Panitumumab Versus Cetuximab in Patients With Metastatic Colorectal Cancer

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ABSTRACT

Background

The anti–epidermal growth factor receptor monoclonal antibodies panitumumab and cetuximab are effective in patients with chemotherapy-refractory wild-type *KRAS* exon 2 metastatic colorectal cancer (mCRC). We report the first randomized, open-label, phase 3 head-to-head study evaluating efficacy and toxicity of panitumumab versus cetuximab in these patients.

Methods

Patients ≥18 years old with chemotherapy-refractory mCRC, ECOG performance status ≤2, and wild-type *KRAS* exon 2 status were randomized 1:1 to receive panitumumab (6 mg/kg Q2W) or cetuximab (initial dose, 400 mg/m^2; 250 mg/m^2 QW thereafter). Overall survival (OS; the primary endpoint) was evaluated for non-inferiority (retention of ≥50% of the cetuximab treatment effect [historical hazard ratio cetuximab+BSC:BSC=0.55]).

Results

Overall, 999 patients were randomized worldwide and received treatment (panitumumab, n=499; cetuximab, n=500). Panitumumab was non-inferior to cetuximab (*P*=0.0007; retention rate, 105.7%; 95%CI=81.9%—129.5%). Median OS was 10.4 (95%CI=9.4—11.6) months with panitumumab and 10.0 (95%CI=9.3—11.0) months with cetuximab (hazard ratio panitumumab:cetuximab=0.97; 95%CI=0.84—1.11); there were no significant differences in OS by region. Incidence of AEs of any grade and grade 3/4 was similar across treatment arms. Grade 3/4 skin toxicity occurred in 13% of

panitumumab patients and 10% of cetuximab patients. Incidence of grade 3/4 infusion reactions was lower in panitumumab patients than cetuximab patients (0.2% versus 1.8%). Incidence of grade 3/4 hypomagnesemia was higher in panitumumab patients (7.1% versus 2.6%).

Conclusions

Panitumumab was non-inferior to cetuximab. Given the high retention rate and anticipated toxicity profile, panitumumab should be considered an effective treatment option for patients with chemotherapy-refractory wild-type *KRAS* exon type 2 mCRC.

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INTRODUCTION

Colorectal cancer (CRC) is the fourth-leading cause of cancer-related death worldwide.[1] For patients with metastatic CRC (mCRC), irinotecan/oxaliplatin-based chemotherapy in combination with targeted therapy has improved median overall survival (OS) beyond 2 years,[2,3] increasing the number of chemotherapy-refractory patients eligible for third-line therapy. The anti-epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab (a chimeric IgG1 antibody) and panitumumab (a fully-human IgG2 antibody) provide clinical benefit in patients with chemotherapy-refractory mCRC. In the phase 3 CO.17 study, cetuximab monotherapy improved OS and progression-free survival (PFS) compared with best supportive care (BSC).[4] Retrospective analysis demonstrated that benefit was restricted to patients with wild-type *KRAS* exon 2 mCRC.[5] In the phase 3 408 study, panitumumab plus BSC improved PFS and objective response rate (ORR) compared with BSC.[6,7] Subsequent analysis showed that PFS/ORR benefits of panitumumab treatment were limited to patients with wild-type *KRAS* exon 2 mCRC.[8] Panitumumab did not improve OS; however, the study had a crossover design, and 76% of patients in the BSC arm received panitumumab post-progression, which may have influenced the observed OS results.[6,7]

There has been no direct prospective comparison of efficacy and safety between panitumumab and cetuximab in chemotherapy-refractory mCRC. Cross-study comparisons have been hampered by differences in patient demographics, study design, and *KRAS* ascertainment. Moreover, standards of care have evolved since approval of these agents; consequently, re-evaluation of safety and efficacy in this setting is important and necessary. The randomized, double-blind, phase 3 ASPECCT

study (A Study of Panitumumab Efficacy and Safety Compared to Cetuximab) is the first head-to-head comparison of panitumumab and cetuximab in chemotherapy-refractory wild-type *KRAS* exon 2 mCRC. ASPECCT enrolled patients worldwide, is the largest prospective comparison of anti-EGFR agents in mCRC, and is among the largest head-to-head comparisons of biologic agents in mCRC. The study employed a non-inferiority design to evaluate whether panitumumab preserved the OS benefit achieved with cetuximab.[4,5]

METHODS

Patients

Eligible patients (≥18 years) had histologically or cytologically confirmed metastatic adenocarcinoma of the colon/rectum with wild-type *KRAS* exon 2 tumor status (assessment described below), measurable/non-measurable disease per RECIST v1.1,[9] ECOG performance status ≤2, disease progression/intolerability with irinotecan- and oxaliplatin-based therapy, and previously received a thymidylate synthase inhibitor for CRC. Exclusion criteria included prior anti-EGFR therapy, antitumor therapy within 30 days, symptomatic brain metastases requiring treatment, history of other unresolved malignancies, major surgery within 28 days, significant cardiovascular disease/myocardial infarction, history of interstitial lung disease, active/uncontrolled infections within 14 days, serum magnesium below lower limit of normal, and inadequate hematologic, renal, or hepatic function.

The protocol received institutional/ethical approval at each treatment site. Patients provided written informed consent.

