# Final results from a randomized phase 3 study of FOLFIRI ± panitumumab for second-line treatment of metastatic colorectal cancer


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## Abstract


**Background** The study 20050181 demonstrated significant improvements in progression-free survival (PFS), objective response, and a nonsignificant trend toward increased overall survival (OS) with panitumumab–FOLFIRI versus FOLFIRI alone for second-line wild-type (WT) *KRAS* metastatic colorectal cancer (mCRC). Updated long-term data from a prespecified descriptive analysis are reported.

**Patients and methods** Patients receiving one prior mCRC treatment were randomly assigned (1:1) to panitumumab (6.0 mg/kg)–FOLFIRI versus FOLFIRI every 2 weeks. Co-primary end points (PFS and OS) were prospectively analyzed by tumor *KRAS* status.

**Results** One thousand one hundred and eighty-six patients were randomly assigned. In patients with WT *KRAS* tumors, panitumumab–FOLFIRI significantly improved PFS versus FOLFIRI [median 6.7 versus 4.9 months; hazard ratio (HR) 0.82 [95% confidence interval (CI) 0.69, 0.97]; $P = 0.023$]. A trend toward longer OS was observed (median 14.5 versus 12.5 months; HR 0.92 [95% CI 0.78, 1.10]; $P = 0.37$). Response rates improved from 10% to 36% ($P < 0.0001$). From *post hoc* analyses in patients receiving prior oxaliplatin–bevacizumab, panitumumab–FOLFIRI improved PFS (median 6.4 versus 3.7 months; HR 0.58 [95% CI 0.37, 0.90]; $P = 0.014$). PFS and OS appeared longer for worst-grade skin toxicity of 2–4, versus 0–1 or FOLFIRI.

Safety results were as previously reported and consistent with the known toxicities with anti-epidermal growth factor receptor therapy.
**Conclusions** These data confirm the primary efficacy and safety findings of this trial and support panitumumab–FOLFIRI as a second-line treatment of WT *KRAS* mCRC.

## Key words

- antibody
- chemotherapy
- FOLFIRI
- metastatic colorectal cancer
- panitumumab

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## introduction

Colorectal cancer (CRC) is one of the most common cancer types with more than one million new cases diagnosed annually worldwide [1]. Approximately 25% of patients have metastases at diagnosis, and metastases eventually develop in ~50% of patients overall [2]. The addition of vascular endothelial growth factor A-targeted agents to 5-fluorouracil (5-FU)-based chemotherapy has improved outcomes in first- [3–5] and second-line [6] metastatic CRC (mCRC) settings. Epidermal growth factor receptor (EGFR)-targeted agents have also provided benefits when combined with chemotherapy in first- [7, 8] and second-line [9–11] settings and as monotherapy in chemorefractory disease [12, 13]. Tumor *KRAS* status predicts the efficacy of anti-EGFR agents in mCRC patients [14–16] and is a well-established biomarker for patient selection. Despite these advances, most of the patients eventually develop resistance and many ultimately die.
The study 20050181 is an open-label, randomized, global, phase 3 trial investigating the effect of adding panitumumab, an IgG2 class EGFR-targeted, monoclonal antibody, to FOLFIRI as the second-line treatment of patients with mCRC. In the primary analysis of this trial, patients with wild-type (WT) *KRAS* tumors receiving panitumumab had significantly improved progression-free survival (PFS) [9]. A nonsignificant trend toward improved overall survival (OS) was also observed. Here, we report updated efficacy and tolerability data from a prespecified descriptive analysis of this trial planned for 30 months after the last patient was enrolled.

