ORIGINAL RESEARCH

# An analysis of the treatment effect of panitumumab on overall survival from a phase 3, randomized, controlled, multicenter trial (20020408) in patients with chemotherapy refractory metastatic colorectal cancer

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**Abstract** Panitumumab is a fully human monoclonal antibody that targets the epidermal growth factor receptor. Results from the primary analysis of a phase 3, randomized, controlled study showed a statistically significant improvement in progression-free survival for patients receiving panitumumab; however, overall survival was confounded by best supportive care (BSC) patients that crossed over to panitumumab therapy after disease progression. Three post hoc analyses are presented that approximate the panitumumab overall survival treatment effect in both the all-randomized and wild-type (WT) *KRAS* populations by using the BSC patients with mutant (MT) *KRAS* as the comparator group to discount the effect of crossover from BSC to panitumumab. The primary post hoc analysis showed a median overall survival of 6.4 months for all *KRAS*-evaluable patients randomized to panitumumab versus 4.4 months for patients with MT *KRAS* tumors randomized to BSC, yielding an adjusted hazard ratio (95 % CI) of 0.764 (0.598-0.977). Similar results were observed for the two secondary post hoc analyses. These analyses suggest a positive treatment effect of panitumumab in both the overall and WT *KRAS* patient populations consistent with an improvement in overall survival relative to BSC.