Study Design and Treatment

This open-label, randomized, multicenter, phase 3 non-inferiority study was conducted in 27 countries in North and South America, Europe, Asia, Africa, and Australia. Using an automated interactive voice response system, patients were randomized 1:1 to receive either panitumumab 6mg/kg intravenously on day 1 of each 14-day cycle or cetuximab at an initial dose of 400mg/m^2 intravenously followed by 250mg/m^2 intravenously on day 1 of each 7-day cycle. Randomization was stratified by

geographic region (North America/Western Europe/Australia versus rest-of-world) and ECOG performance status (0/1 versus 2). Patients in the cetuximab arm received treatment consistent with product labeling in their respective countries, including premedication with an H1 antagonist before infusion. Premedication for infusion reaction was not required for panitumumab. Treatment continued until disease progression, intolerability, or withdrawal of consent. Infusion was stopped for any grade of infusion reaction. Dosing could be resumed with a 50% infusion-rate reduction for grade 1/2 reactions but was permanently discontinued for grade 3/4 reactions. If toxicity occurred, panitumumab/cetuximab doses could be withheld/reduced per protocol-specified rules. Crossover between panitumumab/cetuximab was not permitted during the study treatment period.

The sponsor, Amgen, designed the study with input from principal investigators and performed subsequent data and statistical analyses. Investigators collected clinical data. The manuscript was assembled by the authors with medical writing assistance (funded by Amgen); all authors approved the manuscript.

Study Endpoints

The primary endpoint was OS (time from randomization to death). Secondary endpoints included PFS (time from randomization to disease progression/death), ORR, and safety.

Assessments

Computed tomography or magnetic resonance imaging of the abdomen, pelvis, and chest were performed at 6±1 weeks and every 8±1 weeks thereafter. Response was

evaluated by investigators per RECIST v1.1.[9] Adverse events (AEs) occurring through 30 days after the last dose day, were graded according to the NCI-CTCAE v3.0,[10] except skin- or nail-related toxicities which were graded using NCI-CTCAE version 3.0 with modifications (**Supplemental Table 1**). All patients were followed for OS for 24 months after randomization of the last patient.

KRAS Testing

KRAS tumor status in formalin-fixed, paraffin-embedded tumor tissue sections was assessed before randomization at one of three laboratories (HistoGeneX, Belgium; LabCorp China, China; LabCorp CTS-RTP, NC, USA). Presence/absence of the seven most common *KRAS* exon 2 mutations was evaluated using the Therascreen KRAS assay (Qiagen, Venlo, Netherlands).[2]

Statistical Analysis

This non-inferiority study was designed to demonstrate that panitumumab retains ≥50% of the OS treatment effect of cetuximab versus BSC. The predicted effect of cetuximab versus BSC on OS was based on the CO.17 study (hazard ratio [HR]=0.55; 95%CI, 0.41–0.74).[5] Assuming a panitumumab versus cetuximab HR of 1.0 and a 20% censoring rate among randomized patients, 1000 patients were required to achieve 90% power with one-sided α=0.025 for the OS inferiority null hypothesis.

Non-inferiority criteria were based on a synthesis approach. An asymptotic standard normal test statistic[11,12] with one-sided α=0.025 was used to test the OS inferiority null hypothesis; a *Z*-score less than −1.96 was significant for non-inferiority. Cox models stratified by the randomization factors were used to estimate HRs and 95%CI for OS

and PFS. Common odds ratio (OR) stratified by the randomization factors and exact 95%CI were calculated for ORR. Non-inferiority was also assessed based on retention rate using the Hasselblad and Kong procedure,[13] in which a historical study demonstrating a treatment effect for an active comparator versus control is used to estimate the fraction of effect preserved by an experimental therapy (retention rate). Consistent with standard guidance for non-inferiority studies,[14,15] the retention rate was required to be ≥50% for panitumumab to be considered non-inferior. If non-inferiority was established, superiority of panitumumab versus cetuximab for OS would be assessed using a Cox proportional hazards model based on the intent-to-treat population. Constancy between this study and CO.17 was evaluated qualitatively by comparing population baseline characteristics and OS benefit between the two studies; no formal statistical analysis of constancy was performed.

Primary analysis of OS and PFS was performed using the primary analysis set (patients receiving ≥1 dose of panitumumab/cetuximab). Primary analysis of ORR used the tumor response analysis set (primary analysis set patients with >1 measurable lesion per RECIST v1.1 at baseline). Descriptive safety analyses, without formal statistical analysis, were conducted using the safety analysis set (primary analysis set patients).

RESULTS

Patients

Between February 2010 and July 2012, 1010 patients with wild-type *KRAS* exon 2 tumor status mCRC were enrolled, 999 were randomized and received ≥1 dose of study treatment (panitumumab, n=499; cetuximab, n=500; **Supplemental Figure S1**). Baseline characteristics were balanced between the treatment arms; 52% were white and 69% were from Asia, Eastern Europe, Africa, or South America (**Table 1**). Ninety percent of patients had metastatic sites outside the liver, and 26% had received prior bevacizumab. At the time of this analysis, 493 patients had discontinued panitumumab and 491 had discontinued cetuximab because of disease progression (panitumumab, n=423; cetuximab, n=422), AE (n=31, n=24), death (n=17, n=15), withdrawal of consent (n=16, n=21), noncompliance (n=3, n=2), and other reasons (n=3, n=6; **Supplemental Figure S1**). Median number of infusions was 7 (range, 1–65) for panitumumab and 14 (range, 1–94) for cetuximab, with median relative dose intensities across all doses of 99% for panitumumab and 98% for cetuximab. Median follow-up time was 41.4 weeks for the panitumumab arm and 40.5 weeks for the cetuximab arm.

Post-progression antitumor therapy was similar between treatment arms (panitumumab, n=205 [41%]; cetuximab, n=211 [42%]), and included cytotoxic chemotherapy (panitumumab, n=155 [31%]; cetuximab, n=165 [33%]), anti-EGFR monoclonal antibodies (n=45 [9%]; n=52 [10%]), and anti–vascular endothelial growth factor therapy (n=35 [7%]; n=33 [7%]).

