Original Study

Check for updates

Final Analysis of Outcomes and *RAS*/*BRAF* Status in a Randomized Phase 3 Study of Panitumumab and Best Supportive Care in Chemorefractory Wild Type *KRAS* Metastatic Colorectal Cancer

Tae Won Kim,[1] Anneli Elme,[2] Joon Oh Park,[3] Anghel Adrian Udrea,[4] Sun Young Kim,[5] Joong Bae Ahn,[6] Ricardo Villalobos Valencia,[7] Srinivasan Krishnan,[8] Nebojsa Manojlovic,[9] Xuesong Guan,[10] Catherine Lofton-Day,[10] A. Scott Jung,[10] Eduard Vrdoljak[11]

Abstract

Tumor *rat sarcoma gene (RAS)* status is a negative anti-epidermal growth factor receptor therapy biomarker in metastatic colorectal cancer (mCRC). Early tumor shrinkage (ETS) and depth of response (DpR) were evaluated for 270 patients with *RAS* wild type mCRC randomized to best supportive care with or without panitumumab (6.0 mg/kg, intravenously, on day 1 of 14-day cycles). Panitumumab improved outcomes, and ETS and DpR might be useful efficacy markers.

Introduction: Tumor *rat sarcoma gene (RAS)* status is a negative predictive biomarker for anti-epidermal growth factor receptor (EGFR) therapy in metastatic colorectal cancer (mCRC). We analyzed outcomes according to *RAS* and *v-Raf murine sarcoma viral oncogene homolog B (BRAF)* mutational status, and evaluated early tumor shrinkage (ETS) and depth of response (DpR) for patients with wild type *RAS*. **Patients and Methods:** Patients with confirmed metastatic colon or rectum adenocarcinoma, wild type *Kristen rat sarcoma gene* tumor exon 2 status, clinical/radiologic disease progression or toxicity during irinotecan or oxaliplatin treatment, and no previous anti-EGFR therapy were randomized 1:1 to receive best supportive care (BSC) with or without panitumumab (6.0 mg/kg, intravenously, on day 1 of each 14-day cycle) in this open-label, multicenter, phase III study (20100007). *RAS* and *BRAF* mutation status were determined using Sanger sequencing. ETS was evaluated as maximum percentage change from baseline to week 8; DpR was calculated as the percentage change for tumor shrinkage at nadir versus baseline. **Results:** Overall, 270 patients had *RAS* wild type mCRC (panitumumab with BSC, n = 142; BSC, n = 128). For patients with wild type *RAS* tumors, median overall survival (OS; hazard ratio [HR], 0.72; $P = .015$) and progression-free survival (PFS; HR, 0.45; $P < .0001$) were improved with panitumumab with BSC versus BSC. Similar improvements were seen for patients with wild type *RAS*, and wild type *BRAF* tumors (OS: HR, 0.75; $P = .04$; PFS: HR, 0.45; $P < .0001$). Median DpR was 16.9% for the evaluable panitumumab with BSC wild type *RAS* population. Overall, 69.5% experienced any type of tumor shrinkage at week 8; 38.2% experienced ≥ 20%

[1]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea
[2]Department of Gastroenterology, Oncology, North Estonia Medical Centre Foundation, Tallinn, Estonia
[3]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
[4]SC MEDISPROF SRL, Cluj-Napoca, Romania
[5]Division of Hemato-Oncology, National Cancer Center, Goyang, Gyeonggi-do, South Korea
[6]Department of Internal Medicine, Yonsei University Health System Severance Hospital, Seoul, South Korea
[7]Department of Medical Oncology, Hospital de Oncologia, Centro Medico Nacional Siglo XXI, IMSS, Mexico City, Mexico
[8]Department of Clinical Research, Dr Rai Memorial Medical Centre, Chennai, Tamil Nadu, India
[9]Department of Digestive Oncology, Clinic for Gastroenterology and Hepatology of Military Medical Academy of Serbia, Belgrade, Serbia
[10]Amgen Inc, Thousand Oaks, CA
[11]Department of Oncology, Center of Oncology, Clinical Hospital Center Split, Split, Croatia

Submitted: Dec 18, 2017; Revised: Feb 21, 2018; Accepted: Mar 14, 2018; Epub: Mar 21, 2018

Address for correspondence: Tae Won Kim, MD, PhD, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro, Songpa-gu, Seoul 138-736, South Korea
Fax: 82-2-3010-6961; e-mail contact: twkimmd@amc.seoul.kr

https://doi.org/10.1016/j.clcc.2018.03.008

shrinkage. Similar improvements in OS and PFS were seen with stratification according to ETS. **Conclusion:** This analysis showed that panitumumab improved outcomes in wild type *RAS* mCRC and indicated that ETS and DpR could be used as additional efficacy markers.

Clinical Colorectal Cancer, Vol. 17, No. 3, 206-14

Keywords: Anti-EGFR therapy, Biomarkers, Gastrointestinal cancer, Randomized controlled trial, Treatment outcome

Introduction

Panitumumab is a fully human anti-epidermal growth factor receptor (EGFR) antibody that is effective as a monotherapy and in combination with chemotherapy for *RAS* wild type metastatic colorectal cancer (mCRC).[1-3] Tumor *RAS* status has been established as a negative predictive biomarker for anti-EGFR therapy in mCRC in combination with chemotherapy in retrospective analyses as well as a monotherapy in the prospective primary analysis of the 20100007 study.[1,2,4,5] The 20100007 primary analysis showed panitumumab with best supportive care (BSC) versus BSC alone yielded better outcomes in wild type *RAS* tumors than in wild type *Kristen rat sarcoma gene (KRAS)* exon 2 mCRC. Significant clinical improvement was seen across all key end points: overall survival (OS), progression-free survival (PFS), and objective response rate (ORR).[4]

Although *RAS* status is predictive for clinical response, additional biomarkers that further characterize the population that will benefit from anti-EGFR treatment would be of significant value. There has been longstanding interest in *v-Raf murine sarcoma viral oncogene homolog B (BRAF)* as a potential mCRC biomarker,[6] and to date, *BRAF* mutational status has been shown to be associated with poor outcomes (ie, prognostic).[1,2,7] There is little support from randomized studies for *BRAF* as a predictive biomarker during panitumumab therapy; however, the predictive value of *BRAF* has been difficult to evaluate because evidence is limited by the poor overall outcomes that patients typically experience.