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## Introduction

Colorectal cancer is the third most common cancer in the world, with more than 1.2 million new cases diagnosed annually [1]. Treatment options for metastatic colorectal cancer (mCRC) include monoclonal antibodies that target the epidermal growth factor receptor (EGFR) [2–7]. Panitumumab (Vectibix®, [Amgen Inc., Thousand Oaks, United States]), a fully human monoclonal antibody that targets the EGFR, is approved in the US as monotherapy for mCRC after disease progression, in the European Union for the treatment of patients with wild-type (WT) *KRAS* mCRC in first-line in combination with FOLFOX (leucovorin, fluorouracil, and oxaliplatin), in second-line in combination with FOLFIRI (leucovorin, fluorouracil, and irinotecan) in patients who have received first-line fluoropyrimidine-based chemotherapy
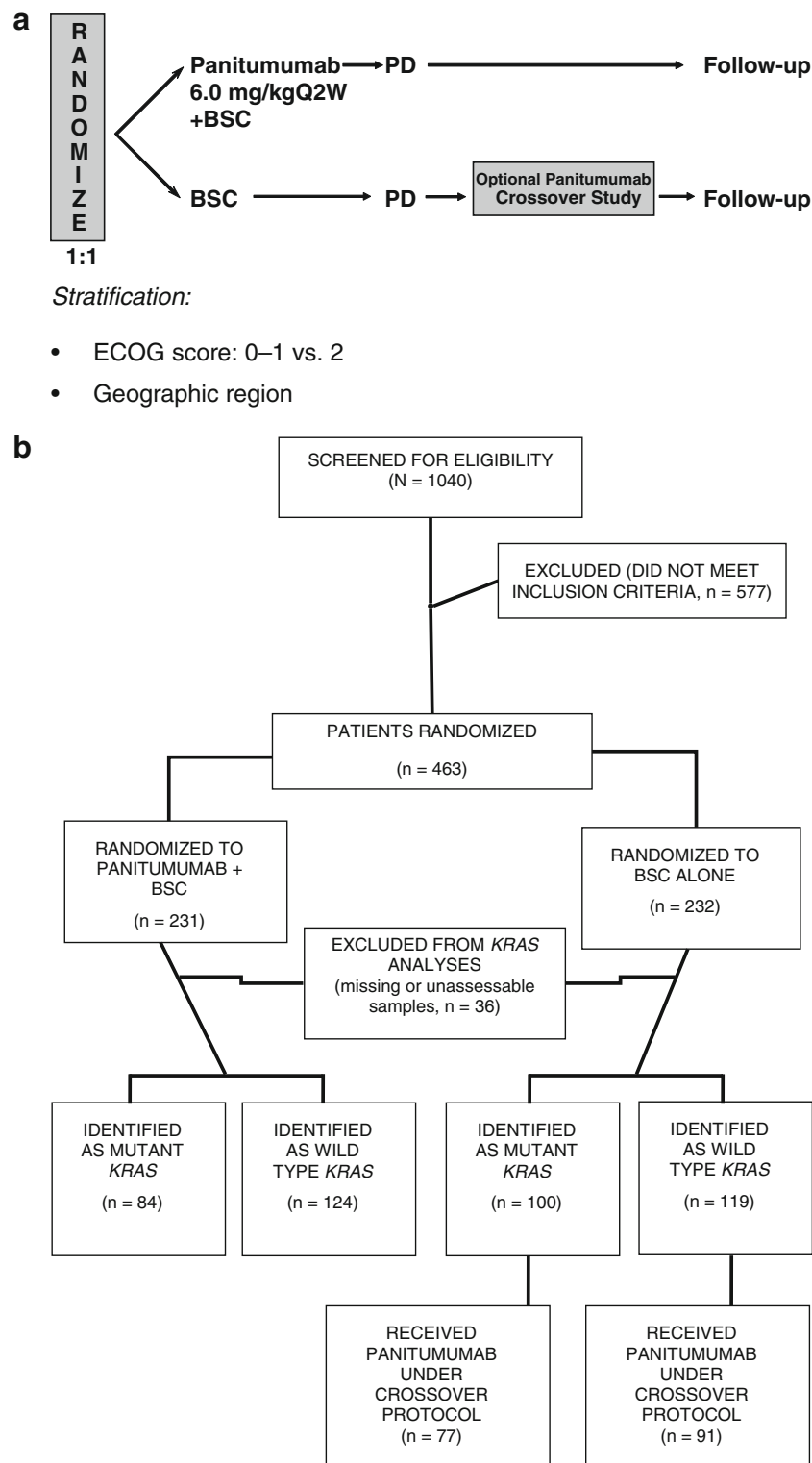
**Fig. 1** **a** 20020408 Study Schema, **b** CONSORT diagram, **c** groups included in the primary post hoc analysis that compared patients with MT *KRAS* (*n*=84) and WT *KRAS* (*n*=124) tumors who received panitumumab versus patients with MT *KRAS* (*n*=100) tumors who received BSC alone. **d** Groups included in the second post hoc analysis that compared patients with WT *KRAS* (*n*=124) tumors who received panitumumab versus patients with MT *KRAS* (*n*=100) tumors who received BSC alone. **e** Groups included in the third post hoc analysis that compared patients with WT *KRAS* tumors who received panitumumab (*n*=124) and BSC alone (*n*=119) versus patients with MT *KRAS* tumors who received panitumumab (*n*=84) and BSC alone (*n*=100)
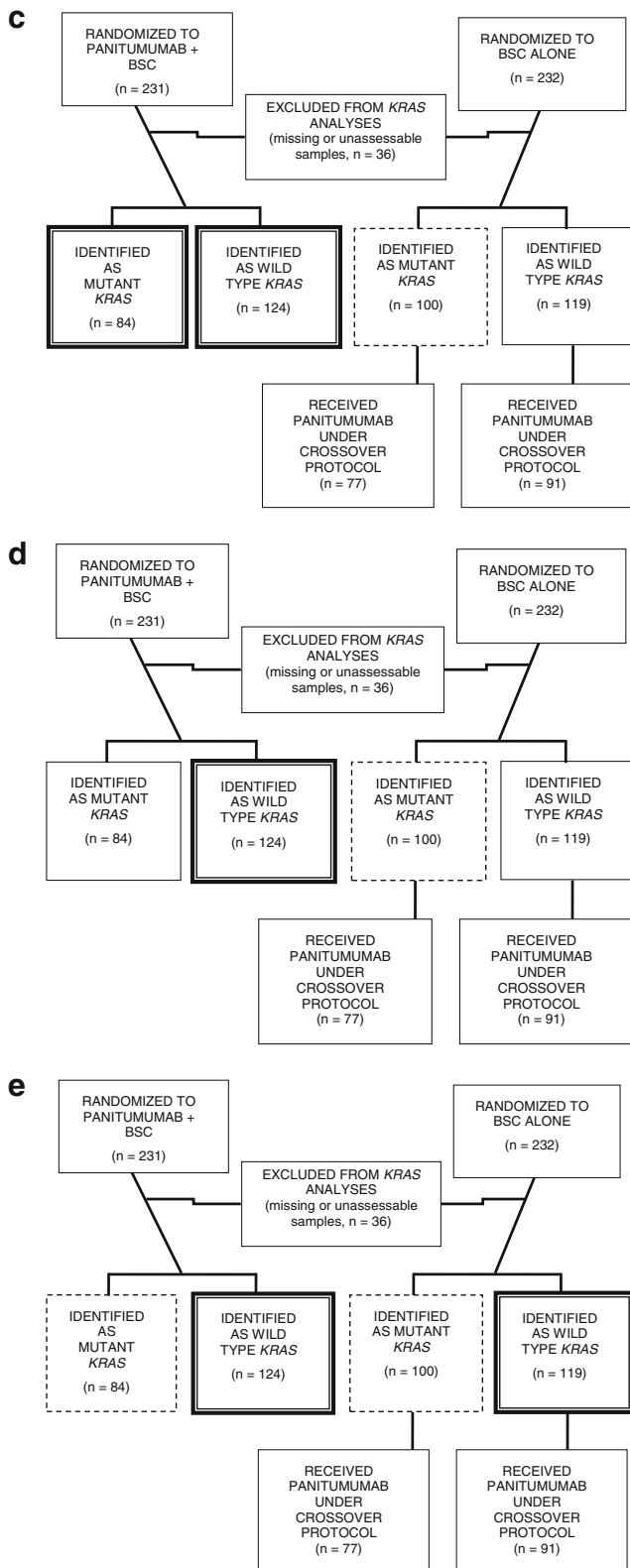
**Fig. 1** (continued)

