FOLFIRI (25), respectively. Similar results have also been reported in cetuximab studies. Recent retrospective analyses of studies evaluating first-line FOLFIRI ± cetuximab [CRYSTAL(26), FIRE-3 (27), and CAPRI-GOIM (28)] or FOLFOX ± cetuximab [OPUS (29)] demonstrated potential predictive value for *RAS* analysis. In the CALGB/SWOG-80405 study of first-line FOLFOX/FOLFIRI plus cetuximab or bevacizumab, there appeared to be little if any improvement in the OS or PFS HR in patients with wild-type *RAS* versus patients with wild-type *KRAS* exon 2 (30). Notably, *RAS* ascertainment was somewhat lower in the cetuximab studies particularly CALGB/SWOG-80405 (CRYSTAL, 69%; OPUS, 75%; FIRE-3, 77%; CALGB/SWOG-80405, 55%; and CAPRI-GOIM, 54%). The distribution of additional *RAS* mutations by chemotherapy backbone in CALGB/SWOG-80405 and interaction testing have yet to be reported. This and the low *RAS* ascertainment limit interpretation of the results. Overall, results from panitumumab and cetuximab studies indicate that patients with *RAS* mutant mCRC are unlikely to benefit from anti-EGFR therapy irrespective of chemotherapy or line of therapy.

These results strongly support routine *RAS* analysis in mCRC. Testing for *RAS* mutations beyond *KRAS* exon 2 better predicts response to treatment and improves patient selection, thereby sparing patients who are unlikely to respond potential toxicities associated with anti-EGFR therapy. Rates of *RAS* mutation beyond *KRAS* exon 2 from 10–26% (14,15,29,31-33) have been reported in recent studies using technologies including pyrosequencing and BEAMing. NCCN (34,35), ESMO (36), and the European Society of Pathology (35) recommend *KRAS/NRAS* genotyping for patients with mCRC, and the Association of Clinical Pathologists Molecular Pathology and Diagnostics Group has issued a guidance document describing *RAS*

testing requirements in the UK (37). Consistency and validation of testing techniques and appropriate timing of their use will be important for clinical application of *RAS* analysis.

Patients with *BRAF* mutations had shorter estimated median PFS and OS than *BRAF* wild-type patients, consistent with previous findings (11,14,33). This difference in prognosis was independent of patients' *RAS* mutation status or panitumumab treatment. In this study, *BRAF* mutations did not have clear predictive value and the results do not provide support for *BRAF* mutation testing to guide anti-EGFR therapy. However, the prognostic information might guide other clinical decisions. To improve outcomes for these patients, recent studies have evaluated feasibility of treatment with anti-EGFR antibodies and other targeted agents (38,39).

The 41% ORR in the wild-type *RAS* panitumumab group represents one of the highest rates reported in the second-line setting, and should be considered when selecting second-line therapy. Evaluation of other measures of tumor response may inform clinical decision-making (although such measures require further prospective confirmation) (40). Depth of tumor response was significantly greater and likelihood of achieving a $\geq 30\%$ reduction in tumor dimensions within 8 weeks of treatment was significantly higher in panitumumab patients. Both outcomes were improved in *RAS* wild-type patients versus *KRAS* exon 2 wild-type patients. Studies with cetuximab have reported associations between early tumor shrinkage (41) and depth of tumor response (42) and survival. Whether similar associations between these measures and survival occur with panitumumab remains to be evaluated.

Selecting patients using extended *RAS* analysis did not alter the safety profile of panitumumab. Consistent with previous studies, toxicities occurring more frequently among panitumumab-treated patients included skin/nail toxicities and hypomagnesemia. There was no evidence of negative interactions between panitumumab and irinotecan in patients with *RAS* mutations, consistent with the CRYSTAL (26) and COIN (43) studies. Poorer OS among *NRAS*-mutant

patients receiving panitumumab plus irinotecan versus irinotecan alone was reported in the PICCOLO study, but these outcomes may have been influenced by the Q3W treatment schedule employed (44). These data were also in contrast to the results seen in the PRIME (14) and OPUS (29) studies, in which outcomes were worse with panitumumab or cetuximab in combination with oxaliplatin-containing therapy (FOLFOX) in patients with *RAS*-mutant tumors, compared with FOLFOX alone.