In addition to biomarker identification, novel clinical evaluations might provide further information on the characteristics of response during anti-EGFR therapy. Although tumor response according to Response Evaluation Criteria in Solid Tumors (RECIST)[8] is a standard and important oncology end point, it does not fully consider duration, depth, or timing of response. Thus, complementary end points such as early tumor shrinkage (ETS; tumor shrinkage at or below a specified threshold within a short period of time after treatment initiation) and depth of response (DpR; maximum tumor shrinkage observed) have been evaluated. ETS might be predictive of survival, indicative of sensitivity to therapy and potential to achieve a response.[9] Additionally, it might improve or delay symptoms or even allow for resection[10] and has been associated with improved OS.[9-11] Similarly, DpR might be associated with longer disease and/or symptom control[9] and has also been associated with improved OS.[9,11] Limited data on these end points in clinical trials with anti-EGFR inhibitors as monotherapy are available; therefore, we sought to evaluate these end points using data from the 20100007 study.

We report the final analysis results from the 20100007 trial (ClinicalTrials.gov registration NCT01412957), a prospective, open-label, randomized, phase III trial. Survival outcomes were analyzed according to *RAS* and *BRAF* mutational status, and ETS and DpR analyses were evaluated for patients with wild type *RAS* tumors.

Patients and Methods

Study Design and Patients

Detailed information regarding patient eligibility criteria and study design has been previously reported.[4] Briefly, eligible patients had histologically or cytologically confirmed diagnosis of adenocarcinoma of the colon or rectum and metastatic disease, wild type *KRAS* tumor exon 2 status assessed centrally, clinical/radiologic disease progression (assessed by investigator in each study center), or toxicity during irinotecan or oxaliplatin treatment, and no previous anti-EGFR therapy. The study protocol was approved by an independent ethics committee at each study center and is available online (see Appendix A in the online version); all patients provided written informed consent.

Treatment

Patients were randomly assigned (1:1) to receive panitumumab (6.0 mg/kg) intravenously on day 1 of each 14-day cycle with BSC (as previously defined[4]) or BSC alone. Randomization was stratified according to geography (Europe vs. Asia vs. rest of the world) and Eastern Cooperative Oncology Group performance status (0 or 1 vs. 2). Study treatment continued until disease progression, consent withdrawal, or panitumumab intolerance (panitumumab with BSC arm only). On-study crossover from BSC to panitumumab with BSC was prohibited.

Mutational Analysis of KRAS, RAS, *and* BRAF

Patient tumor samples were screened for mutations in *KRAS* exon 2 and in codons 12 and 13 to determine study eligibility and for extended *RAS* analyses as previously described.[4] Analyses of *KRAS* exons 3 (codons 59 and 61) and 4 (codons 117 and 146), and *Neuroblastoma rat sarcoma gene (NRAS)* exons 2 (codons 12 and 13), 3 (codons 59 and 61), and 4 (codons 117 and 146) were prespecified in the study protocol and statistical analysis plan. The covariate *BRAF* exon 15 was also prespecified in the study protocol but was evaluated in an exploratory analysis. *RAS* and *BRAF* mutation status were determined by a single central laboratory using bidirectional Sanger sequencing (limit of detection, 5%-25%); *RAS* mutation status was determined before the primary analysis; *BRAF* mutation status was determined after the primary analysis was conducted.

Assessments

Radiographic tumor assessments were performed at week 4 (+ 1 week), week 8 (± 1 week), and every 8 weeks (± 1 week) thereafter

until radiographic or clinical disease progression. Response was evaluated by investigator review (ie, not central review), per RECIST version 1.1.[8] Patients had a safety follow-up visit 30 to 33 days after the last dose of panitumumab (panitumumab with BSC arm) or within 33 days of disease progression or the decision to end treatment (BSC arm). ETS was evaluated as the maximum percentage change from baseline to week 8; positive values indicated tumor reduction and negative values indicated tumor growth. The association between ETS and survival outcome was also examined. DpR was calculated as the percentage change for tumor shrinkage at nadir versus baseline. If no shrinkage occurred, DpR was evaluated as the percentage change at the time of progression versus baseline. Positive values indicated tumor reduction; negative values indicated tumor growth. Adverse events (AEs) were recorded/graded as previously described.[4]

Statistical Analyses

The primary end point was OS (time from randomization to death) for patients with wild type *KRAS* exon 2 mCRC. Secondary end points included PFS (time from randomization to disease progression or death) and ORR (rate of complete or partial response per RECIST version 1.1)[8] for patients with wild type *KRAS* exon 2 status; OS, PFS, and ORR for patients with wild type *RAS* status; and safety. The primary analysis was performed after 250 OS events had occurred. This final analysis was planned for 2 years after the last patient was randomized. Efficacy analyses were performed for the intent-to-treat (wild type *KRAS* exon 2), wild type *RAS* (wild type *KRAS* and *NRAS* exons 2, 3, and 4), and wild type *RAS*/*BRAF* analysis sets (wild type *KRAS* and *NRAS* exons 2, 3, and 4, wild type *BRAF* exon 15). Safety analyses included all patients in the wild type *RAS* analysis set analyzed according to the treatment received.

