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Original Research

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

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KEYWORDS
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Abstract ***Purpose:*** The primary analysis of the ASPECCT study demonstrated that panitumumab was non-inferior to cetuximab for overall survival (OS) in patients with chemotherapy-refractory wild-type *KRAS* exon 2 metastatic colorectal cancer (mCRC). Here, we report the final analysis results of ASPECCT.
Patients and methods: Patients with wild-type *KRAS* exon 2 mCRC who progressed on or were intolerant to irinotecan- or oxaliplatin-based chemotherapy were randomised to receive panitumumab 6 mg/kg once every 2 weeks or cetuximab (400 mg/m^2) followed by 250 mg/m^2 weekly. The primary end-point was OS assessed for non-inferiority. Patients were followed for

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survival for 24 months after the last patient was randomised and a final analysis was conducted. No formal hypothesis testing was done. Post hoc analyses of outcomes by prior bevacizumab exposure, worst-grade skin toxicity (0–1 versus 2–4) and worst-grade hypomagnesaemia (0 versus 1–4) were conducted.

Results: Nine hundred ninety-nine patients were randomised and received ≥1 treatment dose (panitumumab, n = 499; cetuximab, n = 500). Median OS was 10.2 months with panitumumab versus 9.9 months with cetuximab (hazard ratio = 0.94; 95% confidence interval = 0.82–1.07). Median progression-free survival was 4.2 months with panitumumab and 4.4 months with cetuximab (hazard ratio = 0.98; 95% confidence interval = 0.87–1.12). Longer OS was observed for patients with increased skin toxicity and with hypomagnesaemia in both arms. Furthermore, OS was longer for patients with prior bevacizumab exposure treated with panitumumab than with cetuximab. The observed safety profiles were consistent with previous studies.

Conclusion: Consistent with the primary analysis, the final analysis of ASPECCT showed panitumumab was non-inferior to cetuximab for OS for patients with chemotherapy-refractory, wild-type *KRAS* exon 2 mCRC.

Trial registration: ClinicalTrials.gov, NCT01001377.

1. Introduction

For patients with metastatic colorectal cancer (mCRC), improvements in survival after irinotecan- or oxaliplatin-based chemotherapy in combination with targeted therapies [1–5] likely lead to an increase in patients eligible for third-line treatment. Panitumumab, a fully human monoclonal antibody targeting the epidermal growth factor receptor (EGFR), and cetuximab, a chimeric anti-EGFR antibody, have demonstrated clinical efficacy in patients with chemotherapy-refractory wild-type *KRAS* exon 2 mCRC [6–9]. In the phase 3 CO.17 study, cetuximab monotherapy improved overall survival (OS) and progression-free survival (PFS) versus best supportive care (BSC) in patients with wild-type *KRAS* exon 2 tumours [10,11]. Similarly, in the phase 3 20020408 study, panitumumab in combination with BSC improved PFS in patients with wild-type *KRAS* exon 2 mCRC, versus BSC alone [12–14]. A statistically significant OS benefit was not seen with panitumumab monotherapy in the 20020408 study, potentially because of patient crossover from the BSC arm (i.e. from BSC to panitumumab plus BSC after disease progression) [12].

ASPECCT was the first head-to-head, randomised, phase 3 study to evaluate efficacy and safety of panitumumab versus cetuximab for treatment of chemotherapy-refractory wild-type *KRAS* exon 2 mCRC. The primary analysis demonstrated that panitumumab was non-inferior to cetuximab, and the antibodies provided a similar OS benefit to this patient population (median, 10.4 months versus 10.0 months; Z-score = −3.19; $P = 0.0007$; hazard ratio [HR] = 0.97; 95% confidence interval [CI] = 0.84–1.11) [15]. Safety profiles were similar between groups [15]. We report results of the prespecified final descriptive analysis of outcomes in the ASPECCT study, which was planned for 24 months after the final patient was randomised, and results from ad hoc subgroup analyses by prior bevacizumab, skin toxicity, and hypomagnesaemia.

2. Patients and methods

2.1. Study design and patients

Detailed information regarding patient inclusion criteria, study design, and treatment schedules has been previously reported and is described in the Appendix [15]. The protocol received institutional/ethical approval at each site. Patients provided written informed consent.

2.2. 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/m^2 intravenously followed by 250 mg/m^2 intravenously on day 1 of each 7-day cycle. Patients in the cetuximab arm 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 continued until disease progression, intolerability or withdrawal of consent.

2.3. Study end-points

The primary end-point was OS (defined as time from randomisation to death) assessed for non-inferiority.

