



Panitumumab versus 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

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Summary

Background The anti-EGFR monoclonal antibodies panitumumab and cetuximab are effective in patients with chemotherapy-refractory wild-type *KRAS* exon 2 metastatic colorectal cancer. We assessed the efficacy and toxicity of panitumumab versus cetuximab in these patients.

Methods For this randomised, open-label, phase 3 head-to-head study, we enrolled patients (from centres in North America, South America, Europe, Asia, Africa, and Australia) aged 18 years or older with chemotherapy-refractory metastatic colorectal cancer, an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, and wild-type *KRAS* exon 2 status. Using a computer-generated randomisation sequence, we assigned patients (1:1; stratified by geographical region and ECOG performance status, with a permuted block method) to receive panitumumab (6 mg/kg once every 2 weeks) or cetuximab (initial dose 400 mg/m²; 250 mg/m² once a week thereafter). The primary endpoint was overall survival assessed for non-inferiority (retention of ≥50% of the cetuximab treatment effect; historical hazard ratio [HR] for cetuximab plus best supportive care vs best supportive care alone of 0·55). The primary analysis included patients who received one or more dose of panitumumab or cetuximab, analysed per allocated treatment. Recruitment for this trial is closed. The trial is registered with ClinicalTrials.gov, number NCT01001377.

Findings Between Feb 2, 2010, and July 19, 2012, we enrolled and randomly allocated 1010 patients, 999 of whom began study treatment: 499 received panitumumab and 500 received cetuximab. For the primary analysis of overall survival, panitumumab was non-inferior to cetuximab (*Z* score $-3\cdot19$; $p=0\cdot0007$). Median overall survival was 10·4 months (95% CI 9·4–11·6) with panitumumab and 10·0 months (9·3–11·0) with cetuximab (HR 0·97; 95% CI 0·84–1·11). Panitumumab retained 105·7% (81·9–129·5) of the effect of cetuximab on overall survival seen in this study. The incidence of adverse events of any grade and grade 3–4 was similar across treatment groups. Grade 3–4 skin toxicity occurred in 62 (13%) patients given panitumumab and 48 (10%) patients given cetuximab. The occurrence of grade 3–4 infusion reactions was lower with panitumumab than with cetuximab (one [$<0\cdot5\%$] patient vs nine [2%] patients), and the occurrence of grade 3–4 hypomagnesaemia was higher in the panitumumab group (35 [7%] vs 13 [3%]). We recorded one treatment-related fatal adverse event: a lung infection in a patient given cetuximab.

Interpretation Our findings show that panitumumab is non-inferior to cetuximab and that these agents provide similar overall survival benefit in this population of patients. Both agents had toxicity profiles that were to be expected. In view of the consistency in efficacy and toxicity seen, small but meaningful differences in the rate of grade 3–4 infusion reactions and differences in dose scheduling can guide physician choice of anti-EGFR treatment.

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Introduction

Colorectal cancer is the fourth-leading cause of cancer-related death worldwide.¹ For patients with metastatic colorectal cancer, irinotecan-based and oxaliplatin-based chemotherapy in combination with targeted therapy can improve median overall survival to more than 2 years,^{2,3} increasing the number of patients with chemotherapy-refractory disease eligible for third-line treatment. The anti-EGFR monoclonal antibodies cetuximab (a chimeric immunoglobulin G1 antibody) and panitumumab (a

fully-human immunoglobulin G2 antibody) provide clinical benefit in patients with chemotherapy-refractory metastatic colorectal cancer. In the phase 3 CO.17 study,⁴ cetuximab monotherapy improved overall survival and progression-free survival (PFS) compared with best supportive care. Retrospective analysis showed that benefit was restricted to patients with wild-type *KRAS* exon 2 disease.⁵ In the phase 3 408 study,^{6,7} panitumumab plus best supportive care improved PFS and the proportion of patients who had an objective response

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compared with best supportive care.^{6,7} Subsequent analysis showed that these benefits of panitumumab treatment were restricted to patients with wild-type *KRAS* exon 2 disease.⁸ Panitumumab did not improve overall survival, but the study had a crossover design, and 90 (76%) of 119 patients in the best supportive care group received panitumumab post-progression, which might have affected the overall survival results.^{6,7} Consequently, the effect of panitumumab on overall survival has been uncertain.

We know of no previous direct prospective comparison of efficacy and safety between panitumumab and cetuximab in chemotherapy-refractory metastatic colorectal cancer. 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. In addition to anti-EGFR therapy, guidelines for treatment of metastatic colorectal cancer incorporate several targeted agents including bevacizumab, aflibercept, and regorafenib.^{9,10} These agents are typically used in combination with chemotherapy or, in the case of regorafenib for patients with *KRAS* wild-type disease, after failure of chemotherapy, anti-VEGF therapy, and anti-EGFR therapy. Consequently, re-assessment of safety and efficacy in this setting is important and necessary. The global, randomised, open-label, phase 3 ASPECCT study (A Study of Panitumumab Efficacy and Safety Compared to Cetuximab) is, to the best of our knowledge, the first head-to-head comparison of panitumumab and cetuximab in chemotherapy-refractory metastatic colorectal cancer, the first to prospectively screen for patients with wild-type *KRAS* exon 2 disease, the largest prospective comparison of anti-EGFR agents in metastatic colorectal cancer, and is among the largest head-to-head comparisons of biological agents in metastatic colorectal cancer. We used a non-inferiority design to assess whether panitumumab preserved the overall survival benefit noted previously with cetuximab, the standard of care in this population of patients.^{4,5,9,10}