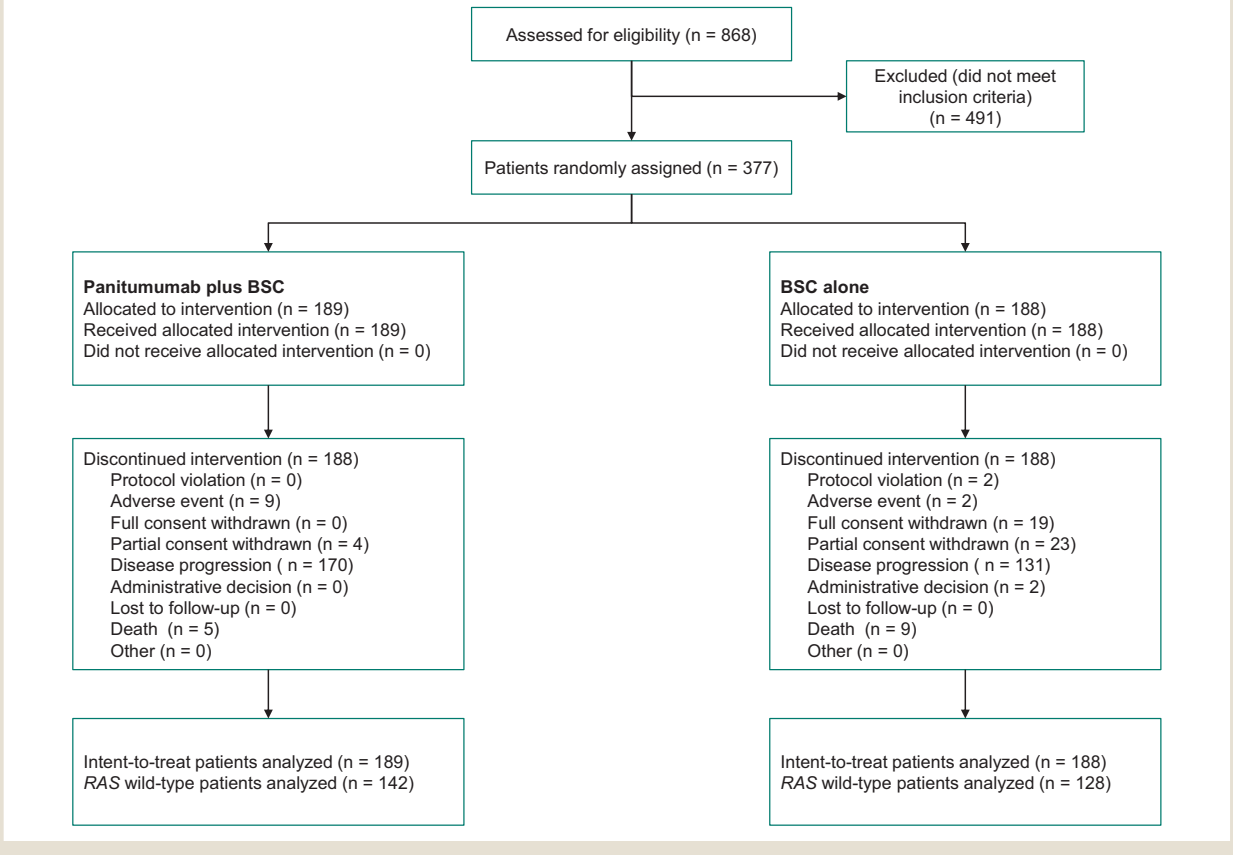
For time to event end points, hazard ratios (HRs) and 95% confidence intervals (CIs) for panitumumab with BSC relative to BSC alone were estimated from a Cox model, stratified according to the randomization factors, and evaluated using the Kaplan–Meier method. Two ETS cutoff values (20% and 0%) were used to evaluate the potential association of ETS with OS and PFS. Descriptive statistics were calculated for DpR. The prognostic relevance of *BRAF* for OS and PFS was assessed using a Cox model HR (*BRAF* wild type vs. *BRAF* mutant). For objective response, the common odds ratio (OR) across strata of randomization factors and exact 95% CIs were calculated. For the final analysis, no hypothesis was formally tested; all *P* values are descriptive.

Results

Patients

Overall, 377 patients with wild type *KRAS* exon 2 tumors were included in the intent-to-treat analysis; 270 patients had *RAS* wild

Figure 1 Consolidated Standards of Reporting Trials Diagram



Abbreviation: BSC = best supportive care.

type mCRC (panitumumab with BSC, n = 142; BSC, n = 128; Figure 1). Baseline demographic and clinical characteristics of the wild type *RAS* population are presented in Appendix B, Supplemental Table B.1 in the online version. Patients in the panitumumab with BSC arm had a median duration of treatment of 18.5 (range, 2.0-111.7) weeks and a median number of infusions of 9 (range, 1-51); patients in the BSC arm had a median duration of treatment of 5.2 (range, 0-51.0) weeks. At the time of analysis, median follow-up time was 43.7 weeks in the panitumumab with BSC arm and 23.6 weeks for the BSC arm.

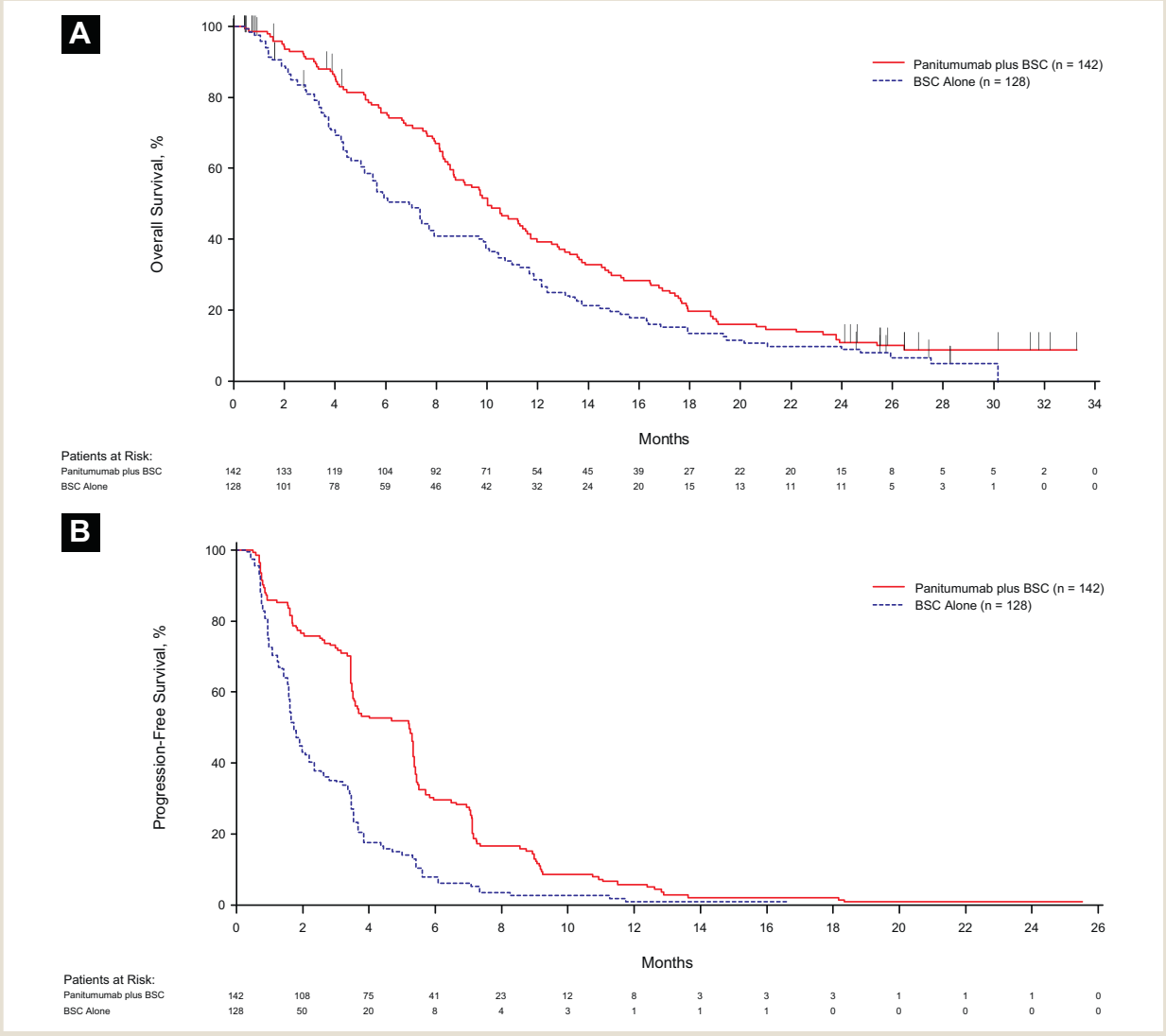
Extended RAS *and* BRAF *Mutational Analysis*