(excluding irinotecan), and in third-line as monotherapy, and in Canada as monotherapy for the treatment of patients with

EGFR-expressing WT *KRAS* mCRC after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

During the conduct of a phase 3 trial (the 20020408 study) that prospectively compared panitumumab plus best supportive care (BSC) to BSC alone in patients with mCRC, a strong correlation emerged with a lack of EGFR inhibitor activity in patients with mutant (MT) *KRAS* tumors [8]. The primary endpoint of this study was progression-free survival (PFS). Patients randomized to BSC could cross over to panitumumab therapy in the event of disease progression on-study. Results from the primary analysis showed a statistically significant improvement in PFS for patients receiving panitumumab; however, the overall survival (OS) hazard ratio (HR) for panitumumab versus BSC was 1.00, a result confounded by the 176 (76 %) BSC patients that crossed over to panitumumab therapy after disease progression; crossover occurred early, with a median time to crossover of 7 weeks (range, 6.6 to 7.3 weeks) [2].

Patients with MT *KRAS* tumors do not benefit from anti-EGFR therapy, a finding confirmed in other studies and meta-analyses of EGFR inhibitors [9–13]. In the MT *KRAS* group in our study, no OS difference was observed between treatment arms, as evidenced by an HR (95 % CI) of 1.02 (0.75 to 1.39) [8]. In other studies, *KRAS* status was not prognostic for OS in patients that received BSC, chemotherapy, and chemotherapy with bevacizumab [4, 14–19]. Two meta-analyses examining tumor *KRAS* status and anti-EGFR monoclonal antibodies in mCRC show MT KRAS mCRC is associated with reduced overall and progression-free survival [12, 13]. Therefore, patients with MT *KRAS* receiving BSC with disease progression that went on to receive panitumumab likely did not benefit from panitumumab therapy. For this reason, using the MT *KRAS* BSC group as the comparator may remove confounding from crossover as opposed to using the entire BSC alone group, which includes patients with WT *KRAS* that benefited from panitumumab.

This paper describes the results from three post hoc analyses of the 20020408 study that present approximations of the panitumumab OS treatment effect in both the all-randomized (ITT) and *KRAS* WT populations when crossover from BSC to panitumumab is discounted by using the BSC patients with MT *KRAS* as the comparator group.

## Patients and methods

### Patients

The patients and methods for this study were previously described [2]. Briefly, eligible patients had documented disease progression after failure of fluoropyrimidines, prespecified exposure to oxaliplatin and irinotecan, Eastern

**Table 1** Demographics and disease characteristics

| | Primary analysis | Primary and secondary analyses | Secondary analysis | Tertiary analysis | Tertiary analysis |
|---|---|---|---|---|---|
| | WT and MT *KRAS* panitumumab | MT *KRAS* BSC | WT *KRAS* panitumumab | WT *KRAS* panitumumab or BSC | MT *KRAS* panitumumab or BSC |
| | *n*=208 | *n*=100 | *n*=124 | *n*=243 | *n*=184 |
| Sex, *n* (%) | | | | | |
| Male | 130 (63) | 64 (64) | 83 (67) | 159 (65) | 111 (60) |
| Age, years | | | | | |
| Median (min, max) | 62.0 (27, 82) | 62.0 (27, 83) | 62.5 (29, 82) | 63.0 (29, 82) | 62.0 (27, 83) |
| Race, *n* (%) | | | | | |
| White | 206 (99) | 97 (97) | 122 (98) | 240 (99) | 181 (98) |
| ECOG, *n* (%) | | | | | |
| 0 | 96 (46) | 37 (37) | 53 (43) | 93 (38) | 80 (43) |
| 1 | 84 (40) | 47 (47) | 56 (45) | 118 (49) | 75 (41) |
| 2 | 28 (13) | 15 (15) | 15 (12) | 31 (13) | 28 (15) |
| 3 | 0 (0) | 1 (1) | 0 (0) | 1 (<1) | 1 (<1) |
| Primary tumor type, *n* (%) | | | | | |
| Colon | 139 (67) | 65 (65) | 86 (69) | 168 (69) | 118 (64) |
| Rectal | 69 (33) | 35 (35) | 38 (31) | 75 (31) | 66 (36) |
| Number of sites of disease | | | | | |
| 1 | 58 (28) | 20 (20) | 38 (31) | 68 (28) | 40 (22) |
| 2 | 84 (40) | 49 (49) | 50 (40) | 104 (43) | 83 (45) |
| 3 | 42 (20) | 25 (25) | 21 (17) | 43 (18) | 46 (25) |
| 4 | 22 (11) | 2 (2) | 14 (11) | 24 (10) | 10 (5) |
| 5 | 2 (1) | 4 (4) | 1 (1) | 2 (1) | 5 (3) |
| Sites of disease | | | | | |
| Liver | 161 (77) | 81 (81) | 96 (77) | 199 (82) | 146 (79) |
| Lung | 128 (62) | 64 (64) | 69 (56) | 138 (57) | 124 (67) |
| Lymph nodes | 47 (23) | 24 (24) | 31 (25) | 67 (28) | 40 (22) |
| Abdomen | 35 (17) | 20 (20) | 23 (19) | 40 (16) | 32 (17) |
| Pelvic site | 22 (11) | 9 (9) | 11 (9) | 18 (7) | 20 (11) |
| Bone | 14 (7) | 3 (3) | 9 (7) | 15 (6) | 8 (4) |
| Chest | 9 (4) | 4 (4) | 6 (5) | 8 (3) | 7 (4) |
| Gastrointestinal | 8 (4) | 3 (3) | 5 (4) | 8 (3) | 6 (3) |
| Skin | 3 (1) | 1 (1) | 1 (1) | 2 (1) | 3 (2) |
| Spleen | 2 (1) | 1 (1) | 1 (1) | 2 (1) | 2 (1) |
| Central nervous system | 1 (<1) | 0 (0) | 1 (1) | 1 (<1) | 0 (0) |
| Head | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Neck | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Other | 19 (9) | 11 (11) | 9 (7) | 13 (5) | 21 (11) |
| Any prior chemotherapy[a] | 208 (100) | 100 (100) | 124 (100) | 243 (100) | 184 (100) |
| Prior adjuvant chemotherapy | 77 (63) | 40 (40) | 50 (40) | 82 (34) | 67 (36) |
| Prior anti-tumor therapy[b] | 12 (6) | 2 (2) | 7 (6) | 12 (5) | 7 (4) |
| Prior radiotherapy (includes radiofrequency ablation) | 54 (26) | 29 (29) | 29 (23) | 62 (26) | 54 (29) |
| Last regimen prior to study entry | | | | | |
| Oxaliplatin containing regimens | 88 (42)) | 43 (43) | 57 (46) | 106 (44) | 74 (40) |
| Irinotecan containing regimens | 97 (47) | 50 (50) | 55 (44) | 110 (45) | 92 (50) |
| Both oxaliplatin and irinotecan | 1 (<1) | 0 (0) | 1 (1) | 3(1) | 0(0) |
| | 19 (9) | 6 (6) | 10 (8) | 21 (9) | 15 (8) |