Methods

Study design and patients

This open-label, randomised, multicentre, phase 3 non-inferiority study was done in 27 countries in North America, South America, Europe, Asia, Africa, and Australia. Eligible patients (aged ≥ 18 years) had histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum with wild-type *KRAS* exon 2 tumour status (described below), measurable or non-measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1,¹¹ an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, disease progression (clinical or radiological)¹¹ or intolerance to irinotecan-based and oxaliplatin-based therapy, and had

previously received a thymidylate synthase inhibitor (including fluorouracil, capecitabine, raltitrexed, or fluorouracil-uracil) for colorectal cancer. Exclusion criteria included previous anti-EGFR therapy, antitumour therapy within 30 days, symptomatic brain metastases needing treatment, history of other unresolved malignancies, major surgery within 28 days, significant cardiovascular disease or myocardial infarction, history of interstitial lung disease, active or uncontrolled infections within 14 days, serum magnesium concentrations below lower limit of normal, inadequate haematological function (absolute neutrophil count $< 1.5 \times 10^9$ per L, platelet count $< 75 \times 10^9$ per L, or haemoglobin < 80 g/L), inadequate renal function (creatinine $> 1.5 \times$ upper limit of normal), and inadequate hepatic function (total bilirubin $> 1.5 \times$ upper limit of normal, or aspartate aminotransferase or alanine aminotransferase $> 3 \times$ upper limit of normal [$> 5 \times$ upper limit of normal if the patient had liver metastases]).

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

Randomisation and masking

Using an automated interactive voice response system (ICON Clinical Research, Dublin, Ireland), we randomly assigned patients (1:1) to either panitumumab or cetuximab treatment. Randomisation was done using a permuted block method and was stratified by geographical region (North America, western Europe, and Australia vs rest of the world) and ECOG performance status (0 or 1 vs 2). The randomisation sequence was generated at Amgen. Patients and investigators were not masked to treatment assignment (open-label treatment). The study's statistical team was masked to treatment assignments.

Treatment

Patients received either panitumumab 6 mg/kg intravenously on day 1 of each 14-day cycle or cetuximab at an initial dose of 400 mg/m² intravenously followed by 250 mg/m² intravenously on day 1 of each 7-day cycle. Patients in the cetuximab group received treatment consistent with product labelling in their respective countries, including premedication with an H1 antagonist before infusion. Premedication for infusion reaction was not required for panitumumab. Treatment with panitumumab or cetuximab 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 or cetuximab doses could be withheld or reduced per protocol-specified rules. Briefly, if grade 3–4 toxicity occurred, treatment could be withheld for up to 4 weeks, then resumed if the toxicity resolved.

For second and third occurrences of a toxicity, doses of study drug could be reduced to 80% or 60% of the starting dose, respectively. Doses could be escalated if toxicity did not recur, but treatment was permanently discontinued for a fourth recurrence. We calculated relative dose intensity as the ratio of the actual dose intensity (actual cumulative dose divided by the duration of treatment exposure period of interest) to the planned dose intensity. Crossover between panitumumab and cetuximab was not allowed during the study treatment period, which was defined as the time from starting panitumumab or cetuximab until stopping these treatments due to any cause. After the study treatment period had ended, patients could receive any treatment as per their physician's decision.

Assessments

We performed CT or MRI of patients' abdomen, pelvis, and chest at 6 weeks (plus or minus 1 week) and every 8 weeks (plus or minus 1 week) thereafter. Response was evaluated by investigators per RECIST version 1.1. There was no central review of response. We graded adverse events occurring from the day of the first dose of panitumumab or cetuximab through 30 days after the last dose day according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 3.0),¹² except for skin-related or nail-related toxicities, which were graded using NCI-CTCAE version 3.0 with modifications (appendix). Laboratory assessments were done every 4 weeks. Patients were followed-up for overall survival for 24 months after randomisation of the last patient. We assessed patient-reported outcomes using the EQ-5D Health Index Scale, the EQ Visual Analog Scale, and the FACT Colorectal Symptom Index (FCSI).

KRAS testing

We assessed KRAS tumour status in formalin-fixed, paraffin-embedded tumour tissue sections before randomisation at one of three laboratories (HistoGeneX, Belgium; LabCorp China, China; LabCorp CTS-RTP, NC, USA). Presence or absence of the seven most common KRAS exon 2 mutations was assessed with the Therascreen KRAS assay (Qiagen, Venlo, Netherlands).² Only central testing for KRAS mutations could be used to assess eligibility.

Outcomes

The primary endpoint was overall survival (time from randomisation to death), analysed for all patients who received at least one dose of their assigned study treatment. Secondary endpoints were PFS (time from randomisation to disease progression or death), the proportion of patients with an objective response, time to treatment failure (time from randomisation to the date that a decision was made to end the treatment period for any reason), time to response (time from

randomisation to first objective response), duration of response (time from first objective response to disease progression as per RECIST version 1.1), and safety.

Statistical analysis

This non-inferiority study was designed to assess whether panitumumab retains 50% or more of the overall survival treatment effect of cetuximab versus best supportive care. The predicted effect of cetuximab versus best supportive care on overall survival was based on findings from 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 in randomly allocated patients, we needed 1000 patients to achieve 90% power with one-sided α of 0.025 for the overall survival inferiority null hypothesis.

Criteria for non-inferiority of the HR for panitumumab versus cetuximab compared with the HR for cetuximab versus best supportive care were based on a synthesis approach. We used an asymptotic standard normal test statistic^{13,14} with one-sided α of 0.025 to test the overall