Results for patients according to *KRAS* exon 2 status are presented in Appendix B, Supplemental Table B.2 in the online version; analyses of extended *RAS* and *BRAF* mutation status are presented in Appendix B, Supplemental Table B.3 in the online version. *RAS* ascertainment in the intent-to-treat population was 86% (324 of 377); 17% of patients (54 of 324) with wild type *KRAS* exon 2 tumors had *RAS* mutations. *BRAF* ascertainment in the intent-to-treat population was 84%(317 of 377); 6.3% of patients (n = 20 of 317; panitumumab with BSC, n = 9; BSC, n = 11) had *BRAF* mutations. Mutations in *KRAS* (exons 3 and 4), *NRAS* (exons 2, 3, and 4), and *BRAF* (exon 15) were mutually exclusive.

Efficacy in the Wild Type RAS *Population*

Panitumumab with BSC significantly improved OS versus BSC alone. For patients with wild type *RAS* tumors, median OS was 10.0 (95% CI, 8.7-11.6) months in the panitumumab with BSC

Figure 2 **Survival in Patients With Wild Type *RAS* Tumors. (A) Overall Survival and (B) Progression-Free Survival in Patients With Wild Type *RAS* Tumors. (C) Overall Survival and (D) Progression-Free Survival in Patients With Wild Type *RAS* Tumors Treated With Panitumumab With BSC According to Presence of ETS (≥ 20% or < 20%). (E) Prognostic Value of *BRAF* Mutation Status on Overall Survival in Patients With Wild Type *RAS* Tumors**



Abbreviations: BSC = best supportive care; ETS = early tumor shrinkage.

