Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer


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Background: The Panitumumab Randomized trial In combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy (PRIME) demonstrated that panitumumab–FOLFOX4 significantly improved progression-free survival (PFS) versus FOLFOX4 as first-line treatment of wild-type (WT) KRAS metastatic colorectal cancer (mCRC), the primary end point of the study.

Patients and methods: Patients were randomized 1:1 to panitumumab 6.0 mg/kg every 2 weeks + FOLFOX4 (arm 1) or FOLFOX4 (arm 2). This prespecified final descriptive analysis of efficacy and safety was planned for 30 months after the last patient was enrolled.

Results: A total of 1183 patients were randomized. Median PFS for WT KRAS mCRC was 10.0 months [95% confidence interval (CI) 9.3–11.4 months] for arm 1 and 8.6 months (95% CI 7.5–9.5 months) for arm 2; hazard ratio (HR) = 0.80; 95% CI 0.67–0.95; P = 0.01. Median overall survival (OS) for WT KRAS mCRC was 23.9 months (95% CI 20.3–27.7 months) for arm 1 and 19.7 months (95% CI 17.6–22.7 months) for arm 2; HR = 0.88; 95% CI 0.73–1.06; P = 0.17 (68% OS events). An exploratory analysis of updated survival (>80% OS events) was carried out which demonstrated improvement in OS; HR = 0.83; 95% CI 0.70–0.98; P = 0.03 for WT KRAS mCRC. The adverse event profile was consistent with the primary analysis.

Conclusions: In WT KRAS mCRC, PFS was improved, objective response was higher, and there was a trend toward improved OS with panitumumab–FOLFOX4, with significant improvement in OS observed in an updated analysis of survival in patients with WT KRAS mCRC treated with panitumumab + FOLFOX4 versus FOLFOX4 alone (P = 0.03). These data
support a positive benefit-risk profile for panitumumab–FOLFOX4 for patients with previously untreated WT KRAS mCRC. KRAS testing is critical to select appropriate patients for treatment with panitumumab.

Key words: antibody, chemotherapy, FOLFOX, metastatic colorectal cancer, panitumumab

introduction

Colorectal cancer (CRC) is the third most common cancer in the world [1]. Panitumumab is a fully human monoclonal antibody that targets the epidermal growth factor receptor (EGFR) and has shown antitumor activity across multiple lines of therapy for nonmutated KRAS metastatic colorectal cancer (mCRC) [2–4]. KRAS is a well-established biomarker predictive of anti-EGFR monoclonal antibody efficacy in patients with mCRC [2, 5–9].

Results from the primary analysis of the Panitumumab Randomized trial In combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy (PRIME), a global, phase III trial that prospectively investigated panitumumab in combination with FOLFOX4 chemotherapy as first-line treatment of patients with mCRC, met the primary end point: panitumumab–FOLFOX4 significantly improved progression-free survival (PFS) for patients with previously untreated WT KRAS mCRC versus patients that received FOLFOX4 alone [3]. This article reports the results of the prespecified final descriptive analysis of PFS and OS that was planned for 30 months after the last patient was enrolled. For the primary PFS analysis reported previously, median follow-up time from randomization to data cutoff for all patients in the WT KRAS stratum was 55.0 weeks (range, 0–109 weeks) and was 80.0 weeks (range, 0–201 weeks) in the final analysis reported here.

patients and methods

patients, study design, and treatment schedule

Eligible patients were ≥18 years old with previously untreated metastatic adenocarcinoma of the colon or rectum and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2. Fluourouracil-based adjuvant chemotherapy was allowed if disease recurrence occurred 6 months after completion; however, prior oxaliplatin was not allowed. At least one measurable lesion (≥20 mm) was required. Paraffin-embedded tumor tissue from the primary tumor or metastasis had to be available for central biomarker analyses. Patients were randomized in a 1:1 ratio to receive either panitumumab–FOLFOX4 or FOLFOX4 alone stratified by geographic region (Western Europe, Canada, and Australia versus rest of world) and ECOG PS (0 or 1 versus 2). Panitumumab was administered at 6 mg/kg every 2 weeks (Q2W) on day 1 before FOLFOX4 chemotherapy without premedication.