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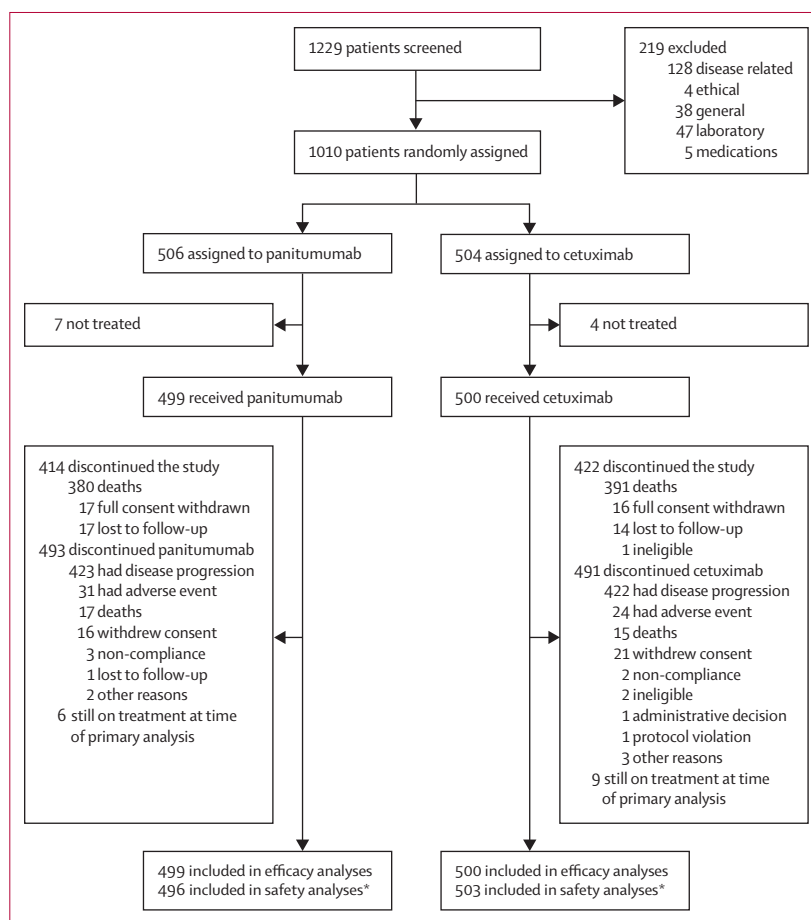


Figure 1: Trial profile

*Four patients were randomly assigned to the panitumumab group but received cetuximab treatment because of a randomisation notification error; one patient was randomly assigned to cetuximab but received panitumumab because of a misunderstanding of the randomisation notification at the treatment site.

survival inferiority null hypothesis: a Z score less than -1.96 was significant for non-inferiority. We used Cox models stratified by the randomisation factors to estimate HRs and 95% CI for overall survival and PFS. We calculated common odds ratios (ORs) stratified by the randomisation factors and exact 95% CIs for the proportion of patients with an objective response. We also assessed non-inferiority based on retention rate using the Hasselblad and Kong procedure,¹⁵ in which a historical study showing 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,¹⁶ the retention rate had to be 50% or more for panitumumab to be regarded as non-inferior. If non-inferiority was established, superiority of panitumumab versus cetuximab for overall survival

would be assessed using a Cox proportional hazards model based on the intent-to-treat population. We qualitatively assessed constancy between this study and CO.17 by comparing population baseline characteristics and overall survival benefit between the two studies; we did no formal statistical analysis of constancy. We did a sensitivity analysis assessing potential effects of post-protocol anti-EGFR monoclonal antibody therapy using Shao's semiparametric approach.¹⁷ Formal tests for heterogeneity were not prespecified and were not done.

Primary analysis of overall survival and PFS was done in the primary analysis set (all patients who received ≥ 1 dose of panitumumab or cetuximab, analysed per the treatment to which they were randomised). Primary analysis of the proportion of patients with an objective response used the tumour response analysis set (primary analysis set patients with ≥ 1 measurable lesion per RECIST version 1.1 at baseline). Patients were regarded as unevaluable for response if lesions present at baseline could not subsequently be assessed. We did descriptive safety analyses, without formal statistical analysis, using the safety analysis set (patients receiving ≥ 1 dose of panitumumab or cetuximab analysed per treatment received). The patient-reported outcomes and health-resource utilisation analysis sets included all patients in the primary analysis set with a baseline and one or more post-baseline patient-reported outcome or health-resource utilisation assessments (analysed per treatment allocation). We used SAS (version 9.2) for statistical analyses.

This trial is registered with ClinicalTrials.gov, number NCT01001377.

Role of the funding source

The study sponsor designed the study with input from principal investigators and did subsequent data and statistical analyses. Investigators (TJP, MP, TWK, JL, SC, PR, ASS, AT, and ST) collected clinical data. Statistical analyses were done at Amgen by KZ. All authors (including SM, KZ, and RS who are employees of Amgen) participated in data interpretation. The paper was assembled by the authors with medical writing assistance (funded by Amgen); all authors approved the final version. The corresponding author had full access to all data and final responsibility to submit for publication.

Results

Between Feb 2, 2010, and July 19, 2012, we enrolled and randomly allocated 1010 patients to treatment, 999 of whom began study treatment (figure 1). Baseline characteristics were much the same between the two groups (table 1). 90% patients had metastatic sites outside the liver, and 26% had received prior bevacizumab (table 1). At the time of this analysis on Feb 5, 2013, 493 patients had discontinued panitumumab and 491 had discontinued cetuximab (figure 1). Median duration of

	Panitumumab (N=499)	Cetuximab (N=500)
Age in years (median [IQR])	61.0 (54–67)	60.5 (53–68)
Men	315 (63%)	318 (64%)
Ethnic origin		
White	266 (53%)	258 (52%)
Asian	222 (44%)	228 (46%)
Hispanic or Latino	6 (1%)	7 (1%)
Black	2 (<0.5%)	4 (<1%)
Japanese	1 (<0.5%)	0
Other	2 (<0.5%)	3 (<1%)
Time from primary diagnosis to randomisation in months (median [IQR])	25.3 (16.3–40.8)	27.0 (16.5–45.6)
Time from metastatic diagnosis to randomisation in months (median [IQR])	19.6 (12.9–29.4)	19.8 (13.2–30.6)
ECOG performance status		
0	154 (31%)	163 (33%)
1	303 (61%)	297 (59%)
2	42 (8%)	40 (8%)
Location of primary tumour		
Colon	292 (59%)	326 (65%)
Rectum	207 (42%)	174 (35%)
Histological type		
No subtype	195 (39%)	189 (38%)
Mucinous	51 (10%)	47 (9%)
Appendiceal	0	2 (<0.5%)
Other	26 (5%)	27 (5%)
Unknown	227 (45%)	235 (47%)
Prior bevacizumab	126 (25%)	132 (26%)
Sites of metastatic disease		
Liver only	52 (10%)	50 (10%)
Other sites with or without liver involvement	447 (90%)	450 (90%)
Region		
North America, western Europe, Australia	154 (31%)	156 (31%)
Rest of the world	345 (69%)	344 (69%)

Data are n (%) unless otherwise specified. ECOG=Eastern Cooperative Oncology Group.