Figure 2 Continued

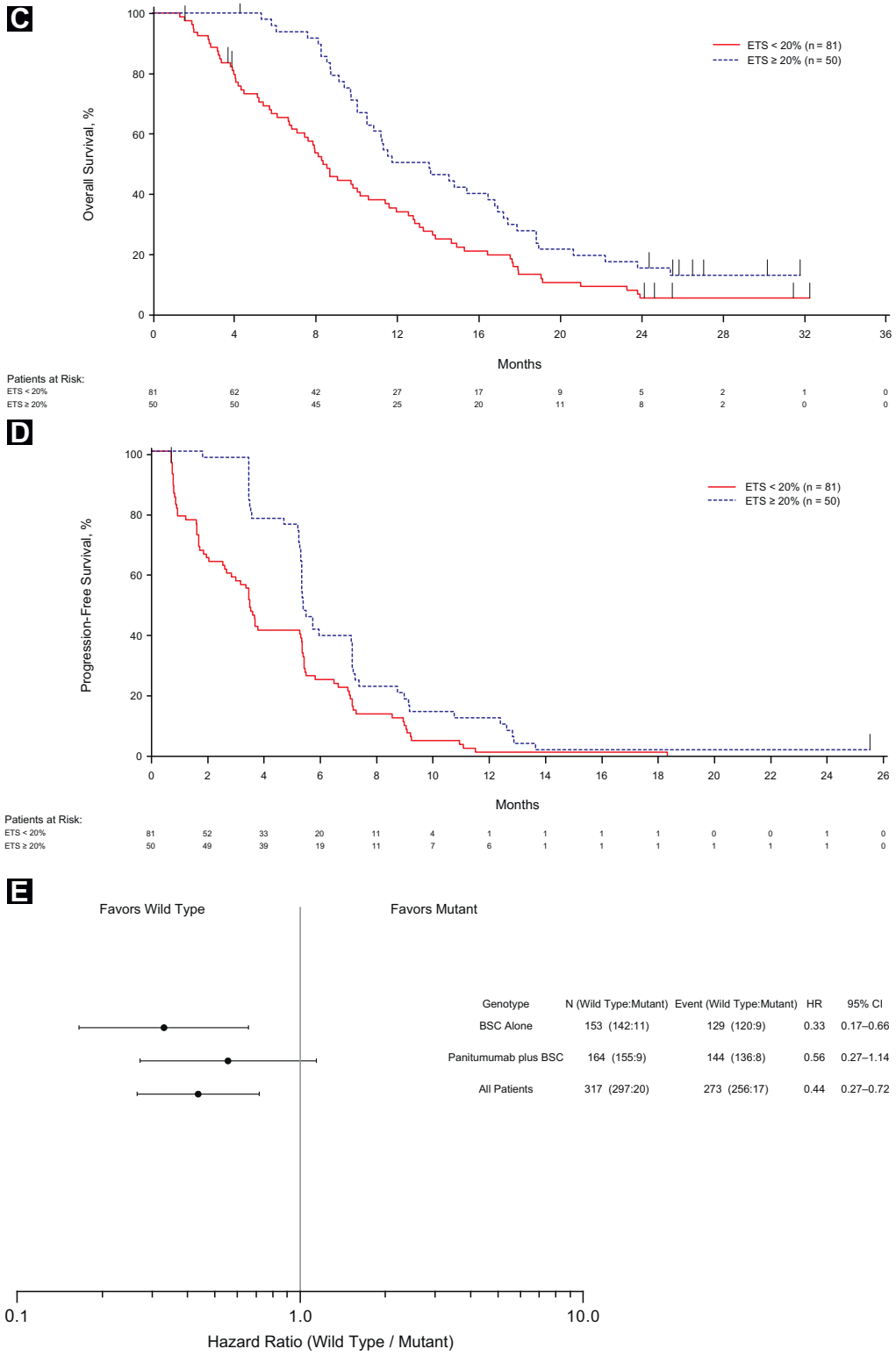


Table 1 Overall Survival and Progression-Free Survival

	Panitumumab With BSC	BSC Alone
Wild Type *RAS*, n	142	128
Overall Survival		
Median (95% CI), months	10 (8.7-11.6)	6.9 (5.2-7.9)
Hazard ratio (95% CI)	0.721 (0.553-0.940)	
P	.015	
Progression-Free Survival		
Median (95% CI), months	5.2 (3.5-5.3)	1.7 (1.6-2.2)
Hazard ratio (95% CI)	0.452 (0.348-0.588)	
P	<.0001	
Wild Type *RAS*, Wild Type *BRAF*, n	128	114
Overall Survival		
Median (95% CI), months	10.2 (8.7-11.7)	7.4 (5.7-10.0)
Hazard ratio (95% CI)	0.749 (0.566-0.993)	
P	.0436	
Progression-Free Survival		
Median (95% CI), months	5.3 (3.6-5.4)	1.8 (1.6-2.6)
Hazard ratio (95% CI)	0.452 (0.343-0.596)	
P	<.0001	
Wild Type *RAS*, Mutant *BRAF*, n	9	11
Overall Survival		
Median (95% CI), months	4.1 (3.8-NE)	3.0 (1.3-4.1)
Hazard ratio (95% CI)	0.390 (0.100-1.513)	
P	.1597	
Progression-Free Survival		
Median (95% CI), months	1.5 (0.8-3.7)	1.3 (0.9-1.8)
Hazard ratio (95% CI)	0.277 (0.071-1.080)	
P	.0502	

Abbreviation: BSC = best supportive care.

arm (n = 142) versus 6.9 (95% CI, 5.2-7.9) months in the BSC arm (n = 128; HR, 0.72; 95% CI, 0.55-0.94; $P = .015$; Figure 2A, Table 1). In analyses of patient subgroups defined according to baseline characteristics, OS generally favored panitumumab with BSC versus BSC alone (see Appendix B, Supplemental Figure B.1 in the online version). PFS was improved among patients in the panitumumab arm versus those in the BSC-alone arm. Median PFS was 5.2 (95% CI, 3.5-5.3) months in the panitumumab with BSC arm versus 1.7 (95% CI, 1.6-2.2) months in the BSC arm (HR, 0.45; 95% CI, 0.35-0.59, $P < .0001$; Figure 2B, Table 1).

Patients in the panitumumab with BSC arm had an ORR of 31.0% versus 2.3% in patients in the BSC arm (OR, 20.0; 95% CI, 5.9-101.6; $P < .0001$); no patient in either arm had a complete response. In the panitumumab with BSC arm for patients who had response (n = 44), median time to response was 1.61 (interquartile range [IQR], 0.89-2.28) months, and median duration of response was 3.7 (95% CI, 3.6-6.2) months.

Efficacy in the Wild Type RAS *Population With* BRAF *Mutations*

In patients with wild type *RAS*, wild type *BRAF* tumors, median OS was 10.2 (95% CI, 8.7-11.7) months in the panitumumab with BSC arm (n = 128) versus 7.4 (95% CI, 5.7-10.0) months in the BSC arm (n = 114; HR, 0.75; 95% CI, 0.57-0.99; $P = .04$). Median PFS was 5.3 (95% CI, 3.6-5.4) months in the panitumumab with BSC arm versus 1.8 (95% CI, 1.6-2.6) months in the BSC arm (HR, 0.45; 95% CI, 0.34-0.60; $P < .0001$). In patients with wild type *RAS*, mutant *BRAF* tumors, median OS was 4.1 (95% CI, 3.8-13.9) months in the panitumumab with BSC arm (n = 9) versus 3.0 (95% CI, 1.3-4.1) months in the BSC arm (n = 11; HR, 0.39; 95% CI, 0.10-1.51; $P = .16$). Median PFS was 1.5 (95% CI, 0.8-3.7) months in the panitumumab with BSC arm versus 1.3 (95% CI, 0.9-1.8) months in the BSC arm (HR, 0.28; 95% CI, 0.07-1.08; $P = .05$; Table 1). Among patients with wild type *RAS* (n = 270), few patients with *BRAF*-mutant tumors (n = 20) were identified. *BRAF* mutations were associated with poor prognosis for OS (HR, 0.33 [wild type *BRAF* to mutant *BRAF* in the BSC arm]; 95% CI, 0.17-0.66; Figure 2E).