Efficacy

At the time of this analysis, 383 (77%) patients in the panitumumab arm and 392 (78%) in the cetuximab arm had died. The non-inferiority test was positive (Z-score=−3.19; *P*<0.0007), confirming that panitumumab retained ≥50% of the OS benefit of cetuximab over BSC. Median OS was 10.4 (95%CI=9.4–11.6) months in the panitumumab arm and 10.0 (95%CI=9.3–11.0) months in the cetuximab arm (HR=0.97; 95%CI=0.84−1.11; **Figure 1A**). OS was similar between the treatment arms across all the predefined patient subgroups: HRs ranged from 0.77 to 1.19, and the 95%CI for each subgroup encompassed 1 (**Figure 1B**). The panitumumab arm was estimated to retain 105.7% (95%CI=81.9%–129.5%) of the cetuximab effect on OS observed in this study. Notably, the minimum preservation of the cetuximab treatment effect on OS by panitumumab was 81.9% (lower bound of the confidence interval). Panitumumab was not found to be superior to cetuximab.

At the time of this analysis, 477 patients in the panitumumab arm and 477 patients in the cetuximab arm had died or experienced disease progression per RECIST v1.1. Median PFS was 4.1 (95%CI=3.2–4.8) months in the panitumumab arm and 4.4 (95%CI=3.2–4.8) months in the cetuximab arm (HR=1.00; 95%CI=0.88–1.14; **Figure 2A**). PFS was similar between the treatment arms for all patient subgroups analyzed, and the 95%CI for each subgroup encompassed 1 (**Figure 2B**).

ORR was 22.0% (95%CI=18.4–26.0) in the panitumumab arm and 19.8% (95%CI=16.3–23.6) in the cetuximab arm (OR=1.15; 95%CI=0.83–1.58; **Table 2**). Two patients (0.4%) in the panitumumab arm had a complete response; none in the cetuximab arm had a complete response. Best response of stable disease for ≥5

weeks occurred in 46.5% of patients receiving panitumumab and 48.7% receiving cetuximab.

Constancy

The assumption of constancy of the cetuximab treatment effect between this study and the CO.17 cetuximab wild-type *KRAS* exon 2 group was considered validated. Outcomes were similar in the two studies (median OS, 10.0 versus 9.5 months; median PFS, 4.4 versus 3.7 months; ORR, 19.8% versus 12.8%).[5] Skin toxicities were the most frequently occurring AEs in both studies.[4] Patient demographics, including median age (ASPECCT, 60.5 years; CO.17, 63.0 years) and percentage of patients with colon cancer (65.2%; 59.6%) were consistent between studies.[5] Cetuximab was administered at the same dose and schedule.[4,5]

Safety

Overall incidence of treatment-emergent AEs was similar between treatment arms for AEs of any grade (panitumumab, 98%; cetuximab, 98%), serious AEs (30%; 34%), grade 3 AEs (36%; 32%), and grade 4 AEs (8%; 5%). Ten percent of cetuximab-treated patients and 6% of panitumumab-treated patients had fatal AEs.

AEs of interest are summarized in **Table 3**. The incidence of infusion reactions was lower in the panitumumab arm (2.8%) than the cetuximab arm (12.5%). Grade 3/4 infusion reactions occurred in one patient (0.2%) receiving panitumumab arm and nine patients (1.8%) receiving cetuximab. The incidence of grade 3/4 hypomagnesemia was greater among patients receiving panitumumab (7%) compared with those receiving cetuximab (3%). Six patients in the panitumumab arm (1.2%) and two in the cetuximab

arm (0.4%) discontinued because of hypomagenesemia. Twenty-five patients (5%) in the panitumumab arm and 14 (3%) in the cetuximab arm had dose modifications for hypomagnesemia. The incidence of grade 3/4 skin and subcutaneous tissue toxicity was similar between the panitumumab (13%) and cetuximab arms (10%).

Twenty-nine patients (6%) receiving panitumumab had fatal adverse events compared with 50 (10%) receiving cetuximab. In both treatment arms, most fatal AEs were attributed to disease progression (panitumumab, 20 [69% of all fatal AEs]; cetuximab, 34 [68% of all fatal AEs]). Fatal AEs not attributable to disease progression occurring in ≥2 patients were acute renal failure (panitumumab, n=2; cetuximab, n=0), sepsis (n=2; n=0), lung infection (n=0; n=2), and pneumonia (n=0; n=2). The only treatment-related fatal AE was a lung infection occurring in a cetuximab-treated patient.

DISCUSSION

This randomized, open-label, global, phase 3 non-inferiority study that enrolled 1010 patients is the first head-to-head comparison of panitumumab and cetuximab in patients with chemotherapy-refractory mCRC. Using robust statistical analysis, we demonstrated that panitumumab was non-inferior to cetuximab for OS based on the study-defined criteria of a ≥50% retention rate of the OS benefit of cetuximab. Moreover, OS, PFS, and ORR were consistent with anti-EGFR antibody class outcomes reported in the 408 and CO.17 studies.[5,8] *KRAS* status was evaluated prospectively, ensuring that all enrolled patients were wild-type *KRAS* exon 2. Previous phase 3 studies evaluating anti-EGFR monoclonal antibodies evaluated *KRAS* status retrospectively with ascertainment rates of 69% for cetuximab[5] and 92% for panitumumab.[8] The results demonstrate the value of head-to-head studies not only in evaluating an agent against an active comparator (an approach infrequently employed in oncology), but also providing physicians with comprehensive efficacy and toxicity information that can guide treatment decisions.

