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

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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 III 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 (HR) 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% confidence interval [CI], 0.54–0.91); P = 0.007 vs. 0.73 (95% CI, 0.59–0.90); P = 0.004; OS HR, 0.81 (95% CI, 0.63–1.03); P = 0.08 vs. 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 with the wild-type KRAS exon 2 population. These findings support RAS testing for patients with mCRC.

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See related commentary by Salazar and Ciardiello, p. 5415

Introduction

The epidermal growth factor receptor (EGFR) is overexpressed in colorectal cancer (1), and plays an important role in cellular proliferation and metastasis in metastatic colorectal cancer (mCRC; ref. 2). The RAS family of small GTPases plays a central role in signaling downstream from the EGFR (3). Activating mutations in RAS can result in persistent signaling in the absence of ligand binding to the EGFR, and resistance to therapy with the anti-EGFR monoclonal antibodies panitumumab and cetuximab (3, 4). KRAS and NRAS activation result in different patterns of intracellular signaling, and mutations in KRAS and NRAS arise in different cellular contexts and are not functionally redundant (5). KRAS exon 2 mutations are an established predictive biomarker 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 III 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.

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 and LightCycler; Roche Diagnostics), DNA for RAS analysis was extracted from banked formalin-fixed paraffin-embedded patient tumor specimens (DNA Extraction Mini Kit; Qiagen). Specimens containing <50% tumor area were macerodissected.

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

### Results

#### Patients

Among the 1,186 patients randomized, RAS status was ascertained in 1,014 (85%) patients (Supplementary Fig. S1; Supplementary 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 or 4 and 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 1,186 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; ref. 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; Fig. 1A) in patients with wild-type KRAS exon 2 compared with 0.70 (95% CI, 0.54–0.91; P = 0.007; Fig. 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 was 0.83 (95% CI, 0.95–1.01; P = 0.42; Fig. 2A). Among patients with any RAS mutation, the HR for panitumumab plus FOLFIRI versus FOLFIRI alone was 0.86 (95% CI, 0.71–1.05; P = 0.14; Fig. 2B). Findings were similar for OS (Fig. 2C and D) in patients with any RAS mutation. Among patients with mutated KRAS exon 2, the HR for panitumumab plus FOLFIRI versus FOLFIRI alone was 0.85 (95% CI, 0.68–1.06); for OS the HR was 0.94 (95% CI, 0.76–1.15; Fig. 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).

### Table 1. Baseline demographic and clinical characteristics by RAS status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Wild-type RAS</th>
<th>Mutated RAS</th>
<th>Panitumumab alone (N = 299)</th>
<th>FOLFIRI alone (N = 294)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>136 (65)</td>
<td>140 (66)</td>
<td>165 (55)</td>
<td>177 (60)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>60 (28–81)</td>
<td>60 (33–85)</td>
<td>61 (29–84)</td>
<td>64 (29–86)</td>
</tr>
<tr>
<td>Race, white</td>
<td>203 (98)</td>
<td>202 (95)</td>
<td>284 (95)</td>
<td>283 (96)</td>
</tr>
<tr>
<td>ECOG performance status 0–1</td>
<td>196 (94)</td>
<td>198 (93)</td>
<td>284 (95)</td>
<td>275 (94)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western Europe, Canada, Australia</td>
<td>136 (65)</td>
<td>139 (65)</td>
<td>184 (62)</td>
<td>182 (62)</td>
</tr>
<tr>
<td>Rest of the world</td>
<td>72 (35)</td>
<td>74 (35)</td>
<td>115 (38)</td>
<td>112 (38)</td>
</tr>
<tr>
<td>Primary tumor type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>119 (57)</td>
<td>148 (69)</td>
<td>201 (67)</td>
<td>186 (63)</td>
</tr>
<tr>
<td>Rectal</td>
<td>89 (43)</td>
<td>65 (31)</td>
<td>98 (33)</td>
<td>108 (37)</td>
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<tr>
<td>Sites of metastatic disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver only</td>
<td>37 (18)</td>
<td>49 (23)</td>
<td>46 (15)</td>
<td>40 (14)</td>
</tr>
<tr>
<td>Liver plus other</td>
<td>140 (67)</td>
<td>134 (63)</td>
<td>215 (71)</td>
<td>204 (69)</td>
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<tr>
<td>Subsequent therapies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>21 (10)</td>
<td>25 (12)</td>
<td>39 (13)</td>
<td>30 (10)</td>
</tr>
<tr>
<td>EGFR mAb</td>
<td>21 (10)</td>
<td>68 (32)</td>
<td>24 (8)</td>
<td>91 (31)</td>
</tr>
<tr>
<td>Oxaliplatin, irinotecan, or FU</td>
<td>93 (45)</td>
<td>107 (50)</td>
<td>138 (46)</td>
<td>151 (51)</td>
</tr>
</tbody>
</table>