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## methods

### patients, study design, and treatments

Detailed information regarding patient inclusion criteria, study design, and treatment schedules have been previously reported [9]. Briefly, patients who had progressed while receiving or within 6 months of one prior fluoropyrimidine-based mCRC therapy were randomly assigned (1:1) to panitumumab–FOLFIRI or FOLFIRI alone. Randomization was stratified by the Eastern Cooperative Oncology Group (ECOG) score (0–1 versus 2), prior oxaliplatin exposure (yes/no), and prior bevacizumab exposure (yes/no).
Patients received panitumumab (6 mg/kg; intravenous infusion) on day 1 of a 2-week cycle. This was initially administered over 60 ± 15 min before chemotherapy; if well tolerated, subsequent infusions were given over 30 ± 10 min. The FOLFIRI regimen comprised of irinotecan (180 mg/m$^2$ intravenous infusion over 90 min) on day 1 given sequentially or in parallel to leucovorin (400 mg/m$^2$intravenous infusion over 120 min), 5-FU (400 mg/m$^2$ intravenous bolus) on day 1, and 5-FU (2400–3000 mg/m$^2$ intravenous infusion over 46 h) on days 1 and 2. Treatments were administered biweekly until disease progression (PD), consent withdrawal, or unacceptable toxicity.
All patients with measurable disease at the baseline central review had their objective tumor response assessed by the investigator and blinded central radiology review using modified Response Evaluation Criteria in Solid Tumors (RECIST) every 8 weeks until PD [17]. Responses (complete or partial) were confirmed for ≥28 days

after response criteria were first met. Patients were followed for safety for ≥30 days after last study drug administration and for survival every 3 months. Patient-reported outcomes (PROs) were assessed using the EUROQOL EQ-5D Health State Index (HSI) Score and the EQ5-D Overall Health Rating (OHR) every 8 weeks until PD.
Adverse events (AEs) were collected throughout treatment and safety follow-up and graded according to National Cancer Institute Common Toxicity Criteria for AEs version 3.0, including modifications for certain skin and nail toxicities [18]. The study protocol was approved by independent ethics committees, and signed informed consent was obtained for each patient.

### *KRAS* mutation analysis

Tumor sampling, *KRAS* testing, and analyses by *KRAS* status were prospectively planned; *KRAS* testing was carried out in a blinded central laboratory using the DxS Test Kit (Manchester, UK) [9].

### statistical analyses

The two co-primary objectives: effect of panitumumab on PFS (by blinded central radiology review) and OS, were prospectively analyzed by tumor *KRAS* status. Other key end points included objective response rate (ORR), PROs, and tolerability, including AEs of interest (those known to be associated with EGFR inhibitors and/or FOLFIRI).
The primary analyses of PFS and OS were by the two-sided stratified log-rank test [stratified by ECOG performance status (0–1 versus 2), prior bevacizumab (yes/no), and prior oxaliplatin exposure (yes/no)] [9]. Secondary analyses used a Cox proportional hazard model, also stratifying PFS and OS by ECOG status, prior bevacizumab, and prior oxaliplatin exposure.
After the primary analysis [9], data continued to be collected for patients remaining on the study. All patients were followed for survival for ∼30 months after the last patient was enrolled. Post-PD therapy was also recorded. No formal hypothesis testing was planned for this final analysis, but descriptive estimates for key end points were to be updated. A sensitivity analysis of PFS was carried out, which excluded late death events occurring >60 days after last tumor assessment/randomization date, whichever was later [7]. A *post hoc* analysis of outcomes by the worst-grade skin toxicity (ST) experienced (0–1 versus 2–4) was carried out to investigate a possible correlation among patients alive without PD at day 28. A stratified Cox proportional hazards model was used to examine the relationship between worst-grade ST and PFS/OS.
A prespecified subgroup analysis of outcomes by prior oxaliplatin or oxaliplatin–bevacizumab exposure was also carried out. EQ-5D HSI Score and OHR were analyzed using the mixed-effect repeated-measure model.

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## results

### patients

Of the 1186 patients randomized, 1083 (91%) had tumor *KRAS* data [9]. The mean (SD) follow-up was 63.5 (47.3) weeks for patients with WT *KRAS* tumors. Demographics and disease characteristics were similar between treatments, as reported previously [9].
The actual median follow-up for patients with WT *KRAS* tumors was 59.0 (range 1–190) weeks for those receiving panitumumab–FOLFIRI and 45.5 (range 2–206) weeks for those receiving FOLFIRI alone. For patients with mutant (MT) *KRAS* tumors, actual median follow-up was 45.5 (range 1–180) weeks and 41.0 (1–179) weeks, respectively. The most common reason for ending treatment was PD, irrespective of tumor *KRAS* status.

### efficacy

#### *progression-free survival*

At the time of analysis, 93% of patients with WT *KRAS* tumors had progressed or died versus 96% of those with MT *KRAS* tumors, irrespective of treatment received. In patients with WT *KRAS* tumors, median PFS in the panitumumab–FOLFIRI versus FOLFIRI groups was 6.7 versus 4.9 months, respectively. The addition of panitumumab resulted in an 18% relative risk reduction for PD or death [hazard ratio (HR) 0.82 [95% confidence interval (CI) 0.69, 0.97]; $P = 0.023$] (Figure 1A). In patients with MT *KRAS* tumors, median PFS was similar between treatments (5.3 versus 5.4 months; HR 0.94 [95% CI 0.78, 1.14]; $P = 0.56$) (Figure 1B).