**Table 1** (continued)

| | Primary analysis | Primary and secondary analyses | Secondary analysis | Tertiary analysis | Tertiary analysis |
|---|---|---|---|---|---|
| | WT and MT *KRAS* panitumumab | MT *KRAS* BSC | WT *KRAS* panitumumab | WT *KRAS* panitumumab or BSC | MT *KRAS* panitumumab or BSC |
| | $n=208$ | $n=100$ | $n=124$ | $n=243$ | $n=184$ |
| Fluoropyrimidine without oxaliplatin or irinotecan | | | | | |
| Other | 0 (0) | 1 (1) | 1 (1) | 3 (1) | 3 (2) |
| Region, *n* (%) | | | | | |
| Western Europe | 157 (75) | 77 (77) | 93 (75) | 187 (77) | 141 (77) |
| Central/Eastern Europe | 19 (9) | 7 (7) | 9 (7) | 19 (8) | 17 (9) |
| Rest of world | 32 (15) | 16 (16) | 22 (18) | 37 (15) | 26 (14) |
| EQ-5D score at baseline, median (min, max)[c] | 0.76 (0.16, 1.00) | 0.73 (0.59, 1.00) | 0.76 (0.16, 1.00) | 0.74 (0.16, 1.00) | 0.73 (0.59, 1.00) |
| FACT-CRC raw score at baseline, mean (SD) | 77.8 (15.3) | 77.4 (16.6) | 78.8 (14.7) | 78.9 (14.3) | 76.9 (16.3) |

[a] Patients had multiple prior regimens

[b] Does not include systemic chemotherapy; does include carboplatin as chemo-embolization

[c] EQ-5D score range, 0.0 (death) to 1.0 (perfect health)

Cooperative Oncology Group (ECOG) performance status 0-2, no brain metastases, no systemic chemotherapy, or radiotherapy within 30 days before randomization, and no prior anti-EGFR therapy.

Study design and treatment schedule

This was an open-label, multicenter, phase 3 trial. Patients were randomized 1:1 to receive panitumumab plus BSC or BSC alone, and randomization was stratified by geographic region (Western Europe versus Central and Eastern Europe versus rest of the world [Canada, Australia, and New Zealand]), and ECOG performance status score (0 or 1 versus 2). Panitumumab was administered intravenously over 1 h at 6.0 mg/kg every 2 weeks (Q2W). Treatment was administered until disease progression or unacceptable toxicity (Fig. 1a).

As mentioned previously, BSC patients could receive panitumumab after investigator-assessed disease progression.

The protocol was approved by the ethics committee at participating sites, and all patients signed informed consent before any study-related procedures were performed.