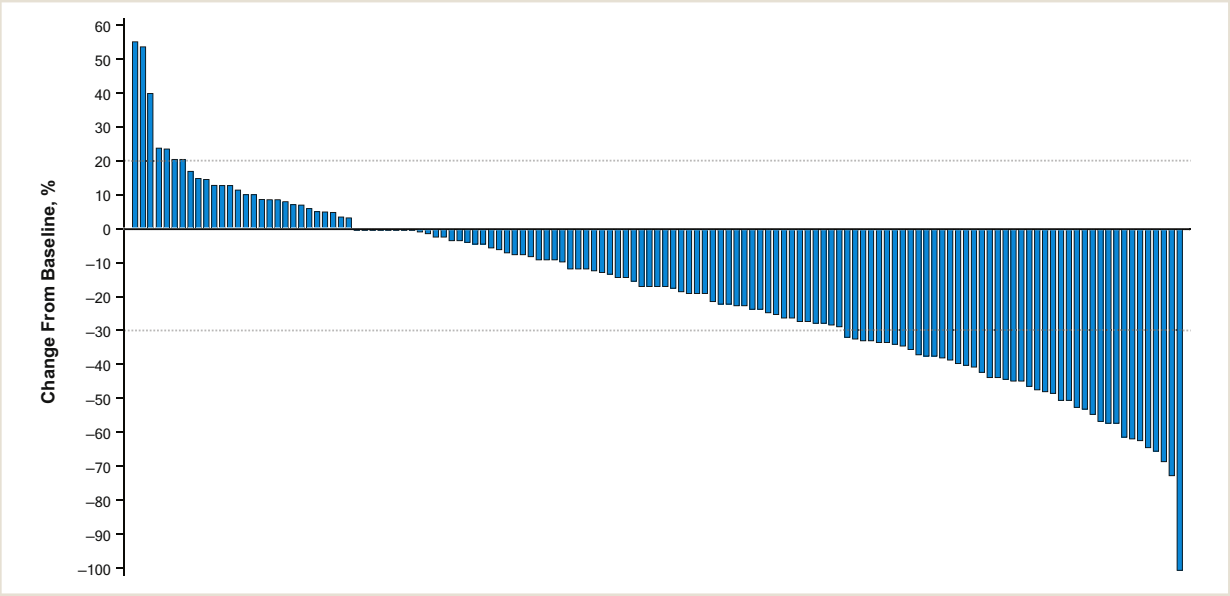
For patients with wild type *RAS*, wild type *BRAF* tumors, those in the panitumumab with BSC arm (n = 128) had an ORR of 33.6% versus 2.6% in patients in the BSC arm (n = 114; OR, 20.5; 95% CI, 5.9-102.9; $P < .0001$). For patients with wild type *RAS*, mutant *BRAF* tumors, those in the panitumumab with BSC arm (n = 9) had an ORR of 11.1% versus 0% in patients in the BSC arm (n = 11; OR, not estimable; 95% CI, 0.06 to not estimable; $P = .91$).

Depth of Response and ETS in the Wild Type RAS *Population*

In the panitumumab with BSC arm of the wild type *RAS* population evaluable for DpR (n = 130), median DpR was 16.9% (IQR, 0%-37.5%). The maximum percentage reduction of target lesions per patient is shown in Figure 3; 97 patients (68%) had some degree of reduction in lesion dimensions at any point during the study.

Because ETS has previously been associated with improved survival in combination therapy studies,[10,12] we evaluated ETS in this monotherapy study. The percent change in target lesions from baseline to nadir at week 4 or week 8 was analyzed (n = 131). Overall, 69.5%(n = 91) of patients experienced any type of tumor shrinkage at week 8, and 38.2%(n = 50) experienced ≥ 20% tumor shrinkage. When patients were stratified according to ETS ≥ 20% or < 20%, those with ETS ≥ 20% (n = 50) had a median OS of 13.6 (95% CI, 10.5-16.9) months and those with ETS < 20% (n = 81) had a median OS of 8.5 (95% CI, 7.1-10.6) months (HR, 0.58; 95% CI, 0.40-0.85; $P = .005$; Table 2, Figure 2C). Similarly, median PFS was 5.4 (95% CI, 5.3-7.1) months and 3.5 (95% CI, 2.7-5.3) months, respectively (HR, 0.57; 95% CI, 0.40-0.82; $P = .002$; Figure 2D). When stratified with a threshold of ETS ≥ 0% (n = 91) versus < 0% (n = 40), median OS was 11.5 (95% CI, 10.0-13.7) months and 6.1 (95% CI, 4.0-10.6) months, respectively (HR, 0.62; 95% CI, 0.42-

Figure 3 Maximum Reduction of Target Lesions in Patients With Wild Type *RAS* Treated With Panitumumab With BSC



Abbreviation: BSC = best supportive care.

0.93; $P = .019$); median PFS was 5.4 (95% CI, 5.3-5.7) months and 1.7 (95% CI, 0.9-2.8) months, respectively (HR, 0.39; 95% CI, 0.27-0.57; $P < .0001$).

Safety

In the wild type *RAS* population, 97.2% of those who received panitumumab with BSC (n = 142) and 61.7% of those who received BSC alone (n = 128) experienced an AE of any grade (see Appendix B, Supplemental Table B.4 in the online version). The most common AEs of any grade occurring in ≥ 20% of patients in either treatment arm were rash (39.4%; 0.8%), hypomagnesemia (31.0%; 0.8%), dermatitis acneiform (28.2%; 0%), and pruritus (24.6%; 0%). The incidences of Grade 3 and 4 AEs were 39.4% and 7.0%, respectively, for panitumumab with BSC and 15.6% and 3.1% for BSC alone. Grade 3/4 AEs with ≥ 5% incidence in either treatment arm were rash (7.7%; 0%), hypomagnesemia (7.0%; 0%), dermatitis acneiform (6.3%; 0%), and abdominal pain (2.1%; 6.3%). In the wild type *RAS* population, 5 patients (3.5%) in the panitumumab with BSC arm discontinued treatment because of AEs versus 2 patients (1.6%) in the BSC arm. The incidence of infusion reactions in the panitumumab with BSC arm was 1.4% (n = 2).

Discussion

In this follow-up final analysis, efficacy findings for patients with wild type *RAS* tumors presented in the primary analysis[4] were confirmed without any significant changes. Additionally, median OS for patients with the wild type *KRAS* exon 2 (10.0 months) as well as wild type *RAS* (10.0 months) mCRC treated with panitumumab with BSC was also consistent with other previously reported studies.[13-15] Toxicities were consistent with other

Table 2 Overall Survival and Progression-Free Survival According to ETS in Patients With Wild Type *RAS* Tumors

	ETS Threshold of 20%		ETS Threshold of 0%	
	≥20% (n = 50)	<20% (n = 81)	≥0% (n = 91)	<0% (n = 40)
Overall Survival				
Median (95% CI), months	13.6 (10.5-16.9)	8.5 (7.1-10.6)	11.5 (10.0-13.7)	6.1 (4.0-10.6)
Hazard ratio (95% CI)	0.582 (0.398-0.852)		0.624 (0.420-0.926)	
P	.0054		.0192	
Progression-Free Survival				
Median (95% CI), months	5.4 (5.3-7.1)	3.5 (2.7-5.3)	5.4 (5.3-5.7)	1.7 (0.9-2.8)
Hazard ratio (95% CI)	0.568 (0.395-0.817)		0.389 (0.265-0.571)	
P	.0023		<.0001	

Abbreviation: ETS = early tumor shrinkage.

panitumumab monotherapy studies; no new safety signals were identified.