Table 1: Baseline characteristics

treatment was 14.3 weeks (IQR 6.1–29.3) for panitumumab and 14.1 weeks (6.0–29.0) for cetuximab. Median number of infusions was 7.0 (3.0–13.5) for panitumumab and 14.0 (6.0–28.0) for cetuximab, with median relative dose intensities across all doses of 99% (95–101) for panitumumab and 98% (93–100) for cetuximab. Median follow-up time, defined as the time from randomisation to the last on-study or long-term follow-up visit, was 41.4 weeks (22.1–71.6) for panitumumab and 40.5 weeks (21.3–68.9) for cetuximab.

Use of post-progression antitumour therapy was similar between treatment groups (205 [41%] of 499 patients in the panitumumab group had subsequent treatment vs 211 [42%] of 500 in the cetuximab group), and included cytotoxic chemotherapy (155 patients [31%] vs 165 patients [33%]), anti-EGFR monoclonal antibodies (45 [9%] vs 52 [10%]), and anti-VEGF therapy (35 [7%] vs 33 [7%]).

At the time of analysis, 383 (77%) of 499 patients in the panitumumab group and 392 (78%) of 500 patients in the

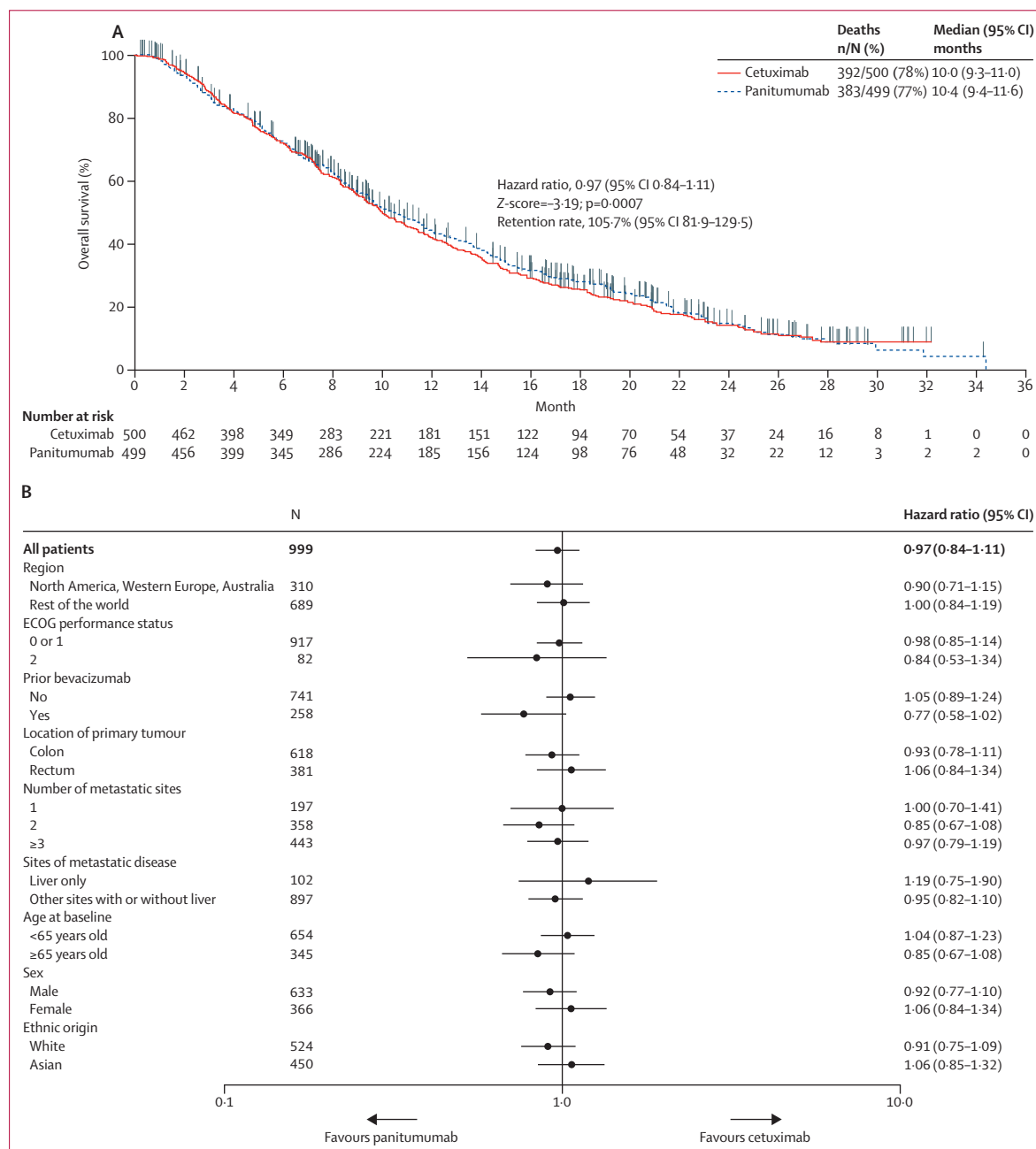


Figure 2: Overall survival
Kaplan-Meier curves for overall survival by treatment group (A). Subset analysis for overall survival (B). ECOG=Eastern Cooperative Oncology Group.