NOTE: Data are presented as n (%) unless otherwise noted.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EU, European Union; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FU, fluorouracil; mAb, monoclonal antibody.
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.
and the HR among patients with wild-type RAS and mutated BRAF was 0.64 (95% CI, 0.32–1.28; 4.7 months vs. 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 (Fig. 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 (Fig. 4 and Supplementary Table S2). ORR was similar for panitumumab plus FOLFIRI and FOLFIRI alone among patients with any RAS mutation (15% vs. 13%; Supplementary Table S1) and for patients with mutated KRAS exon 2 (13% vs. 14%, respectively). Median duration of response among RAS wild-type patients was 9.3 months for panitumumab plus FOLFIRI versus 7.7 months for FOLFIRI alone (Fig. 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 (Fig. 4). Depth of response (assessed by median percentage tumor shrinkage) was greater with panitumumab plus FOLFIRI versus FOLFIRI alone (37% vs. 10%; P < 0.0001; Fig. 4). Similarly, a greater proportion of wild-type RAS patients receiving panitumumab plus FOLFIRI had a ≥30% change in sum of longest diameter of target lesions within the
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, rash, nausea, 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, 24% 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 patients with mCRC 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 months vs. 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 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 vs. FOLFOX4 as first-line therapy; ref. 14), a prospective RAS analysis of the PEAK study (which evaluated panitumumab or bevacizumab plus FOLFOX as first-line therapy; ref. 15), and the original hypothesis-generating analysis of the 408 study (which evaluated panitumumab monotherapy in patients with chemotherapy-refractory disease; refs. 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 neo-adjuvant 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, 69%; 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% to 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 United Kingdom (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; ref. 40). Depth of tumor response was significantly greater and likelihood of achieving a ≥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

Table 2. Summary of adverse events by RAS status

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Panitumumab + FOLFIRI (N = 207)</th>
<th>FOLFIRI alone (N = 213)</th>
<th>Panitumumab + FOLFIRI (N = 298)</th>
<th>FOLFIRI alone (N = 292)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>207 (100)</td>
<td>211 (99)</td>
<td>296 (99)</td>
<td>281 (96)</td>
</tr>
<tr>
<td>Worst grade of 3</td>
<td>114 (55)</td>
<td>78 (37)</td>
<td>137 (46)</td>
<td>100 (34)</td>
</tr>
<tr>
<td>Worst grade of 4</td>
<td>41 (20)</td>
<td>35 (16)</td>
<td>50 (17)</td>
<td>44 (15)</td>
</tr>
<tr>
<td>Worst grade of 5</td>
<td>8 (4)</td>
<td>13 (6)</td>
<td>21 (7)</td>
<td>17 (6)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>94 (45)</td>
<td>67 (31)</td>
<td>110 (37)</td>
<td>90 (31)</td>
</tr>
<tr>
<td>AEs occurring in ≥20% of patients in either treatment arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>142 (69)</td>
<td>122 (57)</td>
<td>181 (61)</td>
<td>167 (57)</td>
</tr>
<tr>
<td>Rash</td>
<td>111 (54)</td>
<td>17 (8)</td>
<td>167 (56)</td>
<td>16 (6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>104 (50)</td>
<td>106 (50)</td>
<td>142 (48)</td>
<td>129 (44)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>81 (39)</td>
<td>69 (32)</td>
<td>102 (34)</td>
<td>104 (36)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>79 (38)</td>
<td>87 (41)</td>
<td>95 (32)</td>
<td>97 (33)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>61 (29)</td>
<td>5 (2)</td>
<td>47 (16)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>59 (29)</td>
<td>62 (29)</td>
<td>82 (28)</td>
<td>84 (29)</td>
</tr>
<tr>
<td>Dermatitis acriform</td>
<td>57 (28)</td>
<td>2 (1)</td>
<td>71 (24)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>56 (27)</td>
<td>34 (16)</td>
<td>71 (24)</td>
<td>49 (17)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>54 (26)</td>
<td>41 (19)</td>
<td>50 (17)</td>
<td>61 (21)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>54 (26)</td>
<td>28 (13)</td>
<td>62 (21)</td>
<td>38 (13)</td>
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<tr>
<td>Alopecia</td>
<td>51 (25)</td>
<td>48 (23)</td>
<td>54 (18)</td>
<td>78 (27)</td>
</tr>
<tr>
<td>Constipation</td>
<td>49 (24)</td>
<td>46 (22)</td>
<td>75 (25)</td>
<td>65 (22)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>46 (22)</td>
<td>11 (5)</td>
<td>65 (22)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>46 (22)</td>
<td>0</td>
<td>40 (13)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>42 (20)</td>
<td>9 (4)</td>
<td>47 (16)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>41 (20)</td>
<td>42 (20)</td>
<td>61 (20)</td>
<td>49 (17)</td>
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<tr>
<td>Skin fissures</td>
<td>41 (20)</td>
<td>1 (&lt;1)</td>
<td>41 (14)</td>
<td>2 (1)</td>
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<tr>
<td>Mucosal inflammation</td>
<td>39 (19)</td>
<td>30 (14)</td>
<td>67 (22)</td>
<td>36 (12)</td>
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<tr>
<td>Anemia</td>
<td>37 (18)</td>
<td>49 (23)</td>
<td>36 (12)</td>
<td>45 (15)</td>
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</table>

Abbreviations: AE, adverse event; FOLFIRI, fluorouracil, leucovorin, and irinotecan.
Panitumumab plus FOLFIRI and RAS Mutations in Colorectal Cancer

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Authors’ Contributions

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Other (investigator, national coordinator, and member of the study steering committee): F. Lordick

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References


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