Statistical analyses

At the time the study was designed, the impact of tumor *KRAS* status on the efficacy of anti-EGFR antibodies was unknown; therefore, these analyses were not pre-specified in the original statistical analysis plan. The emergence of WT *KRAS* status as a requirement for panitumumab efficacy led to the subgroup analyses described here.

The primary objective of these post hoc analyses was to evaluate the OS treatment effect in both the ITT and WT *KRAS* populations after discounting the effect of crossover from the BSC group to panitumumab after disease progression. These exploratory and descriptive analyses included only patients with known *KRAS* status; all subgroups were defined prior to conducting any of the analyses.

The primary post hoc analysis was designed to best emulate what would have been expected in the original trial had there been no crossover from the BSC group to panitumumab; as such, this analysis included all *KRAS*-evaluable patients (both WT and MT) randomized to panitumumab versus patients with MT *KRAS* tumors randomized to BSC.

The second post hoc analysis was similar to the primary post hoc analysis but excluded patients randomized to panitumumab with MT *KRAS* tumors. In this analysis, patients randomized to panitumumab with WT *KRAS* tumors were compared with patients in the BSC group with MT *KRAS* tumors. Since patients with MT *KRAS* tumors were unlikely to benefit from panitumumab, this analysis provided an estimate of the treatment effect of panitumumab in patients with WT *KRAS* tumors.

The third post hoc analysis included all *KRAS*-evaluable patients with WT *KRAS* mCRC versus all patients with MT *KRAS* mCRC, regardless of the therapy to which each patient was randomized. The WT *KRAS* group included patients that received panitumumab and BSC alone, including patients who received panitumumab after failure of BSC treatment, potentially underestimating the panitumumab treatment effect. Similarly, the MT *KRAS* group included

**Fig. 2** Kaplan–Meier estimate
of overall survival for *KRAS*-
evaluable patients randomized
to panitumumab versus patients
randomized to BSC with KRAS
mutant tumors
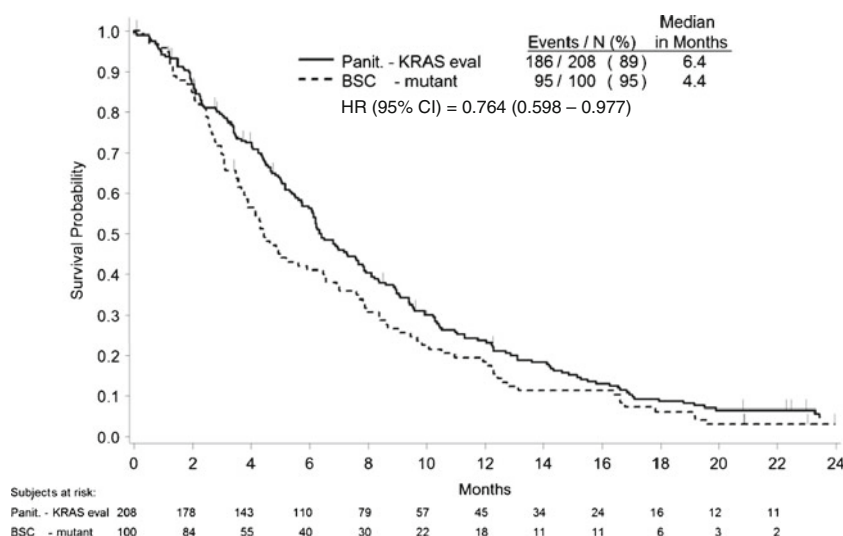


patients that received panitumumab and BSC alone, including patients who received panitumumab after failure of BSC treatment. Neither of these MT *KRAS* groups was likely to benefit from panitumumab.

For all of the post hoc analyses, Kaplan-Meier curves to estimate the OS difference between groups were generated. Crude and adjusted HRs for OS were estimated using Cox proportional hazards models. The crude models included only the geographic region and ECOG performance status score stratification factors. Adjusted models included variables potentially associated with OS, namely age, sex, tumor site, and baseline ECOG performance status score. Since these analyses were post hoc with the objective to approximate the OS treatment effect, no *p* values were calculated, and no assessment of statistical significance was made. All analyses were conducted with SAS software version 9.2 (SAS Institute, Cary, NC).

Sensitivity analyses

A key assumption for these post hoc analyses is a lack of prognostic value of *KRAS* status in patients treated with BSC alone. Although this assumption is supported by the literature, an analysis to examine the OS treatment effect in patients randomized to BSC alone that did not cross over to panitumumab by *KRAS* status was performed [8, 11]. This

subgroup, however, may not be representative of the overall BSC alone population, since the primary reason for lack of crossover was early death.

**Results**

From January 2004 to June 2005, 463 patients were enrolled and randomized, 231 to panitumumab plus BSC versus 232 to BSC-alone. *KRAS* results were available for 427 (92 %) patients, 208 panitumumab plus BSC and 219 BSC alone (Fig. 1b). Of the 219 BSC-alone patients with known *KRAS*, 168 (77 %) crossed over to receive panitumumab at a median time of 7.1 weeks.