Key limitations of this study was that *RAS* analysis was exploratory (not defined in the original study protocol) and that results from the *KRAS* exon 2 analysis were known before this analysis was initiated. Consequently, the potential for bias exists. However, the biomarker hypothesis was developed before the mutational analysis was available and was limited to *RAS/BRAF*. Moreover, tumor specimens and clinical outcome data were derived from a large randomized phase 3 study, and the high rate of *RAS* ascertainment limited the potential for ascertainment bias. *RAS* was evaluated using robust, widely available assay procedures. The small number of patients in some groups limits our ability to draw conclusions regarding outcomes. A variety of confounding factors (eg, post-progression therapy) might have limited our ability to detect improvement in OS.

Results from this study provide compelling evidence for panitumumab plus irinotecan-based therapy as an important second-line therapy for *RAS* wild-type patients supported by phase 3 evidence. Exclusion of patients with *RAS* mutations improved the benefit-risk profile of panitumumab plus FOLFIRI in this setting. The totality of evidence supporting *RAS* analysis supports use of these analytical techniques in upfront testing. A recent meta-analysis of 9 panitumumab and cetuximab studies found improvements in outcomes with extended *RAS* analysis (45). Patient-level meta-analyses across randomized studies (including this study, PRIME (14), PEAK (15), the 408 study (12,13), and ongoing 0007 study [ClinicalTrials.gov,

Panitumumab-FOLFIRI and *RAS* mutations

- 1 NCT01412957], and studies in which patients received bevacizumab) may provide increased
- 2 statistical power for evaluation of *RAS* analysis.
- 3

Panitumumab-FOLFIRI and *RAS* mutations

ACKNOWLEDGMENTS

The authors thank Mark Ekdahl (Amgen, Inc.) for operational assistance and Ali Hassan, PhD, and Anny Wu, PharmD (both Complete Healthcare Communications, Inc.), for medical writing assistance funded by Amgen Inc.

REFERENCES

1. Vectibix[®] (panitumumab). Full Prescribing Information, Amgen Inc., Thousand Oaks, CA, 2014.
2. Radinsky R, Risin S, Fan D, Dong Z, Bielenberg D, Bucana CD, et al. Level and function of epidermal growth factor receptor predict the metastatic potential of human colon carcinoma cells. *Clin Cancer Res* 1995;1:19-31.
3. van Krieken JH, Jung A, Kirchner T, Carneiro F, Seruca R, Bosman FT, et al. KRAS mutation testing for predicting response to anti-EGFR therapy for colorectal carcinoma: proposal for an European quality assurance program. *Virchows Arch* 2008;453:417-31.
4. Young A, Lou D, McCormick F. Oncogenic and wild-type Ras play divergent roles in the regulation of mitogen-activated protein kinase signaling. *Cancer Discov* 2013;3:112-23.
5. Wang Y, Velho S, Vakiani E, Peng S, Bass AJ, Chu GC, et al. Mutant N-RAS protects colorectal cancer cells from stress-induced apoptosis and contributes to cancer development and progression. *Cancer Discov* 2013;3:294-307.
6. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, et al. Wild-type *KRAS* is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;26:1626-34.
7. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, 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.
8. Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, 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.

9. Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;360:1408-17.
10. Van Cutsem E, Kohne CH, Lang I, Folprecht G, Nowacki MP, Cascinu S, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor *KRAS* and *BRAF* mutation status. *J Clin Oncol* 2011;29:2011-9.
11. De Roock W, Claes B, Bernasconi D, De Schutter J, Biesmans B, Fountzilias G, et al. Effects of *KRAS*, *BRAF*, *NRAS*, and *PIK3CA* mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol* 2010;11:753-62.
12. Patterson SD, Peeters M, Siena S, Van Cutsem E, Humblet Y, Laethem JV, et al. Comprehensive analysis of *KRAS* and *NRAS* mutations as predictive biomarkers for single agent panitumumab (pmab) response in a randomized, phase III metastatic colorectal cancer (mCRC) study (20020408). *J Clin Oncol* 2013;31:abstract 3617.
13. Peeters M, Oliner KS, Parker A, Siena S, Van Cutsem E, Huang J, et al. Massively parallel tumor multigene sequencing to evaluate response to panitumumab in a randomized phase III study of metastatic colorectal cancer. *Clin Cancer Res* 2013;19:1902-12.
14. Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, et al. Panitumumab-FOLFOX4 treatment and *RAS* mutations in colorectal cancer. *N Engl J Med* 2013;369:1023-34.
15. Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, 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.
16. Loupakis F, Ruzzo A, Cremolini C, Vincenzi B, Salvatore L, Santini D, et al. KRAS codon 61, 146 and BRAF mutations predict resistance to cetuximab plus irinotecan in KRAS codon 12 and 13 wild-type metastatic colorectal cancer. *Br J Cancer* 2009;101:715-21.
 17. Vaughn CP, Zobell SD, Furtado LV, Baker CL, Samowitz WS. Frequency of KRAS, BRAF, and NRAS mutations in colorectal cancer. *Genes Chromosomes Cancer* 2011;50:307-12.
 18. Janakiraman M, Vakiani E, Zeng Z, Pratilas CA, Taylor BS, Chitale D, et al. Genomic and biological characterization of exon 4 KRAS mutations in human cancer. *Cancer Res* 2010;70:5901-11.
 19. Edkins S, O'Meara S, Parker A, Stevens C, Reis M, Jones S, et al. Recurrent KRAS codon 146 mutations in human colorectal cancer. *Cancer Biol Ther* 2006;5:928-32.
 20. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Available at:
http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v3.pdf.
 Accessed June 2, 2014.
 21. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205-16.
 22. Branson M, Whitehead J. Estimating a treatment effect in survival studies in which patients switch treatment. *Stat Med* 2002;21:2449-63.
 23. Law MG, Kaldor JM. Survival analyses of randomized clinical trials adjusted for patients who switch treatments. *Stat Med* 1996;15:2069-76.