Previous studies indicated *BRAF* mutations do not appear to be negative predictive markers of response to panitumumab, although they might be associated with poor prognosis.[1,2,16] Consistent with these studies,[1,2,16] *BRAF* mutations in 20100007 appeared to be negatively prognostic for OS but did not indicate that benefit could not be achieved with anti-EGFR therapy. Although the duration of PFS observed in patients with wild type *RAS*/mutant *BRAF* tumors was modest with panitumumab with BSC as well as BSC alone, the OS HR still favored the panitumumab with BSC arm versus BSC alone. However, because of the short OS duration observed among patients with *BRAF* mutations, the absolute magnitude of this benefit was small (1.1 months). These results must be interpreted with caution because of the small sample size of the *BRAF* mutant subgroup, consistent with other studies.[1,2] Overall, fewer patients with *BRAF* mutations were observed in this study (5%) versus earlier treatment lines (5%-15%),[1,2] potentially because *BRAF*-mutant patients have poor prognosis, and many might have died before reaching the third-line setting. This might have possibly resulted in a surviving subset of patients with *BRAF* mutations who differed clinically and biologically from those enrolled in first-line studies.

In this study, median DpR was 16.9%, with approximately 68% of the panitumumab with BSC arm achieving some degree of reduction in tumor lesion size. Previous studies have shown improved DpR in the first-line setting with EGFR inhibitors in combination with chemotherapy versus bevacizumab with chemotherapy.[9,12,17] The number of patients with some degree of reduction in tumor dimensions in this study (> 60%) was comparable with previously reported percentages,[9,12,17] despite having previous exposure to multiple agents. Moreover, in this study, the wild type *RAS* population had a median DpR of 16.9% (IQR, 0%-37.5%; range, 0-100). Because the ORR was 31.0% in the panitumumab with BSC arm, it is clear that many patients had a reduction in tumor burden but did not meet the requirement for a 30% reduction in tumor dimensions and/or requirement for confirmation of response stipulated in RECIST version 1.1.[8] Notwithstanding this failure to achieve an objective response per RECIST version 1.1, patients with a reduction in tumor lesion dimensions < 30% clearly derive some measure of benefit from anti-EGFR therapy. These results illustrate that although RECIST is an important objective measure of clinical outcome, there are clinically meaningful changes in tumor dimensions that are not captured.

Panitumumab monotherapy also resulted in ETS. In this analysis of the clinical utility (non-RECIST) of panitumumab, 38.2% of patients had ETS ≥ 20%; this level of tumor shrinkage shortly after treatment initiation represents a clinically meaningful component of treatment (eg, time to response) not captured by RECIST, and might be very interesting for patients with complaints who derive fast alleviation of tumor symptoms after treatment initiation. Importantly, patients in this study treated with panitumumab with BSC with ETS ≥ 20% had longer OS (13.6 months) versus patients with ETS < 20% (8.5 months). Similar associations between ETS and OS were observed in previous combination studies (ie, PRIME and PEAK).[10,12] In the phase III PRIME trial, more patients receiving panitumumab with oxaliplatin, fluorouracil, and leucovorin 4 versus oxaliplatin, fluorouracil, and leucovorin 4 alone had ETS ≥ 20% (72% vs. 57%; $P < .001$) at week 8, which correlated with improved OS (32.5 vs. 12.6 months).[10] In the phase II PEAK trial, panitumumab with modified fluorouracil, leucovorin, and oxaliplatin 6 was associated with a higher rate of ETS (≥ 30%) versus bevacizumab with modified fluorouracil, leucovorin, and oxaliplatin 6 (64% vs. 45%; $P = .02$) and also correlated with improved survival.[12] Moreover, in a meta-analysis of PRIME (Panitumumab Randomized Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy), PEAK (Panitumumab Efficacy in Combination With mFOLFOX6 Against Bevacizumab Plus mFOLOFOX6 in mCRC Subjects With Wild-Type KRAS Tumors), and PLANET (Phase II trial of panitumumab plus FOLFOX4 or FOLFIRI in subjects with KRAS wild-type colorectal cancer and liver-limited disease), ETS during first-line treatment was associated with improved survival in patients with wild type *RAS* mCRC.[18] Together, these results indicate that ETS, even in the refractory setting, appears to be associated with survival benefit and could possibly be used as an additional marker for efficacy, particularly in pretreated patients who receive panitumumab monotherapy.

This analysis was limited by the unblinded nature of the study, the number of biomarkers evaluated, and the lack of patient stratification according to tumor localization. Additionally, evaluations were conducted by investigators rather than at a central location, which might have introduced bias.

Conclusion

Consistent with the primary analysis,[4] the final analysis showed panitumumab improved OS and PFS in patients with chemotherapy-refractory wild type *KRAS* exon 2 and wild type *RAS* mCRC. Additionally, this study indicated ETS and DpR correlate with improvement in OS and PFS, even in later lines of therapy. Although the number of patients with *BRAF* mutations was small, results were prognostic for outcomes and consistent with other studies. Additionally, toxicities were similar to other panitumumab monotherapy studies. Panitumumab should be considered in combination or as monotherapy for effect on survival as well as for the potential for tumor shrinkage. Overall, these results further validate *RAS* as a predictive biomarker for anti-EGFR therapies, substantiate the importance of *RAS* testing at diagnosis, and indicate ETS might be a clinically useful end point for combination treatment because it was an effective predictor of monotherapy response.

Clinical Practice Points

- Tumor *RAS* status has been established as a negative predictive biomarker for anti-EGFR therapy in mCRC.
- In this study, we analyzed data from an open-label, randomized, phase III multicenter study to evaluate whether panitumumab in combination with BSC improved outcomes versus BSC alone in patients with wild type *RAS*, and wild type *RAS*, wild type *BRAF* metastatic colon or rectum adenocarcinoma.
- The final analysis of this study indicated that panitumumab improved outcomes in patients with wild type *RAS*, consistent with the primary analysis, and in patients with in wild type *RAS*, wild type *BRAF* mCRC.
- Median DpR was 16.9% in wild type *RAS* patients treated with panitumumab with BSC.
- Overall, 69.5% of patients experienced any type of tumor shrinkage, and 38.2% experienced ≥ 20% tumor shrinkage.