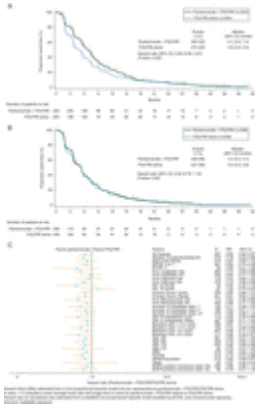

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**Figure 1.**
Kaplan–Meier plot of progression-free survival in patients with (A) wild-type (WT) *KRAS*tumors and (B) mutant (MT) *KRAS* tumors. (C) Progression-free survival Forest plot for patients with WT *KRAS* tumors.

In a sensitivity analysis of PFS censoring late deaths (occurring >60 days after last tumor assessment/randomization), median PFS (95% CI) was 6.7 (5.7, 7.4) versus 4.4 (3.7, 5.5) for patients with WT *KRAS* tumors receiving panitumumab–FOLFIRI versus FOLFIRI alone, respectively (HR 0.73 [95% CI: 0.60, 0.88]; $P = 0.001$). For patients with MT *KRAS* tumors, median PFS (95% CI) was 5.2 (3.9, 5.6) versus 5.3 (3.8, 5.6) for panitumumab–FOLFIRI versus FOLFIRI-alone groups, respectively (HR 0.89 [95% CI: 0.72, 1.1]; $P = 0.30$).
In the WT *KRAS* group, PFS in subgroups defined by baseline covariates consistently favored panitumumab–FOLFIRI versus FOLFIRI alone (Figure 1C). EGFR status by immunohistochemistry appeared to have a little impact on PFS (quantitative interaction test *P*-value: 0.67).

### *overall survival*

At the time of analysis, 88% versus 87% of patients with WT *KRAS* tumors had died in the panitumumab–FOLFIRI versus FOLFIRI alone groups, respectively; in patients with MT *KRAS* tumors, 93% versus 91%, respectively, had died. In the WT *KRAS* population, median OS was 14.5 versus 12.5 months in patients receiving panitumumab–FOLFIRI versus FOLFIRI alone, respectively. This equates to an 8% relative risk reduction for death (HR 0.92 [95% CI 0.78, 1.10]; $P = 0.37$), which did not, however, reach statistical significance (Figure 2A). OS was similar between treatments in patients with MT *KRAS* tumors (difference: 0.7 months; HR 0.93 [0.77, 1.13]; $P = 0.48$) (Figure 2B), suggesting that overall, panitumumab had no detrimental effects with respect to OS when combined with FOLFIRI in these patients.

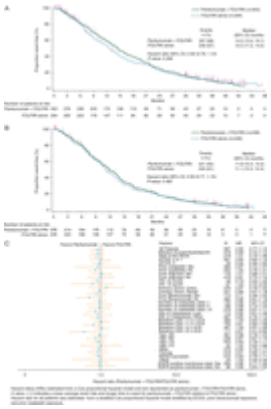

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**Figure 2.**
Kaplan–Meier plots of overall survival (OS) in patients with (A) WT *KRAS* tumors and (B) MT *KRAS* tumors. (C) OS Forest plot for patients with WT *KRAS* tumors.

The OS results may be confounded by the high proportion of patients receiving post-study anti-EGFR therapy (Table 1). Overall, fewer patients receiving panitumumab–FOLFIRI (12%) had subsequent anti-EGFR therapy compared with the FOLFIRI-alone arm (34%); median time to subsequent EGFR therapy was 12.4 versus 7.9 months, respectively. For patients with MT *KRAS* tumors, 9% of those receiving panitumumab–FOLFIRI and 32% of those receiving FOLFIRI received post-study EGFR therapy.

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**Table 1.**
Subsequent anti-cancer therapy by tumor *KRAS* status

In patients with WT *KRAS* tumors receiving panitumumab–FOLFIRI, a nonsignificant trend toward improved OS was observed for most patient subgroups (Figure 2C). EGFR status by immunohistochemistry appeared to have a little impact on OS (quantitative interaction test *P*-value: 0.97).