Objective tumor response was evaluated by blinded central radiology review using modified Response Evaluation Criteria in Solid Tumors every 8 weeks until progression, with confirmation as previously described [3, 10]. Resection of metastases was reported as either complete or partial; the status of the surgical margins was not required to be captured. Patients were followed for safety 30 days after the last study drug administration and for survival every 3 months. Adverse events (AEs) were graded using the Common Terminology Criteria for Adverse Events v3.0 with modifications for specific skin- and nail-related toxicities. Safety results were summarized as previously described [3].

The study protocol was approved by the independent ethics committees, and signed informed consent was obtained for each patient.

KRAS and antibody testing

KRAS testing was carried out in a blinded central laboratory (HistoGeneX, Antwerp, Belgium) using allele-specific polymerase chain reaction (DXs, Manchester, UK), and serum anti-panitumumab antibodies were analyzed as previously described [3].

statistical analysis

The primary objective of this study was to assess the treatment effect of the addition of panitumumab to FOLFOX4 on PFS (blinded central radiology review) as initial therapy for mCRC in patients with WT KRAS tumors and also in patients with MT KRAS tumors. Originally designed to test the treatment effect in all randomized patients (n = 900), the study was amended to compare PFS (primary end point) with OS (secondary end point) according to KRAS status before any efficacy analyses were carried out.

After the primary analysis, study data continued to be collected for patients remaining on study. All patients were followed for survival for up to ~30 months after the last patient was randomized. At that time, the final analysis of efficacy and safety was carried out. No formal hypothesis testing of efficacy or safety end points was planned in this final analysis, but descriptive estimates were to be updated to assess the overall relative treatment profile. Treatment effects on PFS and OS were estimated using stratified Cox proportional hazards models and the Kaplan–Meier method. An exact 95% confidence interval (CI) was estimated for a stratified odds ratio for objective response rate (ORR). In addition, an updated exploratory analysis of OS when >80% of patients in both the WT and MT KRAS exon 2 subgroups had an OS event was conducted, representing the most mature estimate of OS in the study [11]. Unless otherwise indicated, analyses presented in this manuscript were conducted using the prespecified final analysis of the study. The randomization stratification factors were used for the stratified analyses.

Skin toxicity was defined as any treatment-emergent adverse event indicative of a skin disorder, representing a composite category of adverse event terms including but not limited to rash, dermatitis acniform, pruritus, dry skin, skin fissures, and erythema. Retrospective post-hoc analyses were carried out to determine the effect of skin toxicity on efficacy end points, including PFS (by central review) and OS. A stratified Cox proportional hazards model was used to examine the relationship between worst grade skin toxicity severity (grade 2–4; grade 0–1) and PFS/OS. ORR by central review and worst grade skin toxicity was provided.

A sensitivity analysis of PFS was conducted to account for late deaths. This analysis used a definition of PFS (disease progression or death after the first dose of study medication) that censored death events that occurred >60 days after the last tumor assessment or randomization date, whichever was later.

Patient-reported outcomes (PRO) were assessed using the EQ5D Health State Index Score and the EQ-5D Overall Health Rating every 4 weeks (+1 week) while patients were on study treatment, at the safety follow-up visit, and every 8 weeks after the safety visit but before disease progression [12]. PRO data were analyzed using a mixed-effect model repeated measure (MMRM) model to analyze longitudinal PRO data with missing values [13, 14]. Descriptive statistics by treatment arm were provided for each prespecified time of assessment. All statistical tests were carried out at a
two-sided significance level of 5% without adjustment for multiple comparisons and are regarded as descriptive.

**results**

**patients**

As previously described, 1183 patients were enrolled and randomized in this study [3]. Of these, 1096 (93%) had available KRAS status: 656 (60%) WT and 440 (40%) MT. Baseline demographics and disease characteristics were generally balanced within each treatment arm and KRAS stratum (Table 1). For this final analysis, median follow-up time from random assignment to date of last contact for patients with WT KRAS mCRC was 89 weeks (range, 0–199 weeks) for those receiving panitumumab–FOLFOX4 and 74 weeks (range, 0–201 weeks) for those receiving FOLFOX4. For patients with MT KRAS mCRC, median follow-up time was 61 weeks (range, 0–188 weeks) for those receiving panitumumab–FOLFOX4 and 70 weeks (range, 1–188 weeks) for those receiving FOLFOX4.