24. Andre T, Blons H, Mabro M, Chibaudel B, Bachet JB, Tournigand C, et al. Panitumumab combined with irinotecan for patients with KRAS wild-type metastatic colorectal cancer refractory to standard chemotherapy: a GERCOR efficacy, tolerance, and translational molecular study. *Ann Oncol* 2013;24:412-9.
25. Abad A, Massuti B, Gravalos C, Pilar E, Guillen C, Manzano JL, et al. Phase II trial of panitumumab plus FOLFOX4 or FOLFIRI in subjects with KRAS wild-type colorectal cancer and liver-limited disease: The PLANET study. *J Clin Oncol* 2014;32:abstr 3650.
26. Van Cutsem E, Lenz HJ, Kohne CH, Heinemann V, Tejpar S, Melezinek I, et al. Fluorouracil, Leucovorin, and Irinotecan Plus Cetuximab Treatment and RAS Mutations in Colorectal Cancer. *J Clin Oncol* 2015;33:692-700.
27. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, 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.
28. Ciardiello F, Normanno N, Maiello E, Martinelli E, Troiani T, Pisconti S, et al. Clinical activity of FOLFIRI plus cetuximab according to extended gene mutation status by next-generation sequencing: findings from the CAPRI-GOIM trial. *Ann Oncol* 2014;25:1756-61.
29. Bokemeyer C, Kohne C-H, Ciardiello F, Lenz H-J, Heinemann V, Klinkhardt U, et al. Treatment outcome according to tumor RAS mutation status in OPUS study patients with metastatic colorectal cancer (mCRC) randomized to FOLFOX4 with/without cetuximab. *J Clin Oncol* 2014;32:abstract 3505.
30. Lenz H, Niedzwiecki D, Innocenti F, Blanke C, Mahon MR, O'Neil BH, et al. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or of oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for

- patients (pts) with untreated metastatic adenocarcinoma of the colon or rectum (mCRC):
 expanded RAS analyses. *Ann Oncol* 2014;25:Abstract 501O.
31. Price TJ, Bruhn M, Lee C, Hardingham J, Townsend AR, Mann K, et al. Correlation of PI3KCA and extended RAS gene mutation status with outcomes from the phase III AGITG MAX involving capecitabine (C) alone or in combination with bevacizumab (B) with or without mitomycin C (M) in advanced colorectal cancer (CRC). *J Clin Oncol* 2014;32:abstract 3539.
 32. Ciardiello F, Lenz H-J, Kohne C-H, Heinemann V, Tejpar S, Melezinek I, et al. Treatment outcome according to tumor RAS mutation status in CRYSTAL study patients with metastatic colorectal cancer (mCRC) randomized to FOLFIRI with/without cetuximab. *J Clin Oncol* 2014;32:abstract 3506.
 33. Pentheroudakis G, Kotoula V, De Roock W, Kouvatses G, Papakostas P, Makatsoris T, et al. Biomarkers of benefit from cetuximab-based therapy in metastatic colorectal cancer: interaction of EGFR ligand expression with RAS/RAF, PIK3CA genotypes. *BMC Cancer* 2013;13:49.
 34. NCCN clinical practice guidelines in oncology: colon cancer v.3.2014. National Comprehensive Cancer Network. Available at: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed February 11, 2014.
 35. European Society of Pathology. Colon External Quality Assessment Scheme. Available at: <http://kras.egascheme.org>. Accessed July 18, 2014.
 36. Van Cutsem E, Cervantes A, Nordlinger B, Arnold D. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;25 (suppl 3): iii1-iii9.