A non-inferiority design was appropriate given the anticipated similarity in outcomes with cetuximab and panitumumab. Such studies must consider constancy with high-quality historical controls,[11,16,17] in this case the phase 3 CO.17 study.[5] Patient baseline characteristics and median OS for the cetuximab arm (ASPECCT, 10.0 months; CO.17, 9.5 months) were similar between this study and CO.17.[5] Thus, the constancy assumption was met. Notably, this global study extended the findings of the CO.17[5] and 408 studies[8] by demonstrating clinical benefit with both panitumumab and cetuximab in a more geographically and ethnically diverse patient population. HRs for

OS and PFS were similar not only for the study population as a whole, but across all predefined patient subgroups (including geographic region). The similarity in outcomes across subgroups supports broad applicability of these agents among patients with chemotherapy-refractory wild-type *KRAS* exon 2 mCRC. The somewhat low rate of prior bevacizumab use in this study (26%) likely reflects availability of bevacizumab for this geographically diverse patient population.

ASPECCT also allows for a direct, comprehensive evaluation of toxicity with panitumumab and cetuximab in chemotherapy-refractory patients. Both agents had anticipated toxicity for an anti-EGFR agent. Observed rates of toxicity and the incidence of most individual toxicities was similar across the treatment arms. Previous panitumumab and cetuximab studies have used heterogeneous criteria to summarize skin toxicity,[2,4,6,18-23] making cross-study comparisons difficult and leading some to conclude that incidence of skin toxicity is higher with panitumumab than cetuximab. In ASPECCT, the incidence of skin AEs (including rash, dermatitis acneiform, and dry skin), was similar for panitumumab- and cetuximab-treated patients. However, the incidence of infusion reactions was greater among cetuximab-treated patients despite prophylaxis for infusion reactions in this group. This observation is consistent with previous reports for cetuximab[21,24] and panitumumab,[2,6,19,22] and the hypothesis that fully human monoclonal antibodies (such as panitumumab) are less immunogenic than chimeric monoclonal antibodies (such as cetuximab).[25] Additionally, hypomagnesemia occurred more frequently among patients receiving panitumumab, although most events were grade 1/2. Hypomagnesemia is typically manageable by physicians, and was infrequently a cause to withhold or change doses in either arm in this study.

Hypomagnesemia is an on-target AE potentially caused by renal Mg^{2+} wasting due to EGFR inhibition in the kidney.[26] Higher affinity binding of panitumumab to EGFR may contribute to these differences.[27]

Evaluation of potential predictive biomarkers for anti-EGFR monoclonal antibodies in mCRC has been an area of intense scientific interest[28] and the ASPECCT data set offers an opportunity to further assess potential biomarkers in this setting. In particular, evaluation of mutations emerging at the time of clinical progression and their effect on clinical outcomes warrants further investigation.

Anti-EGFR monoclonal antibodies have now been shown to provide clinical benefit in phase 3 studies across all lines of therapy in wild-type *KRAS* exon 2 mCRC,[2,5,8,19,21,29,30] The overlapping treatment effect of panitumumab and cetuximab as monotherapy raises the question of whether these agents are interchangeable when combined with chemotherapy as first- or second-line therapy; further research will be required to evaluate this possibility.

In conclusion, our results demonstrate that panitumumab is non-inferior to cetuximab and that these agents provide similar OS benefit in this heavily pretreated patient population, with >50% of participants having OS longer than 10 months. Furthermore, PFS/ORR results from retrospective analyses were confirmed in a prospective trial of wild-type *KRAS* exon 2 patients. Both agents had anticipated toxicity profiles. Given the consistency in efficacy and toxicity observed, small but meaningful differences in the rate of grade 3/4 infusion reactions differences in dose scheduling may guide physician choice of anti-EGFR therapy.

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TABLES

Table 1. Baseline Characteristics of the Patients, According to Treatment Arm

	Panitumumab N=499	Cetuximab N=500
Median (range) age — years	61.0 (19–86)	60.5 (20–89)
Men — no. (%)	315 (63.1)	318 (63.6)
Race/ethnicity — no. (%)		
White or Caucasian	266 (53.3)	258 (51.6)
Asian	222 (44.5)	228 (45.6)
Hispanic or Latino	6 (1.2)	7 (1.4)
Black or African American	2 (0.4)	4 (0.8)
Japanese	1 (0.2)	0 (0.0)
Other	2 (0.4)	3 (0.6)
ECOG performance status — no. (%)		
0	154 (30.9)	163 (32.6)
1	303 (60.7)	297 (59.4)
2	42 (8.4)	40 (8.0)
Location of primary tumor — no. (%)		
Colon	292 (58.5)	326 (65.2)
Rectum	207 (41.5)	174 (34.8)
Histologic type — no. (%)		
No subtype	195 (39.1)	189 (37.8)
Mucinous	51 (10.2)	47 (9.4)
Appendiceal	0 (0.0)	2 (0.4)
Other	26 (5.2)	27 (5.4)
Unknown	227 (45.5)	235 (47.0)
Prior bevacizumab — no. (%)	126 (25.3)	132 (26.4)
Sites of metastatic disease — no. (%)		

Liver only	52 (10.4)	50 (10.0)
Liver plus other sites	447 (89.6)	450 (90.0)
Region — no. (%)		
North America, Western Europe, Australia	154 (30.9)	156 (31.2)
Rest of the world	345 (69.1)	344 (68.8)

ECOG, Eastern Cooperative Oncology Group.

Table 2. Objective Response Rates*

	Panitumumab N=499	Cetuximab N=500
Best response assessment — no. (%)		
Complete response	2 (0.4)	0 (0)
Partial response	105 (21.6)	96 (19.8)
Stable disease	226 (46.5)	236 (48.7)
Progressive disease	121 (24.9)	124 (25.6)
Not evaluated	5 (1.0)	4 (0.8)
Not done	27 (5.6)	25 (5.2)
Patients with objective response — no.	107	96
Objective response rate — % (95% CI)	22.0 (18.4– 26.0)	19.8 (16.3–23.6)
Odds ratio (95% CI)	1.15 (0.83–1.58)	

*Patients with measurable disease at baseline only.