cetuximab group had died (figure 2). The non-inferiority test confirmed that panitumumab retained 50% or more of the overall survival benefit of cetuximab versus best supportive care (Z score -3.19 , $p < 0.0007$; figure 2). Median overall survival was 10.4 months (95% CI 9.4–11.6) in the panitumumab group and 10.0 months (9.3–11.0) in the cetuximab group (figure 2). Overall survival was similar between the treatment groups across all predefined subgroups of

patients (HR 0.97, 95% CI 0.84–1.11; figure 2). Panitumumab was estimated to retain 105.7% (95% CI 81.9–129.5) of the effect of cetuximab on overall survival seen in this study. The minimum preservation of the treatment effect of cetuximab by panitumumab was 81.9% (lower bound of the 95% CI). Panitumumab was not superior to cetuximab: the HR in the intent-to-treat analysis was very similar to that in the primary analysis (0.97, 95% CI 0.84–1.12; $p = 0.69$).

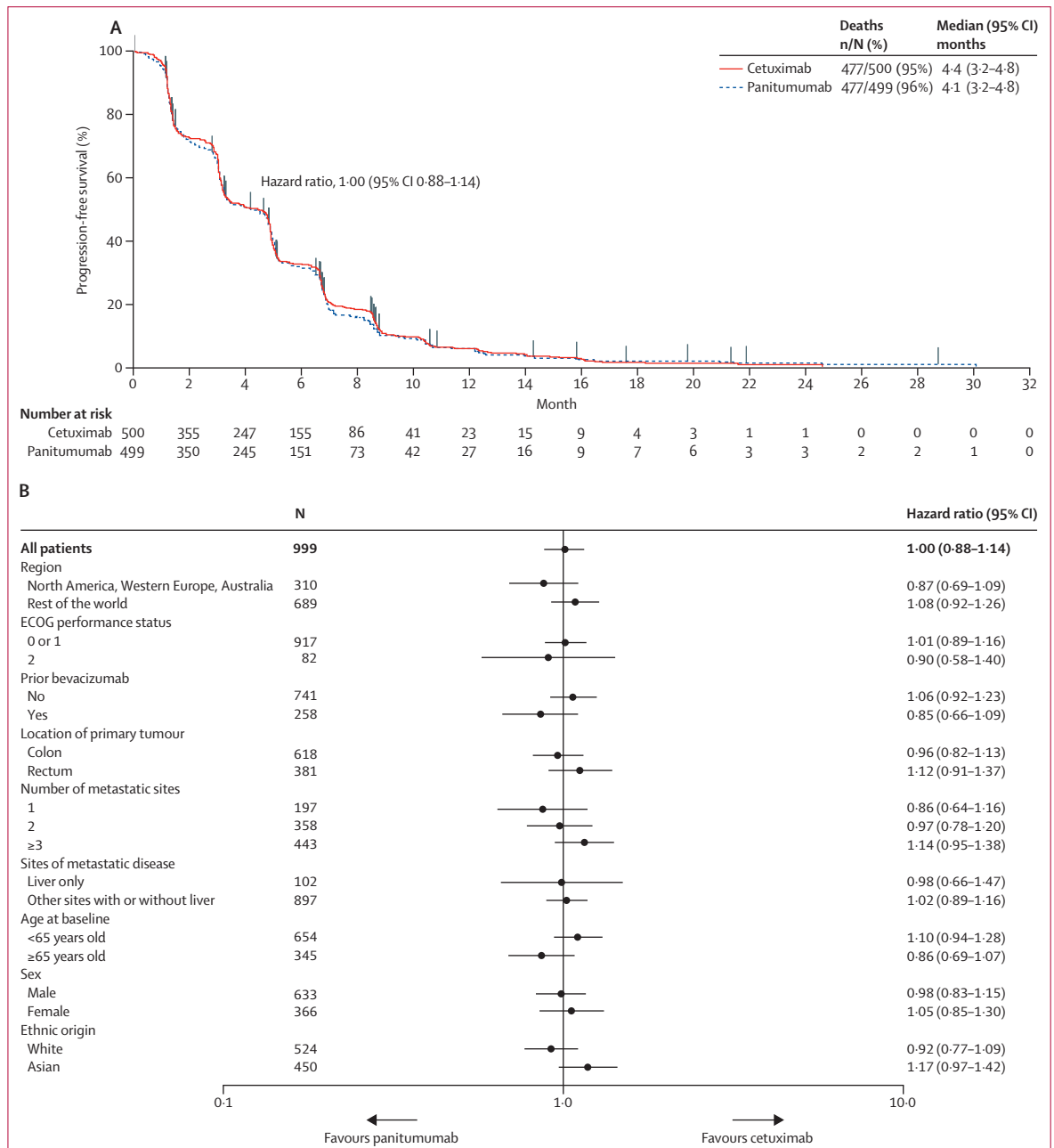


Figure 3: Progression-free survival
 Kaplan-Meier curves for progression-free survival by treatment group (A). Subset analysis for progression-free survival (B). ECOG=Eastern Cooperative Oncology Group.

At the time of analysis, 477 patients in the panitumumab group and 477 patients in the cetuximab group had died or had disease progression per RECIST version 1.1. Median PFS was similar between the two treatment groups overall and in every subgroup (figure 3). Sensitivity analysis adjusting for subsequent anti-EGFR monoclonal antibody therapy did not give a different outcome (HR 1.19, 95% CI 0.66–2.13; $p=0.57$). We did not detect an advantage to receiving subsequent anti-EGFR therapy for patients in the cetuximab group ($p=0.47$) or the panitumumab group ($p=0.81$).