37. Wong NA, Gonzalez D, Salto-Tellez M, Butler R, Diaz-Cano SJ, Ilyas M, et al. RAS testing of colorectal carcinoma-a guidance document from the Association of Clinical Pathologists Molecular Pathology and Diagnostics Group. *J Clin Pathol* 2014;67:751-7.
38. Bendell JC, Atreya CE, André T, Tabernero J, Gordon MS, Bernards R, et al. Efficacy and tolerability in an open-label phase I/II study of MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in combination in patients (pts) with BRAF V600E mutated colorectal cancer (CRC). *J Clin Oncol* 2014;32:abstract 3515.
39. Hong DS, Morris VK, Fu S, Overman MJ, Piha-Paul SA, Kee BK, et al. Phase 1B study of vemurafenib in combination with irinotecan and cetuximab in patients with BRAF-mutated advanced cancers and metastatic colorectal cancer. *J Clin Oncol* 2014;32:abstract 3516.
40. Sotelo MJ, Garcia-Paredes B, Aguado C, Sastre J, Diaz-Rubio E. Role of cetuximab in first-line treatment of metastatic colorectal cancer. *World J Gastroenterol* 2014;20:4208-19.
41. Piessevaux H, Buyse M, Schlichting M, Van Cutsem E, Bokemeyer C, Heeger S, et al. Use of early tumor shrinkage to predict long-term outcome in metastatic colorectal cancer treated with cetuximab. *J Clin Oncol* 2013;31:3764-75.
42. Mansmann UR, Sartorius U, Ruediger PL, Giessen CA, Esser R, Heinemann V. Deepness of response: A quantitative analysis of its impact on post-progression survival time after first-line treatment in patients with mCRC. *J Clin Oncol* 2013;31:abstract 427.
43. Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet* 2011;377:2103-14.

Panitumumab-FOLFIRI and *RAS* mutations

44. Seymour MT, Brown SR, Middleton G, Maughan T, Richman S, Gwyther S, et al.
 Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. *Lancet Oncol* 2013;14:749-59.
45. Sorich MJ, Wiese MD, Rowland A, Kichenadasse G, McKinnon RA, Karapetis CS.
 Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized controlled trials. *Ann Oncol* 2014;26:13-21.

TABLES

Table 1. Baseline Demographic and Clinical Characteristics by RAS Status

Characteristic	Wild-Type RAS		Mutated RAS	
	Panitumumab + FOLFIRI (N=208)	FOLFIRI Alone (N=213)	Panitumumab + FOLFIRI (N=299)	FOLFIRI Alone (N=294)
Men	136 (65)	140 (66)	165 (55)	177 (60)
Median (range) age, y	60 (28–81)	60 (33–85)	61 (29–84)	64 (29–86)
Race, white	203 (98)	202 (95)	284 (95)	283 (96)
ECOG performance status 0–1	196 (94)	198 (93)	284 (95)	275 (94)
Region				
Western EU, Canada, Australia	135 (65)	139 (65)	184 (62)	182 (62)
Rest of world	72 (35)	74 (35)	115 (38)	112 (38)
Primary tumor type				
Colon	119 (57)	148 (69)	201 (67)	186 (63)
Rectal	89 (43)	65 (31)	98 (33)	108 (37)
Sites of metastatic disease				
Liver only	37 (18)	49 (23)	46 (15)	40 (14)
Liver plus other	140 (67)	134 (63)	213 (71)	204 (69)
Subsequent therapies				
Bevacizumab	21 (10)	25 (12)	39 (13)	30 (10)
EGFR mAb	21 (10)	68 (32)	24 (8)	91 (31)
Oxaliplatin, irinotecan, or FU	93 (45)	107 (50)	138 (46)	151 (51)

Data presented as n (%) unless otherwise noted.

ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; EU=European Union; FOLFIRI=fluorouracil, leucovorin, and irinotecan; FU=fluorouracil; mAb=monoclonal antibody.