For these post hoc analyses, different treatment groups were utilized: patients with WT and MT *KRAS* receiving panitumumab (*n*=208), patients with WT *KRAS* enrolled in the panitumumab arm (*n*=124), patients with MT *KRAS* enrolled in the BSC arm (*n*=100), patients with WT *KRAS* receiving panitumumab and BSC (*n*=243), and patients with MT *KRAS* receiving panitumumab and BSC (*n*=184) (Fig. 1c–e). Baseline demographics, disease characteristics, and quality-of-life measures were similar among all comparator groups (Table 1).

The primary analysis results indicate median OS was 6.4 months for all *KRAS*-evaluable patients randomized to

**Table 2** Summary of OS HR estimates from the post hoc analyses

| Description | Crude HR (95 % CI) | Adjusted HR[a] (95 % CI) | Median (months) |
|---|---|---|---|
| WT and MT *KRAS* panitumumab versus MT *KRAS* BSC | 0.777 (0.606–0.996) | 0.764 (0.598–0.977) | 6.4 vs 4.4 |
| WT *KRAS* panitumumab versus MT *KRAS* BSC | 0.668 (0.505–0.883) | 0.656 (0.494–0.872) | 8.1 vs 4.4 |
| WT *KRAS* panitumumab+BSC versus MT *KRAS* panitumumab+BSC | 0.668 (0.546–0.818) | 0.622 (0.506–0.764) | 7.9 vs 4.7 |

[a] HR adjusted for variables potentially associated with OS: age, sex, tumor site, and baseline ECOG score

**Fig. 3** Kaplan–Meier estimate of overall survival for patients randomized to panitumumab with KRAS wild-type tumors versus patients randomized to BSC patients with KRAS mutant tumor
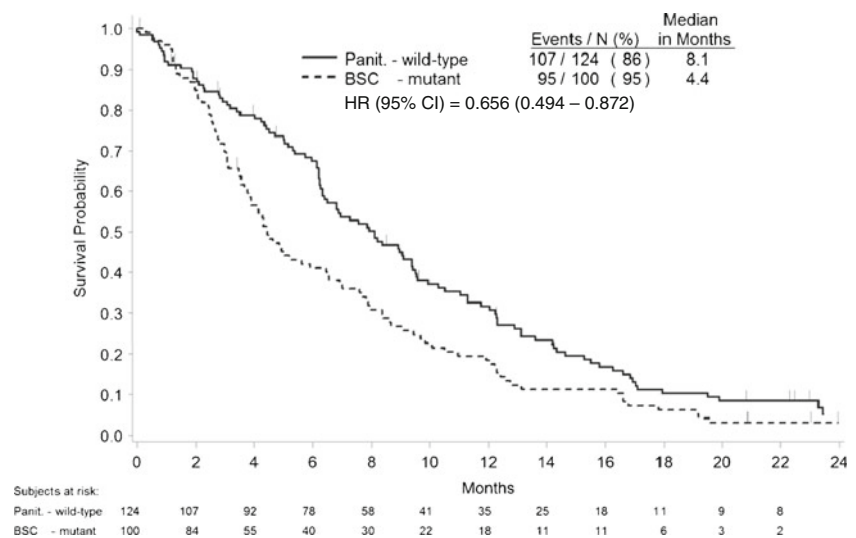


panitumumab versus 4.4 months for patients with MT *KRAS* tumors randomized to BSC (Fig. 2). Table 2 presents the crude and adjusted HRs for the post hoc analyses. This approximation of the all-randomized panitumumab OS treatment effect yielded an adjusted HR (95 % CI) of 0.764 (0.598-0.977).

In the second analysis, median OS was 8.1 months for patients with WT *KRAS* tumors randomized to panitumumab versus 4.4 months for patients with MT *KRAS* tumors randomized to BSC (Fig. 3). This approximation of the WT *KRAS* panitumumab OS treatment effect yielded an adjusted HR (95 % CI) of 0.656 (0.494-0.872; Table 2).

In the third analysis, median OS was 7.9 months for all patients with WT *KRAS* versus 4.7 months for all patients with MT *KRAS* tumors, regardless of treatment group assignment (Fig. 4). This approximation of the WT *KRAS* panitumumab OS treatment effect yielded an adjusted HR (95 % CI) of 0.622 (0.506-0.764; Table 2).

The post hoc analyses presented above depend on the assumption that *KRAS* status has no prognostic effect on OS in patients treated with BSC alone. As such, a sensitivity analysis of patients randomized to BSC that did not cross over to panitumumab by tumor *KRAS* status was performed that found median OS was 1.9 months for patients ($n=28$) with WT *KRAS* tumors and 2.0 months for patients ($n=23$) with MT *KRAS* tumors (Fig. 5). Although this subgroup may not be representative of the overall BSC population, these results support the assumption that tumor *KRAS* status has no prognostic impact on patients treated with BSC alone, upholding this post hoc analysis.