In patients with measurable disease at baseline, we recorded no difference in the proportion of patients who achieved an objective response: 107 (22.0%, 95% CI 18.4–26.0) patients in the panitumumab group had an objective response, compared with 96 (19.8%, 16.3–23.6) in the cetuximab group (OR 1.15, 95% CI 0.83–1.58; table 2). Median time to response was 1.5 weeks (IQR 1.2–3.0) in the panitumumab group and 2.6 weeks (1.2–3.1) in the cetuximab group; median duration of response was 3.8 months (95% CI 3.7–4.8) in the panitumumab group and 5.4 months (3.8–5.5) in the cetuximab group. Median time to treatment failure was 3.4 months (95% CI 3.2–4.6) in the panitumumab group and 3.3 months (3.2–3.9) in the cetuximab group.

The safety analysis included 496 patients in the panitumumab group and 503 patients in the cetuximab group. Overall incidence of treatment-emergent adverse events was similar between treatment groups for adverse events of any grade (485 [98%] in the panitumumab group; 494 [98%] in the cetuximab group) and for serious adverse events (151 [30%] patients in the panitumumab group; 169 [34%] patients in the cetuximab group), grade 3 adverse events, and grade 4 adverse events (table 3). 50 (10%) cetuximab-treated patients and 29 (6%) panitumumab-treated patients had fatal adverse events. Treatment-related adverse events led to treatment discontinuation for 14 (3%) patients in the panitumumab group and 15 (3%) in the cetuximab group. Overall, 173 (35%) patients in the panitumumab group and 181 (36%) in the cetuximab group needed dose reductions because of adverse events.

The incidence of infusion reactions was lower in the panitumumab group (14 [3%] patients) than the cetuximab group (63 [13%] patients; table 3). Grade 3–4 infusion reactions occurred in one patient (<0.5%) receiving panitumumab and nine patients (2%) receiving cetuximab. The incidence of grade 3–4 hypomagnesaemia was greater in patients receiving panitumumab (35 [7%] patients) than in those receiving cetuximab (13 [3%]). Six (1%) patients in the panitumumab group and two (<0.5%) in the cetuximab group discontinued study treatment because of hypomagnesaemia. 25 (5%) patients in the panitumumab group and 14 (3%) in the cetuximab group had dose modifications for hypomagnesaemia. The incidence of grade 3–4 skin and

	Panitumumab (N=499)	Cetuximab (N=500)
Patients with measurable disease	486	485
Complete response	2 (<0.5%)	0
Partial response	105 (22%)	96 (20%)
Stable disease	226 (47%)	236 (49%)
Progressive disease	121 (25%)	124 (26%)
Unevaluable†	5 (1%)	4 (<1%)
Not done‡	27 (6%)	25 (5%)

Data are n or n (%), unless otherwise specified. *Patients with measurable disease at baseline only. †Response could not be assessed per RECIST version 1.1 because lesions present at baseline could not subsequently be assessed. ‡Post-baseline tumour response assessment not done.

Table 2: Best response to treatment by RECIST version 1.1*

subcutaneous tissue toxicities was similar between the panitumumab and cetuximab groups (table 3).

In both treatment groups, most fatal adverse events were attributed to disease progression (20 deaths [69% of all fatal adverse events] in the panitumumab group *vs* 34 deaths [68% of all fatal adverse events] in the cetuximab group). Fatal adverse events not attributable to disease progression occurring in two or more patients were acute renal failure (two [<0.5%] in the panitumumab group *vs* none in the cetuximab group), sepsis (two [<0.5%] *vs* none), lung infection (none *vs* two [<0.5%]), and pneumonia (none *vs* two [<0.5%]). The only treatment-related fatal adverse event was a lung infection in a patient given cetuximab.

Scores on the EQ-5D Health State Index Score, EQ Visual Analog Scale, and FCSI measures were similar for patients in the cetuximab and panitumumab groups (appendix). Similarly, the occurrence of outpatient visits, interventions, admissions to hospital, and emergency room visits were similar between the treatment groups (appendix). The mean duration of hospital stays was 4.0 days (SD 4.3) in the panitumumab group and 8.1 days (8.8) in the cetuximab group.

Discussion

Our findings show that panitumumab is non-inferior to cetuximab for overall survival based on the study-defined criteria of a 50% or greater retention rate of the overall survival benefit of cetuximab. Moreover, our efficacy results were consistent with anti-EGFR antibody class outcomes reported in the 408 and CO.17 studies.^{5,8} We assessed *KRAS* status prospectively, ensuring that all enrolled patients had wild-type *KRAS* exon 2 disease. Previous phase 3 studies assessing anti-EGFR monoclonal antibodies assessed *KRAS* status retrospectively with ascertainment rates of 69% for cetuximab⁵ and 92% for panitumumab.⁸ In addition to similarity with respect to efficacy and toxicity, patient-reported outcomes and health-resource utilisation were similar for patients on panitumumab and those on cetuximab. The results show the utility of head-to-head studies not only in the