**efficacy**

*progression-free survival.* A statistically significant improvement in PFS was observed in patients with WT KRAS mCRC receiving panitumumab–FOLFOX4 versus FOLFOX4 alone (hazard ratio (HR) = 0.80; 95% CI 0.67–0.95; P = 0.01; Figure 1A), confirming the primary analysis; median PFS was 10.0 months (95% CI 9.3–11.4 months) versus 8.6 months (95% CI 7.5–9.5 months), respectively.

Consistent with the primary analysis, in patients with MT KRAS mCRC, PFS was confirmed to be inferior in this final analysis in patients receiving panitumumab–FOLFOX4 versus FOLFOX4 alone (HR = 1.27; 95% CI 1.04–1.55; P = 0.02; Figure 1B); median PFS was 7.4 months (95% CI 6.9–8.1 months) versus 9.2 months (95% CI 8.1–9.9 months), respectively.

The treatment effect of panitumumab in patients with WT KRAS mCRC mostly favored the panitumumab–FOLFOX4 arm across subpopulations defined by baseline covariates (Figure 1C), with significant differences observed using the Quantitative Interaction Test in patients with ECOG 0/1 versus ECOG 2 (P = 0.02) and in patients age <65 years versus age ≥65 years (P = 0.02).

For the sensitivity analysis of PFS with censoring deaths within 28 days after the last dose of study drug in patients with WT KRAS mCRC, the estimated HR was 0.77 (95% CI 0.64–0.93) and the stratified log-rank test P value was 0.008. Median PFS in this analysis was 10.1 months (95% CI 9.3–11.4) in the panitumumab–FOLFOX4 arm and 9.2 months (95% CI 7.5–9.9 months) in the FOLFOX alone arm. In patients with MT KRAS mCRC, the estimated HR was 1.27 (95% CI 1.01–1.60), and the

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**Table 1. Demographics and disease characteristics—WT and MT KRAS mCRC**

<table>
<thead>
<tr>
<th></th>
<th>WT KRAS Panitumumab–FOLFOX4 (N = 325)</th>
<th>FOLFOX4 (N = 331)</th>
<th>MT KRAS Panitumumab–FOLFOX4 (N = 221)</th>
<th>FOLFOX4 (N = 219)</th>
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<tr>
<td>Sex, n (%)</td>
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<tr>
<td>Male</td>
<td>217 (67)</td>
<td>204 (62)</td>
<td>145 (66)</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Median (min, max)</td>
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<td>61 (24, 82)</td>
<td>63 (33, 83)</td>
<td>61 (27, 82)</td>
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<tr>
<td>Race, n (%)</td>
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<tr>
<td>White</td>
<td>296 (91)</td>
<td>307 (93)</td>
<td>196 (89)</td>
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<td>ECOG*, n (%)</td>
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<td>≥2</td>
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<td>Region, n (%)</td>
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<td>Western Europe, Canada, Australia</td>
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<td>186 (56)</td>
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<td>Colon</td>
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<td>Rectal</td>
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<td>Sites of metastatic disease, n (%)</td>
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<tr>
<td>Liver only</td>
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<td>57 (17)</td>
<td>33 (15)</td>
<td>36 (16)</td>
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<td>Liver + other</td>
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<td>227 (69)</td>
<td>155 (70)</td>
<td>159 (73)</td>
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<td>Other only</td>
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<td>47 (14)</td>
<td>31 (14)</td>
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<tr>
<td>1</td>
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<td>68 (21)</td>
<td>40 (18)</td>
<td>43 (20)</td>
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<td>2</td>
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<td>118 (36)</td>
<td>69 (31)</td>
<td>84 (38)</td>
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<td>145 (44)</td>
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<td>55 (17)</td>
<td>35 (16)</td>
<td>26 (12)</td>
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</table>

*One patient in the WT KRAS FOLFOX4 group had an unknown Eastern Cooperative Oncology Group (ECOG) performance status at baseline.
The stratified log-rank test P value was 0.040. Median PFS in this analysis was 7.4 months (95% CI 6.3–8.0 months) in the panitumumab–FOLFOX4 arm and 9.0 months (95% CI 7.7–9.6 months) in the FOLFOX4-alone arm.