An additional sensitivity analysis was performed since patients were not randomized at the level of *KRAS* status. It is possible that imbalances in unmeasured prognostic factors (other than those considered in the adjusted model) may have introduced residual confounding. Thus, a sensitivity analysis using the array approach was conducted to quantify

**Fig. 4** Kaplan–Meier estimate of overall survival for patients with KRAS wild-type versus KRAS mutant tumors
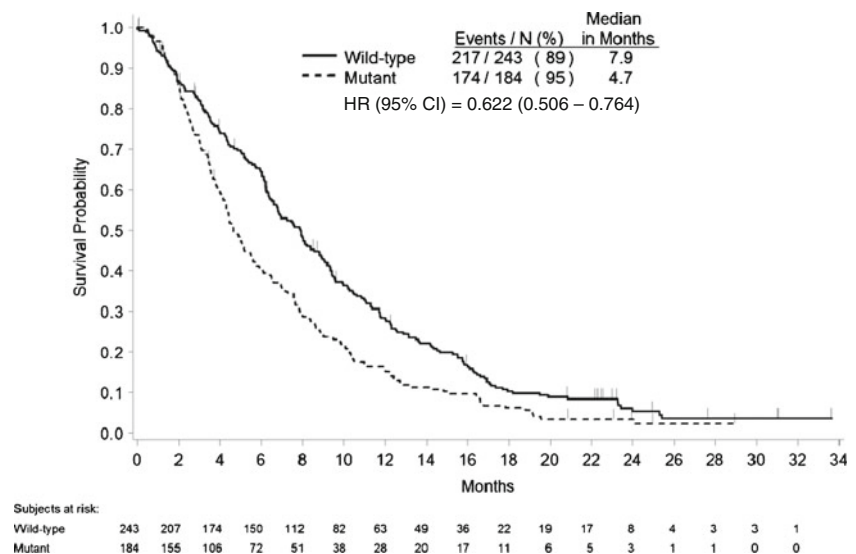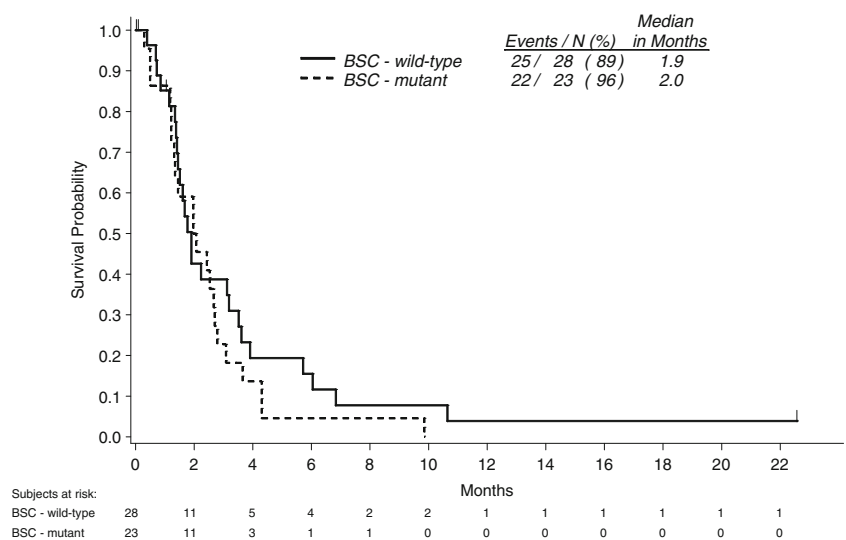
Fig. 5 Kaplan–Meier estimate of overall survival by *KRAS* status among BSC patients that did not crossover to panitumumab



the effect of a known or unknown, unmeasured confounder on the observed association between panitumumab and OS in the ITT population [20].

Using this approach, we fixed the prevalence of a hypothetical confounder in the BSC MT *KRAS* group to 0.3 and varied the strength of the confounder–outcome association (1.0 to 5.5) and the prevalence of the confounder in the panitumumab group (0.0 to 5.0). The interrelationship between these three factors was plotted in three-dimensional graphic representation (Fig. 6).

There is no bias when the confounder is equally distributed between the panitumumab and BSC MT *KRAS* tumor groups. However, with increasing imbalance of the confounder between the two groups, the fully adjusted estimate moves away from the observed HR. Specifically, if the prevalence of the confounder in the panitumumab group is inferior to the prevalence of the confounder in the BSC MT *KRAS* tumor group, then the "true" HR would be higher than the observed HR. This would require the confounder to be strongly associated with the outcome, with RR estimates ranging from 3.5 to 5.5. Conversely, if the prevalence of the confounder in the panitumumab group is superior to the prevalence of the confounder in the BSC MT *KRAS* tumor group, then the "true" HR would be less than the observed HR. Other than age, sex, tumor site, and ECOG performance status score, all of which were controlled for in the adjusted model, the likelihood of an unknown, unmeasured confounder of a magnitude necessary to impact outcomes is slim.