### *objective response*

The addition of panitumumab to FOLFIRI significantly improved ORR in patients with WT *KRAS* tumors (36% versus 10%; odds ratio 5.50; 95% CI 3.32, 8.87; $P < 0.0001$); there was no evidence of benefit in the MT *KRAS* group (13% versus 15%; odds ratio 0.93; 95% CI 0.53, 1.63; $P = 0.89$) (Table 2).

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**Table 2.**
Objective response by tumor *KRAS* status (central radiology review)

### *efficacy outcomes by skin toxicity severity*

Patients alive without PD at day 28 were included in the analyses of efficacy by ST. Median time to worst ST was 28.0 (range 0–587) days in patients with WT *KRAS* tumors. Median time to first grade 2+ ST was 15.5 (Q1, Q3 range: 7.0, 47.5) days in the panitumumab–FOLFIRI arm. In general, baseline characteristics in patients with worst-grade ST of 0–1 and 2–4 during panitumumab–FOLFIRI treatment were similar to those receiving FOLFIRI alone (supplementary Table S1, available at *Annals of Oncology* online).
In patients with WT *KRAS* tumors, those receiving panitumumab–FOLFIRI experiencing a worst-grade ST of 2–4 had longer PFS (median 7.4 versus 5.1 months; HR 0.72 [95% CI 0.60, 0.87]; $P = 0.0006$) than those receiving FOLFIRI alone (Figure 3 and Table 3). Patients with WT *KRAS* tumors receiving panitumumab–FOLFIRI experiencing a worst-grade ST of 0–1 had similar PFS than those receiving FOLFIRI alone (median 4.0 versus 5.1 months; HR 1.15 [95% CI 0.89, 1.48]; $P = 0.28$).

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**Table 3.**
Efficacy summary in patients with WT *KRAS* tumors, by worst-grade skin toxicity

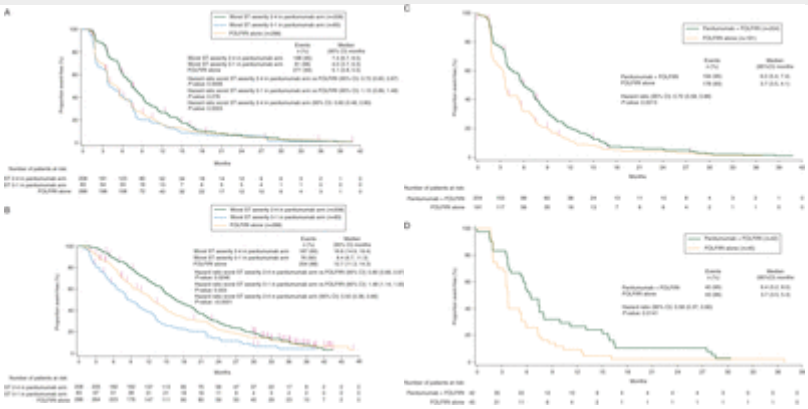

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**Figure 3.**
Kaplan–Meier plots for patients with WT *KRAS* tumors. (A) Progression-free survival (PFS) by worst-grade skin toxicity (ST). (B) OS by worst-grade ST. (C) PFS in patients who had received prior oxaliplatin. (D) PFS in patients who had received prior oxaliplatin–bevacizumab.

Similarly, in patients with WT *KRAS* tumors receiving panitumumab–FOLFIRI, those experiencing a worst-grade ST of 2–4 had longer OS (median 16.6 versus 12.7 months; HR 0.80 [95% CI 0.66, 0.97]; $P = 0.025$) than those receiving FOLFIRI alone (supplementary Figure S1, available at *Annals of Oncology* online; Table 3). Patients with WT *KRAS* tumors receiving panitumumab–FOLFIRI experiencing a worst-grade ST of 0–1 had shorter OS than those receiving FOLFIRI alone (median 8.4 versus 12.7 months; HR 1.48 [95% CI 1.14, 1.93]; $P = 0.003$). An ORR was 43% (95% CI 36, 50) in patients with WT *KRAS* mCRC receiving panitumumab–FOLFIRI experiencing a worst-grade ST of 2–4 ($n = 202$); in patients experiencing a worst-grade ST of 0–1 ($n = 83$), the ORR was 24% (95% CI 15, 35).