For the sensitivity analysis of PFS with censoring deaths within 60 days after the last tumor assessment in patients with WT KRAS mCRC, the estimated HR was 0.77 (95% CI 0.63–0.92), and the stratified log-rank test P value was 0.005. Median PFS in this analysis was 10.0 months (95% CI 9.3–11.4 months) in the panitumumab–FOLFOX4 arm and 8.6 months (95% CI 7.5–9.5 months) in the FOLFOX4-alone arm.

Figure 1. (A) Kaplan–Meier plot of PFS (WT KRAS, Panitumumab–FOLFOX4 versus FOLFOX4 alone). (B) Kaplan–Meier plot of PFS (MT KRAS, Panitumumab–FOLFOX4 versus FOLFOX4 alone). (C) PFS Forest plot—WT KRAS efficacy analysis set.
PFS in this analysis was 9.9 months (95% CI 9.2–11.3 months) in the panitumumab–FOLFOX4 arm and 8.0 months (95% CI 7.5–9.4 months) in the FOLFOX alone arm. In patients with MT KRAS mCRC, the estimated HR was 1.32 (95% CI 1.05–1.65) and the stratified log-rank test P value was 0.016. Median PFS in this analysis was 7.3 months (95% CI 6.3–7.9 months) in the panitumumab–FOLFOX4 arm and 8.9 months (95% CI 7.6–9.4 months) in the FOLFOX4-alone arm.

**overall survival.** In patients with WT KRAS mCRC, median OS was 23.9 months (95% CI 20.3–27.7 months) for panitumumab–FOLFOX4 and 19.7 months (95% CI 17.6–22.7 months) for FOLFOX4. The OS HR was 0.88 (95% CI 0.73–1.06; P = 0.17), with a trend favoring the panitumumab–FOLFOX4 arm (Figure 2A).

In patients with MT KRAS mCRC, median OS was 15.5 months (95% CI 13.1–17.6 months) for panitumumab–FOLFOX4 and 19.2 months (95% CI 16.5–21.7 months) for FOLFOX4. The OS HR was 1.17 (95% CI 0.95–1.45; P = 0.14) favoring the FOLFOX4-alone arm (Figure 2B).

The consistency of the treatment effect on OS was examined by estimating an unadjusted Cox model HR within meaningful subsets defined by the baseline covariates (except covariates for EGFR staining and KRAS status; Figure S1). In the final analysis, the treatment effect favoring the panitumumab–FOLFOX arm in patients with WT KRAS mCRC was generally observed across subpopulations defined by baseline covariates.

Consistent results were observed in the updated OS analysis dataset (82% of all patients with an OS event), the most mature dataset of the PRIME study. In patients with WT KRAS mCRC, a statistically significant improvement in median OS of 23.8 months (95% CI 20.0–27.7 months) for panitumumab–FOLFOX4 versus 19.4 months (95% CI 17.4–22.6 months) for FOLFOX4 was observed (Figure 2C); the OS HR was 0.83 (95% CI 0.70–0.98; P = 0.03) [11]. In patients with MT KRAS mCRC, median OS was 15.5 months (95% CI 13.1–17.6 months) for panitumumab–FOLFOX4 and 19.2 months (95% CI 16.2–21.5 months) for FOLFOX4; the OS HR was 1.16 (95% CI 0.94–1.41; P = 0.16) favoring the FOLFOX4-alone arm [11].

**subsequent therapy**

Results for subsequent therapies are summarized in Table 2. In the WT KRAS subset, after study treatment, 12.9% of patients in the panitumumab–FOLFOX4 arm and 25.4% of patients in the FOLFOX4-alone arm received anti-EGFR-containing therapy; median time to anti-EGFR-containing therapy from random assignment was 21.5 months in the panitumumab–FOLFOX4 arm and 15.6 months in the FOLFOX4-alone arm. In this WT KRAS subset, after study treatment, 58.8% of patients in the panitumumab–FOLFOX4 arm and 64.7% of patients in the FOLFOX4-alone arm received chemotherapy; median time to...
subsequent chemotherapy from random assignment was 11.5 months in the panitumumab–FOLFOX4 arm and 10.0 months in the FOLFOX4-alone arm.