	Panitumumab (N=496)				Cetuximab (N=503)			
	Grades 1-2	Grade 3	Grade 4	Grade 5	Grades 1-2	Grade 3	Grade 4	Grade 5
All adverse events	239 (48%)	180 (36%)	37 (7%)	29 (6%)	258 (51%)	159 (32%)	27 (5%)	50 (10%)
Adverse events occurring in more than 5% of patients in either treatment group								
Rash	225 (45%)	23 (5%)	1 (<0.5%)	0	239 (48%)	18 (4%)	0	0
Dermatitis acneiform	121 (24%)	17 (3%)	0	0	122 (24%)	14 (3%)	0	0
Hypomagnesaemia	101 (20%)	26 (5%)	9 (2%)	0	76 (15%)	10 (2%)	3 (<1%)	0
Diarrhoea	81 (16%)	7 (1%)	3 (<1%)	0	80 (16%)	9 (2%)	0	0
Dry skin	82 (17%)	1 (<0.5%)	0	0	79 (16%)	0	0	0
Pruritus	79 (16%)	4 (<1%)	0	0	87 (17%)	1 (<0.5%)	0	0
Fatigue	61 (12%)	11 (2%)	3 (<1%)	0	70 (14%)	17 (3%)	1 (<0.5%)	0
Decreased appetite	66 (13%)	3 (<1%)	0	0	71 (14%)	7 (1%)	0	0
Nausea	64 (13%)	4 (<1%)	0	0	50 (10%)	7 (1%)	0	0
Abdominal pain	44 (9%)	17 (3%)	0	0	69 (14%)	13 (3%)	1 (<0.5%)	0
Vomiting	50 (10%)	9 (2%)	0	0	44 (9%)	7 (1%)	0	0
Paronychia	47 (9%)	11 (2%)	0	0	65 (13%)	10 (2%)	0	0
Acne	49 (10%)	3 (<1%)	0	0	64 (13%)	5 (1%)	0	0
Skin fissures	41 (8%)	1 (<0.5%)	0	0	40 (8%)	3 (<1%)	0	0
Constipation	40 (8%)	1 (<0.5%)	0	0	69 (14%)	3 (<1%)	0	0
Hypokalaemia	25 (5%)	16 (3%)	0	0	15 (3%)	8 (2%)	0	0
Cough	40 (8%)	0	0	0	38 (8%)	0	0	0
Back pain	31 (6%)	5 (1%)	0	0	36 (7%)	3 (<1%)	0	0
Asthenia	28 (6%)	7 (1%)	0	0	40 (8%)	7 (1%)	1 (<0.5%)	0
Anaemia	18 (4%)	11 (2%)	2 (<0.5%)	0	17 (3%)	11 (2%)	4 (<1%)	0
Fever	29 (6%)	2 (<0.5%)	0	0	52 (10%)	4 (<1%)	0	0
Insomnia	27 (5%)	0	0	0	46 (9%)	0	0	0
Hypocalcaemia	20 (4%)	3 (<1%)	3 (<1%)	0	10 (2%)	5 (1%)	1 (<0.5%)	0
Nail disorder	25 (5%)	1 (<0.5%)	0	0	29 (6%)	2 (<0.5%)	0	0
Stomatitis	23 (5%)	3 (<1%)	0	0	34 (7%)	0	0	0
Weight decreased	25 (5%)	1 (<0.5%)	0	0	21 (4%)	0	0	0
Peripheral oedema	18 (4%)	5 (1%)	0	0	35 (7%)	5 (1%)	0	0
Dyspnoea	17 (3%)	4 (<1%)	1 (<0.5%)	0	31 (6%)	4 (<1%)	2 (<0.5%)	1 (<0.5%)
Mucosal inflammation	21 (4%)	1 (<0.5%)	0	0	22 (4%)	3 (<1%)	0	0
Dyspepsia	19 (4%)	0	0	0	25 (5%)	1 (<0.5%)	0	0
Headache	17 (3%)	0	0	0	36 (7%)	0	0	0
Upper respiratory tract infection	13 (3%)	2 (<0.5%)	0	0	28 (6%)	0	0	0
Other adverse events								
Skin and subcutaneous tissue toxicity*	368 (74%)	60 (12%)	2 (<0.5%)	0	392 (78%)	48 (10%)	0	0
Infusion reactions	14 (3%)	1 (<0.5%)	0	0	63 (13%)	5 (1%)	4 (<1%)	0

Data are number of patients (%). *Includes adverse events in the skin and subcutaneous tissue disorders system organ class of the Medical Dictionary for Regulatory Activities (version 15.1).

Table 3: Incidence of adverse events

assessment of an agent against an active comparator (an approach infrequently used in oncology), but also in providing physicians with comprehensive efficacy and toxicity information that can guide treatment decisions.

A non-inferiority design was appropriate in view of the anticipated similarity in outcomes with cetuximab and panitumumab. Such studies should consider constancy with high-quality historical controls,^{13,18,19} in this case the phase 3 CO.17 study.⁵ We regarded the assumption of constancy of the cetuximab treatment effect between this study and the CO.17 cetuximab wild-type KRAS exon 2

group as validated, based on a prespecified qualitative assessment. Outcomes for cetuximab were similar in the two studies (median overall survival, 10.0 months vs 9.5 months; median PFS, 4.4 months vs 3.7 months; objective response rate, 19.8% vs 12.8%).⁵ Skin toxicities were the most common adverse events 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% and 60%) were consistent between the studies.⁵ Cetuximab was given at the same dose and schedule in both studies.^{4,5}

This global study extended the findings of the CO.17⁵ and 408 studies⁸ by showing clinical benefit with panitumumab and cetuximab in a more geographically and ethnically diverse population of patients (panel). HRs for overall survival and PFS were similar not only for the study population as a whole, but across all predefined subgroups of patients (including geographical region). The similarity in outcomes across subgroups lends support to the broad applicability of these agents in patients with chemotherapy-refractory wild-type *KRAS* exon 2 disease. Our data seemed to suggest a trend towards longer overall survival and PFS with panitumumab in patients who had previously received bevacizumab; however, this finding should be interpreted with care because the trend was not statistically significant. Although this finding was consistent with the trend towards improved outcomes reported for panitumumab plus FOLFIRI versus FOLFIRI alone as second-line treatment in patients given previous bevacizumab treatment,²⁰ the underlying biological mechanism that would lead to such an advantage for panitumumab in this subgroup of patients is unclear. The low use of previous bevacizumab in this study (26%) reflects the variable availability of bevacizumab in this geographically diverse population.