#### *efficacy outcomes by prior therapy*

In general, baseline characteristics in patients receiving panitumumab–FOLFIRI or FOLFIRI alone were similar, irrespective of whether prior oxaliplatin or oxaliplatin–bevacizumab was received. In patients with WT *KRAS* tumors receiving panitumumab–FOLFIRI, those who had received prior oxaliplatin (6.0 versus 3.7 months; HR 0.72 [95% CI 0.58, 0.88]; $P = 0.001$) or oxaliplatin–bevacizumab (6.4 versus 3.7 months; HR 0.58 [95% CI 0.37, 0.90]; $P = 0.014$) demonstrated statistically significant improvements in median PFS compared with those receiving FOLFIRI alone (Figure 3 and supplementary Table S2, available at *Annals of Oncology* online).
Trends toward improved OS were observed in patients with WT *KRAS* tumors receiving panitumumab–FOLFIRI compared with FOLFIRI alone, irrespective of whether they had received prior oxaliplatin (median 14.2 versus 11.3 months; HR 0.87 [95% CI 0.70, 1.07]; $P = 0.18$) or oxaliplatin–bevacizumab (median 16.1 versus 12.1 months; HR 0.69 [95% CI 0.45, 1.08]; $P = 0.10$) (Figure 3 and supplementary Table S2, available at *Annals of Oncology* online).
An ORR was improved in patients with WT *KRAS* tumors receiving panitumumab–FOLFIRI versus FOLFIRI alone, irrespective of prior therapy received (prior oxaliplatin: 32% versus 7%; odds ratio 6.75 [95% CI 3.42, 14.24]; $P < 0.0001$; prior oxaliplatin–bevacizumab: 32% versus 2%; odds ratio 19.74 [95% CI 2.60, 858.81]; $P = 0.0003$) (supplementary Table S2, available at *Annals of Oncology* online).

#### *patient-reported quality of life*

In patients with WT *KRAS* tumors, the compliance rate for the EQ-5D HSI score was 61% in the panitumumab–FOLFIRI arm versus 57% in the FOLFIRI-alone arm; corresponding rates for the EQ-5D OHR score were 60% versus 57%, respectively. Similar compliance rates (ranging from 59%–64%) were observed in patients with MT *KRAS* tumors.
Given a minimal clinically important difference of 0.08 for the HSI and 7 points for the OHR, there were no statistically significant or clinically meaningful differences in change in EQ-5D scores from baseline between treatments. In patients with WT *KRAS* tumors, the difference in least squares-adjusted mean scores from baseline in the EQ-5D HSI was −0.02 (95% CI −0.05, 0.01), and was −0.72 [95% CI −2.66, 1.22]) for the OHR score.
In patients with WT *KRAS* tumors, there were no clinically meaningful differences between patients with a worst-grade ST of 2–4 versus 0–1 on the EQ-5D HSI (difference in least squares-adjusted mean scores from baseline: −0.20 [95% CI −0.38, −0.02] or the OHR (difference −0.86 [95% CI −5.19, 3.47]).

### safety

Overall, safety results were consistent with those observed in the primary analysis [9]. AEs leading to discontinuation of panitumumabwere reported in 16% of patients in both the WT and MT *KRAS* groups. Grade 3/4 AEs of interest differing by >5% between treatments were consistent with those expected for EGFR inhibitors and comprised ST and hypokalemia in the WT *KRAS* group, and ST stomatitis/oral mucositis in the MT *KRAS* group, as reported previously [9].
Three (1%) patients with WT *KRAS* tumors receiving panitumumab had an infusion reaction reported as an AE (one grade 2 and two grade 4). An infusion reaction was also reported as an AE (grade 1) in one (<1%) patient with MT *KRAS* mCRC receiving panitumumab.
Analyses of grade 3/4 AEs of interest by ST severity (supplementary Table S3, available at *Annals of Oncology* online) and prior therapy were also carried out and did not reveal significant differences by the grade of ST or by previous therapy received, respectively.
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## discussion