Table 3. Patient Incidence of Adverse Events

	Panitumumab N=496		Cetuximab N=503	
Incidence of adverse events – no. (%)				
Any grade	485 (97.8)		494 (98.2)	
Grade 3	180 (36.3)		159 (31.6)	
Grade 4	37 (7.5)		27 (5.4)	
Grade 5	29 (5.8)		50 (9.9)	
Adverse events occurring in >5% of patients in either treatment arm — no. (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Rash	249 (50.2)	24 (4.8)	257 (51.1)	18 (3.6)
Dermatitis acneiform	138 (27.8)	17 (3.4)	136 (27.0)	14 (2.8)
Hypomagnesemia	136 (27.4)	35 (7.1)	89 (17.7)	13 (2.6)
Diarrhea	91 (18.3)	10 (2.0)	89 (17.7)	9 (1.8)
Dry skin	83 (16.7)	1 (0.2)	79 (15.7)	0 (0.0)
Pruritus	83 (16.7)	4 (0.8)	88 (17.5)	1 (0.2)
Fatigue	75 (15.1)	14 (2.8)	88 (17.5)	18 (3.6)
Decreased appetite	69 (13.9)	3 (0.6)	78 (15.5)	7 (1.4)
Nausea	68 (13.7)	4 (0.8)	57 (11.3)	7 (1.4)
Abdominal pain	61 (12.3)	17 (3.4)	83 (16.5)	14 (2.8)
Vomiting	59 (11.9)	9 (1.8)	51 (10.1)	7 (1.4)
Paronychia	58 (11.7)	11 (2.2)	75 (14.9)	10 (2.0)

Acne	52 (10.5)	3 (0.6)	69 (13.7)	5 (1.0)
Skin fissures	42 (8.5)	1 (0.2)	43 (8.5)	3 (0.6)
Constipation	41 (8.3)	1 (0.2)	72 (14.3)	3 (0.6)
Hypokalemia	41 (8.3)	16 (3.2)	23 (4.6)	8 (1.6)
Cough	40 (8.1)	0 (0.0)	38 (7.6)	0 (0.0)
Back pain	36 (7.3)	5 (1.0)	39 (7.8)	3 (0.6)
Asthenia	35 (7.1)	7 (1.4)	48 (9.5)	8 (1.6)
Anemia	31 (6.3)	13 (2.6)	32 (6.4)	15 (3.0)
Pyrexia	31 (6.3)	2 (0.4)	56 (11.1)	4 (0.8)
Insomnia	27 (5.4)	0 (0.0)	46 (9.1)	0 (0.0)
Hypocalcemia	26 (5.2)	6 (1.2)	16 (3.2)	6 (1.2)
Nail disorder	26 (5.2)	1 (0.2)	31 (6.2)	2 (0.4)
Stomatitis	26 (5.2)	3 (0.6)	34 (6.8)	0 (0.0)
Weight decreased	26 (5.2)	1 (0.2)	21 (4.2)	0 (0.0)
Peripheral edema	23 (4.6)	5 (1.0)	40 (8.0)	5 (1.0)
Dyspnea	22 (4.4)	5 (1.0)	38 (7.6)	7 (1.4)
Mucosal inflammation	22 (4.4)	1 (0.2)	25 (5.0)	3 (0.6)
Dyspepsia	19 (3.8)	0 (0.0)	26 (5.2)	1 (0.2)
Headache	17 (3.4)	0 (0.0)	36 (7.2)	0 (0.0)
Upper respiratory tract infection	15 (3.0)	2 (0.4)	28 (5.6)	0 (0.0)
Other adverse events — no. (%)				
Skin and subcutaneous tissue toxicity*	430 (86.7)	62 (12.5)	440 (87.5)	48 (9.5)
Infusion reactions	14 (2.8)	1 (0.2)	63 (12.5)	9 (1.8)

*Includes adverse events in the “Skin and Subcutaneous Tissue Disorders” system organ class of the Medical Dictionary for Regulatory Activities version 15.1.