Our trial also allows for a direct, comprehensive assessment of toxicity with panitumumab and cetuximab in patients with chemotherapy-refractory disease. Both agents showed the toxicities that one would anticipate with an anti-EGFR agent. Overall toxicity and the incidence of most individual toxicities were similar across the treatment groups. Previous panitumumab and cetuximab studies have used heterogeneous criteria to summarise skin toxicity,^{2,4,6,21–26} making cross-study comparisons difficult and leading some investigators to conclude that incidence of skin toxicity is higher with panitumumab than it is with cetuximab. In ASPECCT, the incidence of skin adverse events (including rash, dermatitis acneiform, and dry skin), was similar for panitumumab-treated and cetuximab-treated patients. However, the incidence of infusion reactions was greater in cetuximab-treated patients despite prophylaxis for infusion reactions in this group. This finding is consistent with previous reports for cetuximab^{24,27} and panitumumab,^{2,6,22,25} and the hypothesis that fully human monoclonal antibodies (eg, panitumumab) are less immunogenic than chimeric monoclonal antibodies (eg, cetuximab).²⁸ Hypomagnesaemia was more common in patients receiving panitumumab, although most events were grade 1–2. In most instances, hypomagnesaemia can be managed by the treating physician, and was infrequently a cause to withhold or change doses in either group in this study. Hypomagnesaemia is an on-target adverse event potentially caused by renal magnesium wasting due to EGFR inhibition in the kidney.²⁹ Higher affinity binding of panitumumab to EGFR might contribute to

these differences.³⁰ Although the once every 2 weeks versus once weekly frequency of clinic visits in the panitumumab versus cetuximab group might have affected the assessment of toxicity, we believe this possibility is unlikely for two reasons. First, the most common toxicity events in both groups were skin toxicities that are typically long-lasting and unlikely to go unnoticed. Second, if frequency of clinic visits contributed to differences in toxicity reporting we would anticipate this effect to be seen across all toxicities. Instead, we noted differences for only some toxicities.

Assessment of potential predictive biomarkers for anti-EGFR monoclonal antibodies in metastatic colorectal cancer has been an area of much scientific interest.³¹ In particular, analyses have indicated that *RAS* mutations beyond *KRAS* exon 2 are predictive of outcomes in patients receiving panitumumab treatment.^{32,33} On the basis of the results of these analyses, panitumumab treatment might be inappropriate not only for patients with *KRAS* exon 2 mutations, but also for those with mutations in *KRAS* exons 3 and 4 and in *NRAS* exons 2, 3, and 4. Moreover, the consistency of results in extended *RAS* analyses in patients receiving panitumumab³² or cetuximab³⁴ in combination with chemotherapy suggest that similar selection criteria might be appropriate in the chemotherapy-refractory setting. The ASPECCT study provides a robust dataset to do additional biomarker analyses in the monotherapy setting in metastatic colorectal cancer. However, absence

Panel: Research in context

Systematic review

We searched PubMed for studies describing the use of panitumumab or cetuximab in patients with chemotherapy-refractory metastatic colorectal cancer using the search terms “panitumumab”, “cetuximab”, and “colorectal cancer”. We identified no direct comparison of the two agents in patients with chemotherapy-refractory wild-type *KRAS* exon 2 disease.

Interpretation

To the best of our knowledge, our study is the first head-to-head comparison of panitumumab and cetuximab in patients with chemotherapy-refractory metastatic colorectal cancer. Our findings suggest that panitumumab is non-inferior to cetuximab in patients with chemotherapy-refractory wild-type *KRAS* exon 2 disease and that these two agents provide similar overall survival benefit in this setting. Both agents had toxicity profiles as anticipated. In view of the consistency in efficacy and toxicity seen for panitumumab and cetuximab in this study, physician choice of treatment can be guided by small but meaningful differences in the rate of grade 3–4 infusion reactions and differences in dose scheduling. The results show the value of head-to-head studies with an active comparator (an infrequently used approach in oncology) in providing physicians with clinical data that can guide treatment decisions.

of a control group in ASPECCT will limit the ability to derive additional meaningful conclusions on the predictive nature of *KRAS* and *NRAS* mutations in this setting. Instead, further assessment of mutations emerging at the time of clinical progression and their effect on clinical outcomes is planned for this dataset.

Information about prior therapy received was collected at screening. Due to the method by which this data was collected, and taking into account the blurring of lines of therapy in current practice, we were unable to calculate the number of lines of previous therapies. However, on the basis of the similar patient demographics, equivalent prior bevacizumab treatment, and time to trial entry between the two study groups, we do not expect between-group differences in the number of previous lines of treatment.

Anti-EGFR monoclonal antibodies have now been shown to provide clinical benefit in phase 3 studies across all lines of treatment in wild-type *KRAS* exon 2 disease.^{2,5,8,22,24,35,36} The overlapping efficacy and safety, and known mechanism of action between panitumumab and cetuximab as monotherapy, raises the question of whether these agents are potentially interchangeable not only as monotherapy, but also in earlier lines of treatment with irinotecan-based and oxaliplatin-based chemotherapy, a finding consistent with clinical practice.^{2,9,10,22,24,36} Further research will be needed to assess this possibility. Additionally, ASPECCT does not directly address the sequencing and timing of anti-EGFR therapy and further investigation will be needed to assess effects of prior targeted therapy on outcomes.

Our results show that panitumumab is non-inferior to cetuximab and that these agents provide similar overall survival benefit in this heavily pretreated patient population, with more than 50% of participants having overall survival longer than 10 months. Both agents had toxicity profiles as expected. In view of the consistency in efficacy and toxicity seen, small but meaningful differences in the rate of grade 3 or 4 infusion reactions and differences in dose scheduling can guide physician choice of anti-EGFR therapy.

Contributors

TJP, MP, and RS designed the study. TJP, MP, TWK, JL, SC, PR, ASS, AT, and ST collected clinical data. KZ did the statistical analyses. All authors participated in data interpretation and drafting and revising the paper. All authors approved the final version.

Declaration of interests

TJP and MP have served on advisory boards for Amgen Inc. PR has received research funding from Amgen Inc. ST has received speaker honoraria from Merck. SC has served as a speaker for and received research grants from Amgen Inc and Merck, and has received honoraria and payment for expert testimony from Roche. KZ, SM, and RS are employees and stockholders of Amgen Inc. TWK, JL, ASS, and AT declare that they have no competing interests.

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