- Patients with ETS ≥ 20% had improved OS (HR, 0.58). OS (HR, 0.75) and PFS (HR, 0.45) were also significantly improved in wild type *RAS*, wild type *BRAF* mCRC patients treated with panitumumab with BSC.
- Early tumor shrinkage and DpR correlated with improvement in OS and PFS, even in later lines of therapy.
- This study further validates *RAS* as a predictive biomarker for anti-EGFR therapies, underscoring the importance of *RAS* testing at diagnosis, and indicating that ETS might be a clinically useful end point to inform future combination treatment because it was an effective predictor of response to monotherapy.

Acknowledgments

The authors thank the patients, their families and friends, the study staff, and the 20100007 investigators. The authors also thank Emily Plummer, PhD (former employee of Amgen Inc) and Meghan Johnson, PhD (Complete Healthcare Communications, LLC, a CHC Group company, West Chester, PA), whose work was funded by Amgen Inc, for medical writing assistance in the preparation of the manuscript. This work was supported by Amgen Inc.

Disclosure

Dr Tae Won Kim has served as a consultant for, and received research funds from, Bayer, Amgen, and Roche. Dr Elme has served as a consultant for Amgen, Roche, and Merck Sharpe & Dohme, and has received travel expenses from Amgen and Roche. Dr Park has received research grants from Celgene and AstraZeneca, has served as a consultant for Celgene, Taiho, and Shire, and has received honoraria from Celgene and Shire. Dr Udrea has served as a consultant for Bristol Myers Squibb, Roche, and Amgen, has received honoraria from Roche, Amgen, Sandoz, AstraZeneca, and Pfizer, and has received travel expenses from Astellas, Pfizer, and Janssen. Dr Manojlovic has served on speakers bureaus for Bayer, Roche, and Merck. Drs Guan, Lofton-Day, and Jung are employees of and own stock in Amgen Inc. Dr Vrdoljak has received research grants from Roche, has served as a consultant for Astellas, Pfizer, Amgen, Merck, Novartis, Roche, and AstraZeneca, has received honoraria from Pfizer, Roche, and AstraZeneca, and received travel expenses from Pfizer and Roche. The remaining authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental figures, tables, and appendixes accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2018.03.008

References

1. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med* 2013; 369:1023-34.
2. Peeters M, Oliner KS, Price TJ, et al. Analysis of KRAS/NRAS mutations in a phase III study of panitumumab with FOLFIRI compared with FOLFIRI alone as second-line treatment for metastatic colorectal cancer. *Clin Cancer Res* 2015; 21: 5469-79.
3. Patterson SD, Peeters M, Siena S, et al. Comprehensive analysis of KRAS and NRAS mutations as predictive biomarkers for single agent panitumumab (pmab) response in a randomized, phase III metastatic colorectal cancer (mCRC) study (20020408) (abstract 3617). *J Clin Oncol* 2013; 31(Suppl).
4. Kim TW, Elme A, Kusic Z, et al. A phase 3 trial evaluating panitumumab plus best supportive care vs best supportive care in chemorefractory wild type KRAS or RAS metastatic colorectal cancer. *Br J Cancer* 2016; 115:1206-14.
5. Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild type KRAS exon 2 metastatic colorectal cancer. *J Clin Oncol* 2014; 32:2240-7.
6. Phipps AI, Buchanan DD, Makar KW, et al. BRAF mutation status and survival after colorectal cancer diagnosis according to patient and tumor characteristics. *Cancer Epidemiol Biomarkers Prev* 2012; 21:1792-8.
7. Llovet P, Sastre J, Ortega JS, et al. Prognostic value of BRAF, PI3K, PTEN, EGFR copy number, amphiregulin and epiregulin status in patients with KRAS codon 12 wild type metastatic colorectal cancer receiving first-line chemotherapy with anti-EGFR therapy. *Mol Diagn Ther* 2015; 19:397-408.
8. Eisenhauer EA, Therasse P, Bogaerts J, et al. New Response Evaluation Criteria in Solid Tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45: 228-47.
9. Heinemann V, Stintzing S, Modest DP, et al. Early tumour shrinkage (ETS) and depth of response (DpR) in the treatment of patients with metastatic colorectal cancer (mCRC). *Eur J Cancer* 2015; 51:1927-36.
10. Douillard JY, Siena S, Peeters M, et al. Impact of early tumour shrinkage and resection on outcomes in patients with wild type RAS metastatic colorectal cancer. *Eur J Cancer* 2015; 51:1231-42.
11. Cremolini C, Loupakis F, Antoniotti C, et al. Early tumor shrinkage and depth of response predict long-term outcome in metastatic colorectal cancer patients treated with first-line chemotherapy plus bevacizumab: results from phase III TRIBE trial by the Gruppo Oncologico del Nord Ovest. *Ann Oncol* 2015; 26:1188-94.
12. Rivera F, Karthaus M, Hecht JR, et al. Tumor response outcomes in first-line treatment of wild type (WT) RAS metastatic colorectal carcinoma (mCRC) following modified FOLFOX6 (mFOLFOX6) + either panitumumab (pmab) or bevacizumab (bev) (abstract 3535). *J Clin Oncol* 2015; 33(Suppl).
13. Amado RG, Wolf M, Peeters M, et al. Wild type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008; 26:1626-34.
14. Price TJ, Peeters M, Kim TW, et al. Panitumumab vs. cetuximab in patients with chemotherapy-refractory wild type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol* 2014; 15:569-79.
15. Price T, Kim TW, Li J, et al. Final results and outcomes by prior bevacizumab exposure, skin toxicity, and hypomagnesaemia from ASPECCT: randomized phase 3 non-inferiority study of panitumumab versus cetuximab in chemorefractory wild type KRAS exon 2 metastatic colorectal cancer. *Eur J Cancer* 2016; 68:51-9.
16. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol* 2010; 11:753-62.
17. Stintzing S, Modest DP, Von Weikersthal LF, et al. Independent radiological evaluation of objective response, early tumor shrinkage, and depth of response in FIRE-3 (AIO KRK-0306) in the final RAS evaluable population. *Ann Oncol* 2014; 25:1-41.
18. Rivera F, Karthaus M, Valladares-Ayerbes M, et al. An exploratory study-level meta-analysis assessing the impact of early tumor shrinkage on overall survival in patients with RAS wild type metastatic colorectal cancer receiving first-line treatment in three randomised panitumumab trials. (abstract PD-031). *Ann Oncol* 2016; 27(Suppl 2):ii102-17.