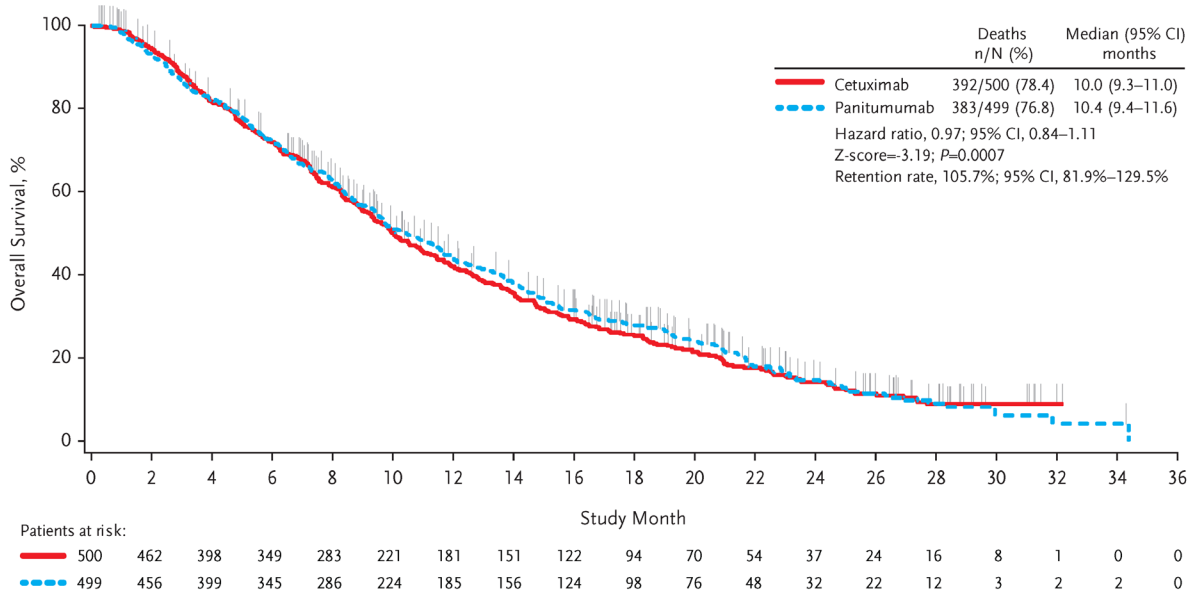
FIGURE LEGENDS

Figure 1. (A) Kaplan-Meier curves for overall survival by treatment group. (B) Subset analysis for overall survival

Figure 2. (A) Kaplan-Meier curves for progression-free survival by treatment group. (B) Subset analysis for progression-free survival.

Figure 1

A


Deaths n/N (%)
Median (95% CI) months
Cetuximab 392/500 (78.4) 10.0 (9.3–11.0)
Panitumumab 383/499 (76.8) 10.4 (9.4–11.6)
Hazard ratio, 0.97; 95% CI, 0.84–1.11
Z-score=-3.19; P=0.0007
Retention rate, 105.7%; 95% CI, 81.9%–129.5%
Overall Survival, %
Study Month
Patients at risk:
500 462 398 349 283 221 181 151 122 94 70 54 37 24 16 8 1 0 0
499 456 399 345 286 224 185 156 124 98 76 48 32 22 12 3 2 2 0

B

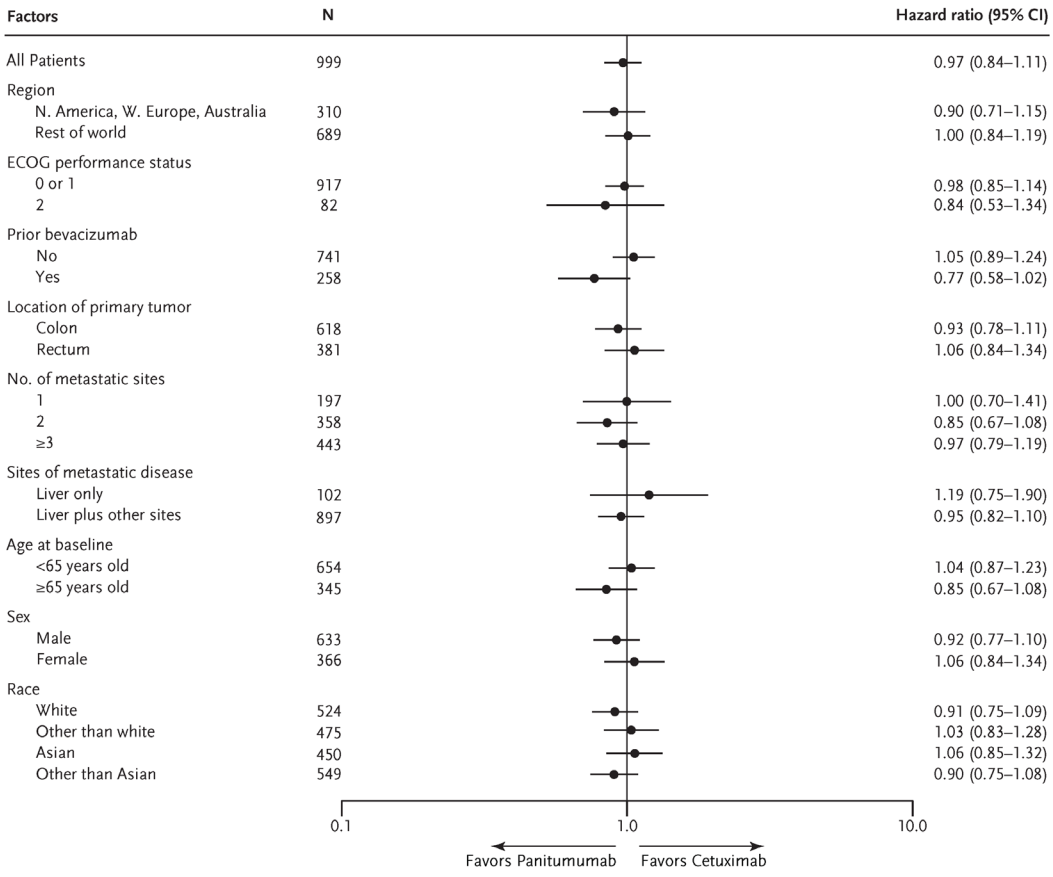
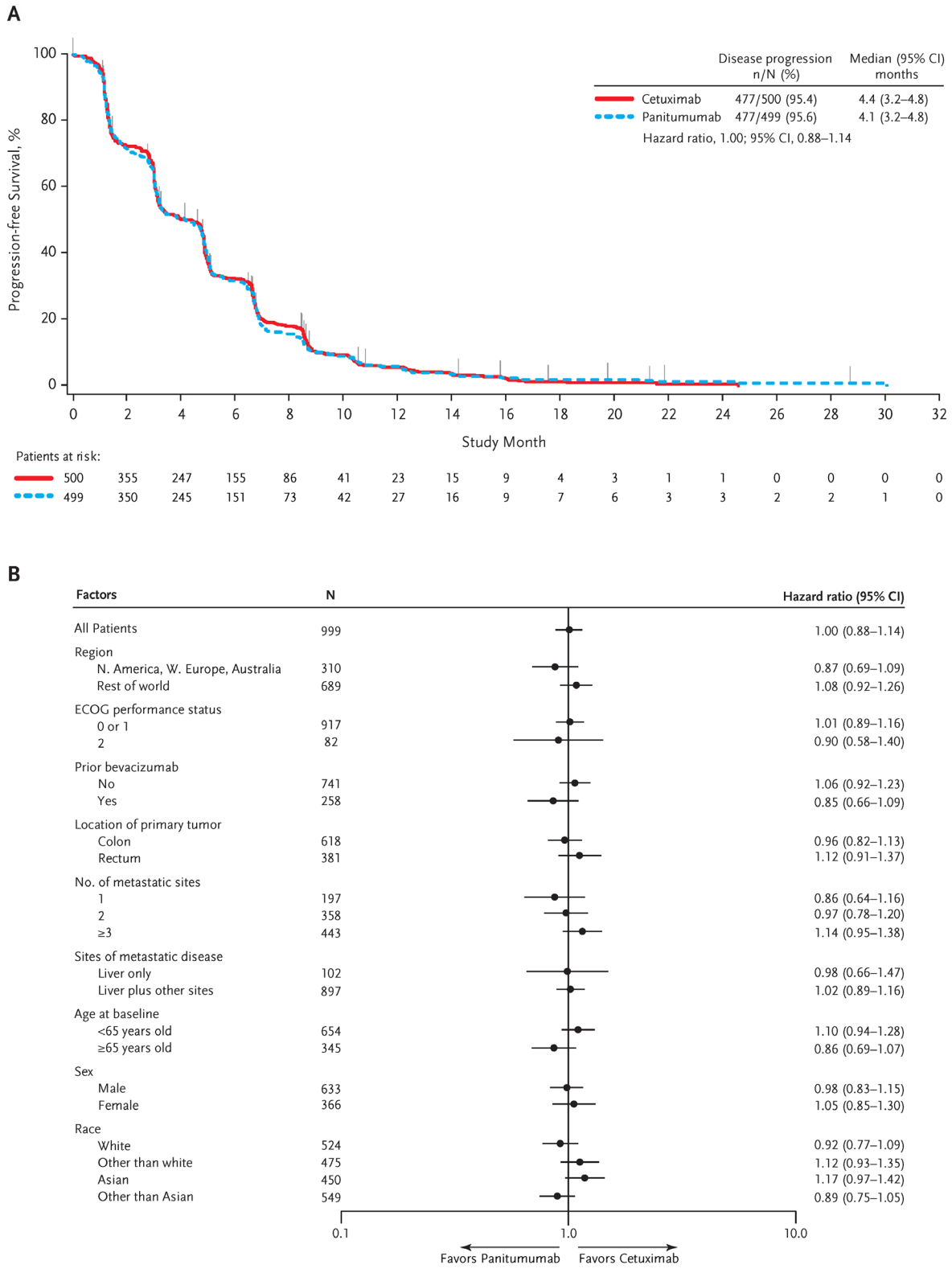