This sensitivity analysis demonstrates through quantification of the effect of a known or unknown, unmeasured confounder on the observed association between panitumumab

Fig. 6 Array approach for confounding bias
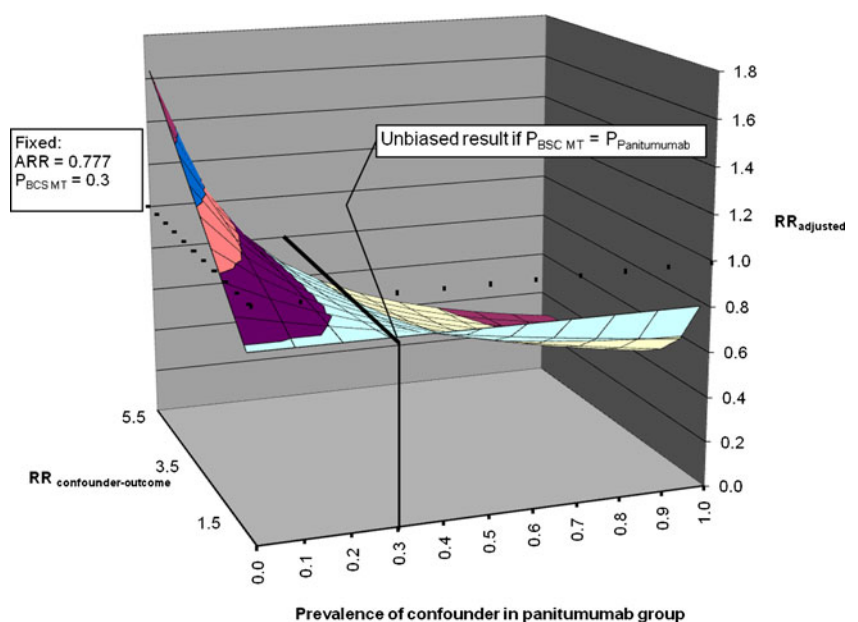
and OS that, if these post hoc analyses are subject to bias, that either a confounder with an unlikely magnitude of impact exists or the observed OS effect is valid in spite of the bias.

## Discussion

The results from these analyses suggest that crossover from BSC to panitumumab had an impact on OS in both the overall and WT *KRAS* patient populations. Controlling for these crossover patients demonstrated a trend toward improved OS that could have been detected in the original study if crossover were not permitted. Since patients with MT *KRAS* tumors were unlikely to benefit from panitumumab therapy and the evidence suggests *KRAS* has no OS prognostic effect with BSC alone, this post hoc analysis gives an approximation of the all-randomized treatment effect of panitumumab on OS after discounting the impact of crossover from BSC to panitumumab treatment in the original trial. In a similar manner, the second and third analyses provided approximations of the treatment effect of panitumumab on OS in patients with WT *KRAS* tumors, also discounting the effect of crossover. In these analyses, the HRs were consistently under 1, suggesting a positive panitumumab treatment effect. Of note, a similar improvement in OS was observed with cetuximab therapy relative to BSC alone in a trial in which no crossover was allowed in a similar patient population [4]. The results of these post hoc analyses are consistent with the statistically significant PFS effect from the primary analysis of this study.

Post hoc analyses and the conclusions that can be drawn from them are limited by bias. Concerns included the introduction of bias through patient selection, whether tumor *KRAS* status was prognostic for OS with BSC alone, and the treatment effect of panitumumab, if any, on OS in patients with MT *KRAS* tumors. Patient selection bias was minimized because the demographics and disease characteristics of the control groups represented a random sample of patients enrolled in the study. Indeed, the demographics and disease characteristics of the control groups were similar to all other comparator groups in these analyses. The assumption that tumor *KRAS* status is not prognostic for OS is supported in both the literature and in the trend toward no difference between patients with WT and MT *KRAS* tumors in patients randomized to BSC that did not cross over to panitumumab. In addition, patient treatment decisions were made without knowledge of tumor *KRAS* status. Evidence for the lack of a treatment effect of panitumumab on OS in patients with MT *KRAS* tumors from the original *KRAS* analysis of this study provided further evidence of the lack of bias that might be introduced by using patients with MT *KRAS* tumors as a comparator group.

The crude and adjusted HR estimates in the three analyses were very similar, indicating that the potential confounders considered were relatively well-balanced between the exposure groups. Furthermore, the sensitivity analysis based on the array approach indicated that it is unlikely that the observed results were biased by an unknown or unmeasured confounder [20]. In fact, confounding bias would only be present in extreme conditions, with a confounder very strongly associated with the outcome being largely differentially distributed between the exposure groups. Such a scenario is thought to be unlikely, as we adjusted for known important confounders.

In summary, these analyses show a positive treatment effect of panitumumab on OS in both the overall and WT *KRAS* patient populations that could have been detected in the original study and in the prospective–retrospective analysis by *KRAS* status if crossover from BSC to panitumumab had not been permitted.

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