Table 2. Summary of Adverse Events by RAS Status

Adverse Event, n (%)	Wild-Type RAS		Mutated RAS	
	Panitumumab + FOLFIRI (N=207)	FOLFIRI Alone (N=213)	Panitumumab + FOLFIRI (N=298)	FOLFIRI Alone (N=292)
Any AE	207 (100)	211 (99)	296 (99)	281 (96)
Worst grade of 3	114 (55)	78 (37)	137 (46)	100 (34)
Worst grade of 4	41 (20)	35 (16)	50 (17)	44 (15)
Worst grade of 5	8 (4)	13 (6)	21 (7)	17 (6)
Serious AE	94 (45)	67 (31)	110 (37)	90 (31)
AEs occurring in ≥20% of patients in either treatment arm				
Diarrhea	142 (69)	122 (57)	181 (61)	167 (57)
Fatigue	81 (39)	69 (32)	102 (34)	104 (36)
Neutropenia	79 (38)	87 (41)	95 (32)	97 (33)
Hypomagnesemia	61 (29)	5 (2)	47 (16)	6 (2)
Vomiting	59 (29)	62 (29)	82 (28)	84 (29)
Dermatitis acneiform	57 (28)	2 (1)	71 (24)	1 (0)
Anorexia	56 (27)	34 (16)	71 (24)	49 (17)
Abdominal pain	54 (26)	41 (19)	50 (17)	61 (21)
Stomatitis	54 (26)	28 (13)	62 (21)	38 (13)
Alopecia	51 (25)	48 (23)	54 (18)	78 (27)
Constipation	49 (24)	46 (22)	75 (25)	65 (22)
Dry skin	46 (22)	11 (5)	65 (22)	10 (3)
Paronychia	46 (22)	0	40 (13)	2 (1)
Pruritus	42 (20)	9 (4)	47 (16)	8 (3)
Pyrexia	41 (20)	42 (20)	61 (20)	49 (17)
Skin fissures	41 (20)	1 (0)	41 (14)	2 (1)
Mucosal inflammation	39 (19)	30 (14)	67 (22)	36 (12)
Anemia	37 (18)	49 (23)	36 (12)	45 (15)

AE=adverse event; FOLFIRI=fluorouracil, leucovorin, and irinotecan.

FIGURE LEGENDS

- Figure 1.** PFS and OS among patients with wild-type *KRAS* exon 2 and among patients with wild-type extended *RAS*. FOLFIRI=fluorouracil, leucovorin, and irinotecan; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; WT=wild-type.
- Figure 2.** PFS and OS among patients with wild-type *KRAS* exon 2 and another *RAS* mutation and among patients with any *RAS* mutation. FOLFIRI=fluorouracil, leucovorin, and irinotecan; HR=hazard ratio; MT=mutated; OS=overall survival; PFS=progression-free survival; WT=wild-type.
- Figure 3.** (A) Hazard ratios for PFS and OS for panitumumab plus FOLFIRI versus FOLFIRI alone by *KRAS* and *RAS* mutation status. (B) Hazard ratios for PFS and OS for wild-type and mutated *BRAF*. *PFS by central assessment. FOLFIRI=fluorouracil, leucovorin, and irinotecan; HR=hazard ratio; MT=mutated; OS=overall survival; PFS=progression-free survival; Pmab=panitumumab; WT=wild-type.

Figure 4 (A) Mean (95% CI) percentage change from baseline in sum of longest diameters for patients with wild-type *RAS*. (B) Objective response rate, duration of response, depth of response, and association between early tumor shrinkage and PFS/OS in patients with wild-type *RAS*. Duration of response was defined as the time from first confirmed objective response to disease progression per RECIST. *Percent tumor shrinkage from baseline; positive values indicate reduction in tumor size, whereas negative values indicate an increase in tumor size; *P*-value for difference between arms determined by Wilcoxon test.

[†]Evaluated for patients with baseline and week 8 tumor measurements; *P*-value for difference between groups within the contingency table determined by Fisher's exact test. FOLFIRI=fluorouracil, leucovorin, and irinotecan.