Factors
N
Hazard ratio (95% CI)
All Patients 999 0.97 (0.84–1.11)
Region
N. America, W. Europe, Australia 310 0.90 (0.71–1.15)
Rest of world 689 1.00 (0.84–1.19)
ECOG performance status
0 or 1 917 0.98 (0.85–1.14)
2 82 0.84 (0.53–1.34)
Prior bevacizumab
No 741 1.05 (0.89–1.24)
Yes 258 0.77 (0.58–1.02)
Location of primary tumor
Colon 618 0.93 (0.78–1.11)
Rectum 381 1.06 (0.84–1.34)
No. of metastatic sites
1 197 1.00 (0.70–1.41)
2 358 0.85 (0.67–1.08)
≥3 443 0.97 (0.79–1.19)
Sites of metastatic disease
Liver only 102 1.19 (0.75–1.90)
Liver plus other sites 897 0.95 (0.82–1.10)
Age at baseline
<65 years old 654 1.04 (0.87–1.23)
≥65 years old 345 0.85 (0.67–1.08)
Sex
Male 633 0.92 (0.77–1.10)
Female 366 1.06 (0.84–1.34)
Race
White 524 0.91 (0.75–1.09)
Other than white 475 1.03 (0.83–1.28)
Asian 450 1.06 (0.85–1.32)
Other than Asian 549 0.90 (0.75–1.08)
0.1
1.0
10.0
Favors Panitumumab
Favors Cetuximab