**objective response**

The ORR in patients with WT KRAS mCRC was 57% (95% CI 51.5–62.6) in the panitumumab–FOLFOX4 arm and 48% (95%
CI 42.0–53.1) in the FOLFOX4-alone arm (Table 3). The odds ratio (95% CI) was 1.47 (1.07–2.04) and \( P = 0.02 \). In patients with MT \( \text{KRAS} \) mCRC, the ORR was 40% (95% CI 33.4–46.9) for the panitumumab–FOLFOX4 arm and 41% (95% CI 34.1–47.7) for the FOLFOX4-alone arm. The odds ratio (95% CI) was 0.98 (0.65–1.47) and \( P = 0.98 \).

**resection**

The complete resection rate in patients with WT \( \text{KRAS} \) mCRC was 10% (31 of 325 patients) in the panitumumab–FOLFOX4 arm and 8% (25 of 331 patients) in the FOLFOX4-alone arm. In an analysis of patients with WT \( \text{KRAS} \) mCRC with baseline metastasis in the liver only \( (n = 118) \), the complete resection rate was 28% (95% CI 17.2–40.8) in the panitumumab–FOLFOX4 arm and 18% (95% CI 8.8–29.9) in the FOLFOX4-alone arm (supplementary Table S1, available at *Annals of Oncology* online).

**patient-reported quality of life**

In patients with WT \( \text{KRAS} \) mCRC, the compliance rate for the EQ-5D was 57%, and 45% of patients had missing data (similar proportions for both treatment arms). Given a minimal clinically important difference of 0.08 for the Health State Index score and 7 points for the Overall Health Rating, no statistically significant or clinically meaningful difference was observed between treatment arms (supplementary Table S2, available at *Annals of Oncology* online) \[15\].
patients with no or mild skin toxicity was observed, indicating skin-related adverse events had no detrimental effect on quality of life (supplementary Table S3, available at Annals of Oncology online).

safety

Grade 3/4 adverse events of interest are listed in Table 4 for all patients with WT or MT KRAS mCRC who received study drug. In patients with WT KRAS mCRC, consistent with the known safety profile of panitumumab, there was at least a 5% difference between the panitumumab–FOLFOX4 versus FOLFOX4-alone arms, respectively, for the following adverse events of interest: skin toxicity (37% versus 2%), diarrhea (18% versus 9%), hypokalemia (10% versus 5%), fatigue (10% versus 3%), mucositis (9% versus <1%), and hypomagnesemia (7% versus <1%). In patients with MT KRAS mCRC, there was at least a 5% difference between the panitumumab–FOLFOX4 versus FOLFOX4-alone arms for the following adverse events of interest: neutropenia (37% versus 48%), skin toxicity (31% versus 1%), diarrhea (20% versus 10%), hypokalemia (9% versus 4%), and hypomagnesemia (6% versus <1%). Adverse events leading to discontinuation of panitumumab therapy were reported in 61 (19%) patients with WT KRAS mCRC and 40 (18%) patients with MT KRAS mCRC. There were two (<1%) grade 3 investigator-reported panitumumab infusion reactions observed in patients with WT KRAS mCRC. No grade 4 or 5 infusion reactions were reported.

discussion

The final analysis of the PRIME study confirms the benefit of the addition of panitumumab to FOLFOX4 as first-line treatment of WT KRAS mCRC from the primary analysis [3]. The primary objective, significantly improved PFS for panitumumab–FOLFOX4, was met with an HR = 0.80 (P = 0.01). With
increased follow-up for overall survival (82% of OS events), the results observed were significantly in favor of the panitumumab arm in an updated exploratory analysis (HR = 0.83, \( P = 0.03 \)) [11]. ORR became significant in the final analysis (57% versus 48%; odds ratio = 1.47) with a descriptive \( P \) value of 0.02, compared with the primary analysis. Although definitive conclusions are limited by small numbers, the complete resection rate was higher in the panitumumab–FOLFOX4 arm for patients with liver-limited disease versus FOLFOX4 alone (28% versus 18%).

Patients with MT or unknown \( \text{KRAS} \) mCRC should not be considered for anti-EGFR antibody therapy. As previously reported in the primary analysis, patients with MT \( \text{KRAS} \) mCRC experienced a statistically significant detrimental effect with the addition of panitumumab to FOLFOX4. Given the similarly negative results observed in the OPUS trial with FOLFOX–cetuximab, these findings are indicative of a pharmacodynamic interaction between anti-EGFR agents and oxaliplatin in MT \( \text{KRAS} \) mCRC [16].