Figure 1

A

Primary Analysis Wild-type *KRAS* exon 2

	Events n/N (%)	Median months (95% CI)
Panitumumab + FOLFIRI	178/303 (59)	5.9 (5.5, 6.7)
FOLFIRI	203/294 (69)	3.9 (3.7, 5.3)

Ascertainment rate: 91%

B

Primary Analysis Wild-type *RAS*

	Events n/N (%)	Median months (95% CI)
Panitumumab + FOLFIRI	120/208 (58)	6.4 (5.5, 7.4)
FOLFIRI	139/213 (65)	4.6 (3.7, 5.6)

Ascertainment rate: 85%

C

Primary Analysis Wild-type *KRAS* exon 2

	Events n/N (%)	Median months (95% CI)
Panitumumab + FOLFIRI	200/303 (66)	14.5 (13.0, 16.0)
FOLFIRI	207/294 (70)	12.5 (11.2, 14.2)

Ascertainment rate: 91%

D

Primary Analysis Wild-type *RAS*

	Events n/N (%)	Median months (95% CI)
Panitumumab + FOLFIRI	130/208 (63)	16.2 (14.5, 19.7)
FOLFIRI	143/213 (67)	13.9 (11.9, 16.0)

Ascertainment rate: 85%

Figure 2

A

Wild-type *KRAS* exon 2 / Mutated Other *RAS*

Panitumumab Plus FOLFIRI	61	55	34	30	19	15	9	6	3	2	0	0	0	0
FOLFIRI alone	46	44	32	28	17	16	8	7	6	4	1	1	1	0

	Events n/N (%)	Median months (95% CI)
— Panitumumab + FOLFIRI	37/61 (61)	3.7 (2.3, 5.8)
--- FOLFIRI	40/46 (87)	3.7 (2.8, 5.1)

B

Mutated *RAS*

Panitumumab Plus FOLFIRI	299	273	199	175	119	104	63	51	39	30	19	12	9	5	2	1	0	0
FOLFIRI alone	294	264	178	154	105	94	58	51	31	23	11	7	3	2	1	1	1	0

	Events n/N (%)	Median months (95% CI)
— Panitumumab + FOLFIRI	199/299 (67)	4.8 (3.7, 5.5)
--- FOLFIRI	201/294 (68)	4.0 (3.6, 5.5)

C

Wild-type *KRAS* exon 2 / Mutated Other *RAS*

Panitumumab Plus FOLFIRI	61	57	49	44	37	32	27	21	15	12	6	3	1	1	1	1	0
FOLFIRI alone	46	42	37	32	26	21	19	10	9	7	6	5	4	3	2	2	0

	Events n/N (%)	Median months (95% CI)
— Panitumumab + FOLFIRI	43/61 (70)	11.3 (8.3, 13.1)
--- FOLFIRI	38/46 (83)	9.2 (7.0, 12.9)

D

Mutated *RAS*

Panitumumab Plus FOLFIRI	299	281	256	228	190	168	139	111	80	57	40	29	20	10	5	2	0
FOLFIRI alone	294	277	240	221	185	160	127	92	70	50	39	32	20	11	7	4	0

	Events n/N (%)	Median months (95% CI)
— Panitumumab + FOLFIRI	224/299 (75)	11.8 (10.4, 13.1)
--- FOLFIRI	231/294 (79)	11.1 (10.2, 12.4)

Figure 3

A

B

Figure 4

A

Panitumumab + FOLFIRI	203	181	143	112	77	63	42	28
FOLFIRI alone	204	180	126	88	53	33	20	12

B

	Panitumumab + FOLFIRI		FOLFIRI Alone	
Wild-type <i>KRAS</i> exon 2, n	297		285	
Objective response rate, n (%)	105 (35)		28 (10)	
95% CI	30–41		7–14	
Median duration of response, mo (95% CI)	7.6 (6.7–9.4)		6.6 (5.7–10.4)	
Wild-type <i>RAS</i> , n	204		207	
Objective response rate, n (%)	83 (41)		21 (10)	
95% CI	34–48		6–15	
Median duration of response, mo (95% CI)	7.7 (6.7–9.9)		9.3 (6.1–12.8)	
Depth of response*, n	177		172	
Median (interquartile range) tumor shrinkage, %	37 (13–56)		10 (–5–26)	
<i>P</i>	<0.0001			
Tumor shrinkage within first 8 weeks for wild-type <i>RAS</i> patients†	<30%	≥30%	<30%	≥30%
Patients, n (%)	114 (63)	67 (37)	168 (93)	12 (7)
<i>P</i>	<0.0001			

Clinical Cancer Research

Analysis of KRAS/NRAS Mutations in a Phase 3 Study of Panitumumab With FOLFIRI Compared With FOLFIRI Alone as Second-Line Treatment for Metastatic Colorectal Cancer

Marc Peeters, Kelly Oliner, Timothy J Price, et al.

Clin Cancer Res Published OnlineFirst September 4, 2015.

Updated version	Access the most recent version of this article at: doi: 10.1158/1078-0432.CCR-15-0526
Author Manuscript	Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org .
Permissions	To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org .