Figure 2

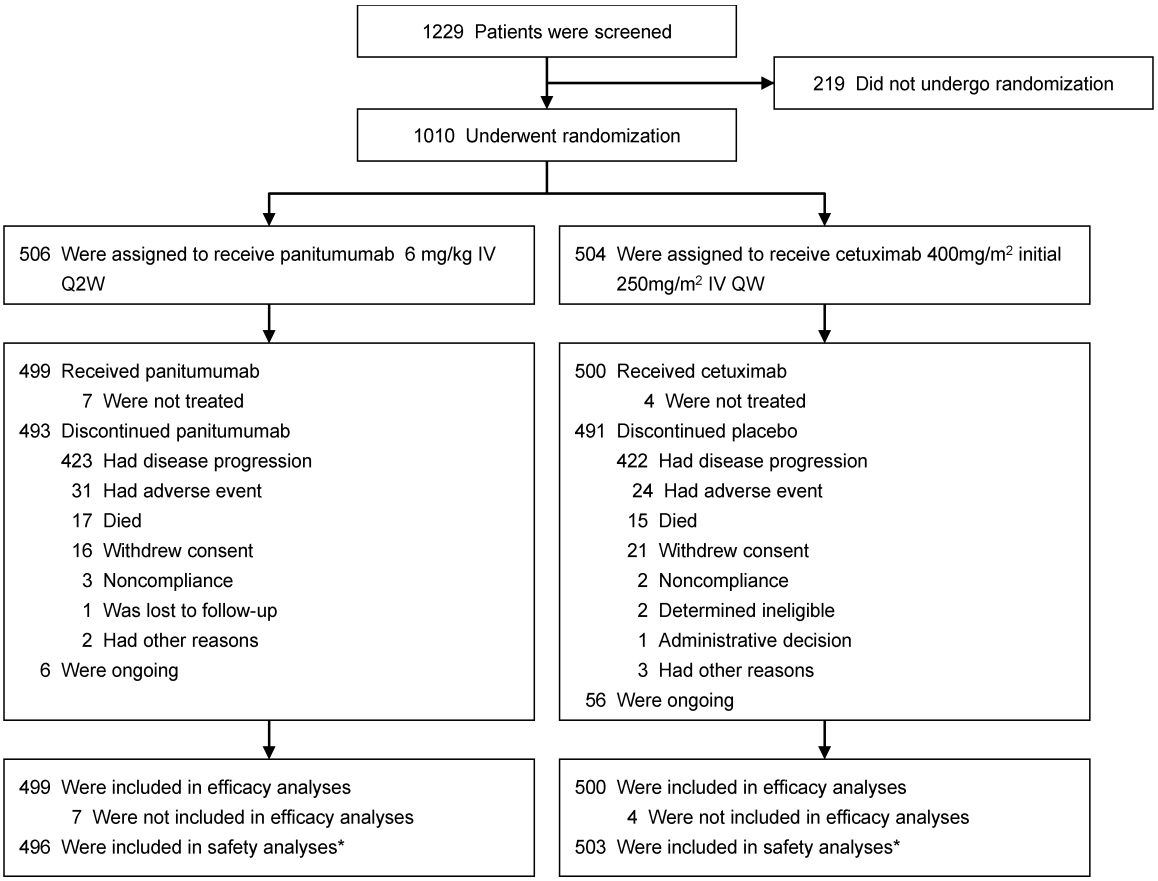

A
Progression-free Survival, %
100
80
60
40
20
0
Disease progression n/N (%)
Median (95% CI) months
Cetuximab 477/500 (95.4) 4.4 (3.2–4.8)
Panitumumab 477/499 (95.6) 4.1 (3.2–4.8)
Hazard ratio, 1.00; 95% CI, 0.88–1.14
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32
Study Month
Patients at risk:
500 355 247 155 86 41 23 15 9 4 3 1 1 0 0 0 0
499 350 245 151 73 42 27 16 9 7 6 3 3 2 2 1 0
B
Factors
N
Hazard ratio (95% CI)
All Patients 999 1.00 (0.88–1.14)
Region
N. America, W. Europe, Australia 310 0.87 (0.69–1.09)
Rest of world 689 1.08 (0.92–1.26)
ECOG performance status
0 or 1 917 1.01 (0.89–1.16)
2 82 0.90 (0.58–1.40)
Prior bevacizumab
No 741 1.06 (0.92–1.23)
Yes 258 0.85 (0.66–1.09)
Location of primary tumor
Colon 618 0.96 (0.82–1.13)
Rectum 381 1.12 (0.91–1.37)
No. of metastatic sites
1 197 0.86 (0.64–1.16)
2 358 0.97 (0.78–1.20)
≥3 443 1.14 (0.95–1.38)
Sites of metastatic disease
Liver only 102 0.98 (0.66–1.47)
Liver plus other sites 897 1.02 (0.89–1.16)
Age at baseline
<65 years old 654 1.10 (0.94–1.28)
≥65 years old 345 0.86 (0.69–1.07)
Sex
Male 633 0.98 (0.83–1.15)
Female 366 1.05 (0.85–1.30)
Race
White 524 0.92 (0.77–1.09)
Other than white 475 1.12 (0.93–1.35)
Asian 450 1.17 (0.97–1.42)
Other than Asian 549 0.89 (0.75–1.05)
0.1
1.0
10.0
Favors Panitumumab
Favors Cetuximab

Panitumumab Versus Cetuximab in Patients With Metastatic Colorectal Cancer

Timothy J Price, Marc Peeters, Tae Won Kim, Jin Li, Stefano Cascinu, Paul Ruff, Atilli Satya Suresh, Anne Thomas, Sergei Tjulandin, Kathy Zhang, Swaminathan Murugappan, Roger Sidhu

Supplemental Material

Supplemental Figure S1: Disposition of patients. *Four subjects were randomized to the panitumumab arm but received cetuximab treatment because of a randomization notification error. One subject was randomized to cetuximab but received panitumumab because of a misunderstanding of the randomization notification at the site.



Supplemental Table S1. Dermatology, Skin, and Nail Assessment Modifications for CTCAE version 3.0

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Nail changes	Discoloration; ridging (koilonychias; pitting) Paronychia: intervention not indicated	Partial or complete loss of nail(s); pain in nailbed(s), Paronychia: intervention indicated	Interfering with ADL	–
Erythema	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling
Pruritis	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	–
Rash: acne/acneiform	Intervention not indicated	Intervention indicated	Associated with pain requiring narcotic analgesics, ulceration, or desquamation	–
Rash/desquamation* [Use for non-acneiform rash or non-folliculitis rash]	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritis or other associated symptoms; localized desquamation or other lesions covering < 50% of BSA	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥ 50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis
Ulceration	–	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (eg, hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (eg complete resection, tissue reconstruction, flap, or grafting)

ADL=activities of daily living; BSA=body surface area.