In addition to \( \text{KRAS} \) exon 2 (codons 12 and 13), activating mutations in \( \text{KRAS} \) exon 3 (at codons 59 and 61) and exon 4 (at codons 117 and 146); \( \text{NRAS} \) exon 2 (at codons 12 and 13), exon 3 (at codons 59 and 61), and exon 4 (at codons 117 and 146); have been demonstrated to be negative predictive biomarkers (collectively called \( \text{RAS} \)) for panitumumab treatment. A recently reported analysis of the PRIME trial showed that approximately 17% of patients with wild-type \( \text{KRAS} \) exon 2 status harbored a mutation in other \( \text{RAS} \) exons [11]. In the primary analysis, the expanded subgroup of patients with mutant \( \text{RAS} \) tumors demonstrated significantly shorter PFS (HR 1.31, 95% CI 1.01–1.60; \( P = 0.008 \)) and OS (HR 1.25, 95% CI 1.02–1.55; \( P = 0.03 \)) in the panitumumab–FOLFOX4 arm versus FOLFOX4 alone, indicating that patients with tumors harboring \( \text{RAS} \) mutations did not benefit from panitumumab treatment and may have been harmed. In the wild-type \( \text{RAS} \) group, an increase in OS of 5.8 (26.0 vs 20.2) months was noted (HR 0.78, 95% CI 0.62–0.99; \( P = 0.04 \)) with the addition of panitumumab to FOLFOX4 versus FOLFOX4 alone.

Skin toxicity is a class effect of anti-EGFR treatment of both monoclonal antibodies and tyrosine kinase inhibitors [20–23]. The development of skin toxicity under panitumumab treatment is an important parameter to consider as a clinical indicator of efficacy. Patients with WT \( \text{KRAS} \) mCRC who develop grade 2–4 skin toxicity have longer PFS and OS as well as a higher RR versus the overall patient population with WT \( \text{KRAS} \) treated with panitumumab–FOLFOX4 (Figures S2 and S3, available at Annals of Oncology online). Patients with WT \( \text{KRAS} \) mCRC who only develop grade 0–1 skin toxicity have shorter PFS and OS, as well as decreased RR with outcomes inferior to those obtained with FOLFOX4 alone in patients with WT \( \text{KRAS} \) mCRC. It is important to consider the limitations of the landmark methodology employed in the skin toxicity analysis, since patients are censored if they had progression or death within 28 days, potentially unmasking a prognostic effect. In addition, approximately one-third of patients under panitumumab treatment develop grade 2–4 skin toxicity later in the treatment course (four cycles and beyond) with efficacy comparable with outcomes with the early development of skin toxicity (Amgen data on file). An important question in the management of patients with WT \( \text{KRAS} \) mCRC who do not develop skin toxicity while receiving panitumumab is to consider discontinuation or dose escalation to induce skin toxicity, as reported with cetuximab [24]. Similarly, in patients with MT \( \text{KRAS} \) mCRC, skin toxicity was associated with differences in outcomes, although always inferior to FOLFOX4 alone, but generating a potential hypothesis on the interaction of the anti-EGFR antibody and the EGFR at the skin level.

The PRIME data showed a class effect, with increased on-target toxicities associated with EGFR inhibitors: skin toxicity, diarrhea, and hypomagnesemia and, despite these increased toxicities, patient-reported quality of life was not altered by the addition of panitumumab to FOLFOX4. Acute allergic reactions were rare, with an incidence of <1% for grade 3 (no grade 4 or 5) and no need for premedication.

The final analysis of the PRIME study confirms the efficacy of panitumumab on PFS and ORR in first-line treatment in patients with WT \( \text{KRAS} \) mCRC, with an acceptable safety profile, few allergic reactions, no need for premedication, and a convenient every 2-week administration schedule that can be administered with FOLFOX4. Patients receiving panitumumab–FOLFOX4 who develop skin toxicity grade 2–4 show consistently greater increases in PFS, OS, and ORR versus patients receiving chemotherapy alone. Panitumumab offers a new option for selected patients based on tumor \( \text{RAS} \) status.

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disclosure

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**references**