Consistent with the primary analysis, the final analysis of this phase 3 study confirms the efficacy and safety of adding panitumumab to FOLFIRI as the second-line treatment of patients with WT *KRAS* tumors, including those who have progressed on prior oxaliplatin or oxaliplatin–bevacizumab-containing regimens. PFS, ORR, and OS results were consistent with the primary analysis of data in this trial [9]. The addition of panitumumab significantly improved PFS and ORR in patients with WT *KRAS* tumors, and there was a trend toward improved OS in these patients (not statistically significant). This finding may have been due to the high incidence of post-PD anti-EGFR therapy use in the FOLFIRI-alone arm. Attenuation of the PFS and OS HRs was observed, likely a result of death events in patients without centrally documented PD. Such events are likely to be influenced by subsequent therapy use, which was more frequent in the FOLFIRI-alone arm than in the panitumumab–FOLFIRI arm. Notably, among the 71 additional patients who died without documented PD in the final analysis (i.e. new death events), the incidence of subsequent anti-EGFR therapy was 45.5% in the FOLFIRI-alone arm and 10.5% in the panitumumab–FOLFIRI arm. Interestingly, the HR in a *post hoc* analysis censoring late death events was lower than that seen in the overall PFS analysis (0.73 versus 0.82, respectively). It should be emphasized that, although PFS attenuation was observed in the final analysis, the magnitude of the panitumumab anti-tumor effect remained consistent between the primary and final analyses. As seen previously with EGFR inhibitors [9, 14, 19–22], addition of panitumumab had a minimal impact on efficacy in patients with MT *KRAS* tumors.

For patients with WT *KRAS* tumors receiving panitumumab, consistent PFS benefits were observed in the prespecified subgroups, including those who had received prior oxaliplatin. PFS was particularly improved in patients who had received prior oxaliplatin–bevacizumab (HR 0.58; $P = 0.014$). These results confirm the feasibility of second-line treatment with panitumumab–FOLFIRI in patients who have previously received these regimens.

The safety results were similar to those seen in the primary analysis [9], with no new or unexpected findings. Although cross-trial comparisons should be interpreted with caution in the absence of head-to-head trials, safety outcomes were as expected based on the results of other panitumumab trials [8, 12, 19] and trials of cetuximab combined with irinotecan-based therapy [7, 11, 23]. As seen previously, the incidence of grade 3/4 infusion reactions during panitumumab treatment was low (0.7%) with no fatal reactions and no specific premedication required ahead of panitumumab administration.

ST is a class effect of EGFR-targeted agents [24]. In line with previous observations [25–27], patients with WT *KRAS* tumors receiving panitumumab–FOLFIRI experiencing higher ST grades (≥2) had improved PFS and OS, as well as higher ORRs, compared with those experiencing no or mild (0–1) ST (*post hoc*, descriptive analysis). OS and PFS appeared shorter for patients with a worst-grade ST of 0–1 in panitumumab-treated patients compared with those receiving FOLFIRI alone; the ORR was also lower in these patients. An important point to note is that the landmark methodology employed in the ST analyses excluded patients who progressed or died within the first 28 days of treatment, which may have potentially unmasked a prognostic effect as patients with adverse outcomes were excluded. Based on these findings, a key question in the management of patients with WT *KRAS* mCRC is whether therapy discontinuation should be considered in patients who do not mount higher ST grades (2–4) early on during panitumumab–FOLFIRI treatment. However, as some panitumumab-treated patients develop ST later in their treatment course (at or beyond the fourth cycle), discontinuation should be considered with caution. Another potential consideration is whether the dose of panitumumabshould be escalated to induce ST; this approach was investigated with cetuximab in the EVEREST trial; results were not practice-changing [28].

Incidences of most grade 3/4 AEs of interest were similar in patients with a worst-grade ST of 0–1 versus 2–4, suggesting that the efficacy benefits observed in patients with grade 2–4 ST were not associated with additional toxicity burden. Given that patients with higher ST grades did not demonstrate inferior quality of life than those with no or mild ST under panitumumab treatment, ST may represent a useful pharmacodynamic biomarker of efficacy for these patients.

Of note, *KRAS* testing in this study was done prospectively and centrally in a blinded fashion and so any differences are unlikely to be due to differences in the quality of *KRAS* testing between centers. To our knowledge, this dataset represents the highest *KRAS*ascertainment rate in a phase 3 second-line trial of EGFR inhibition combined with chemotherapy. Outcomes described in this report by *KRAS* status should therefore be considered rigorous, reliable, and robust.

In conclusion, data from the final analysis of study 20050181 confirm the efficacy and safety conclusions from the primary analysis of this trial and support the use of panitumumab–FOLFIRI as a second-line treatment in patients with WT *KRAS* tumors.