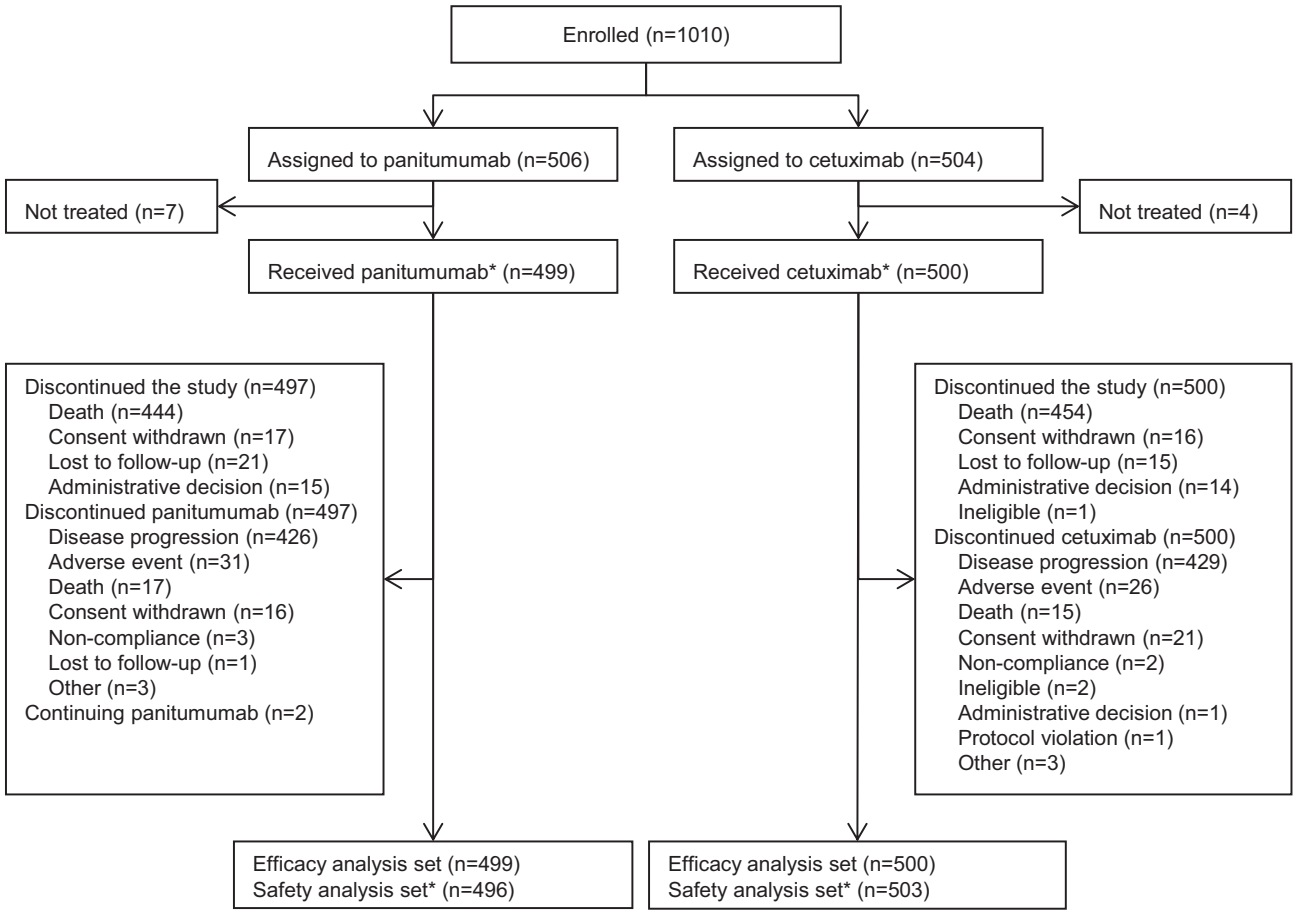

Fig. 1. Disposition of patients in the study (CONSORT). *Four patients were randomly assigned to the panitumumab arm but received cetuximab treatment because of a randomisation notification error; one patient was randomly assigned to cetuximab but received panitumumab because of a misunderstanding of the randomisation notification at the treatment site.

Secondary end-points included PFS (defined as time from randomisation to disease progression/death), objective response rate (ORR) and safety.

2.4. Statistical analysis

This non-inferiority study was designed to demonstrate that panitumumab retained ≥50% of the OS treatment effect of cetuximab versus BSC (previously reported; see Appendix). After the primary analysis, data continued to be collected for patients remaining on study. All patients were followed for survival for 24 months after the last patient was randomised. No formal hypothesis testing was planned for this analysis; however, descriptive statistics of key efficacy and safety end-points were updated. The primary analysis set included all patients who received ≥1 dose of panitumumab or cetuximab; patients were analysed according to the treatment to which they were randomised. The safety analysis set included all patients who received ≥1 dose of panitumumab or cetuximab; patients were analysed according to treatment received.

Post hoc analyses of outcomes by prior bevacizumab exposure, worst-grade skin toxicity (0–1 versus 2–4) and worst-grade hypomagnesaemia (0 versus 1–4) were also conducted (Appendix). For hypomagnesaemia, additional analyses of outcomes by worst-grade hypomagnesaemia and magnesium reduction (≥20% versus <20%) were performed at week 5. Stratified Cox proportional hazards models were used to examine relationships between subgroups, OS and PFS.

3. Results

3.1. Patients

Between February 2010 and July 2012, 1010 patients with wild-type *KRAS* exon 2 mCRC were randomised. Of these, 999 patients received ≥1 dose of study treatment (panitumumab, n = 499; cetuximab, n = 500; Fig. 1). Baseline characteristics were balanced between arms (Table 1). Post-progression antitumour therapy was similar between arms (Table A1). Median follow-up time for all patients was 41.3 weeks.

3.2. Efficacy outcomes

3.2.1. Overall survival

At the time of final analysis (September 15, 2014), 446 patients (89%) patients treated with panitumumab and 456 patients (91%) treated with cetuximab had died, versus 383 (77%) and 392 (78%), respectively, reported in the primary analysis (February 5, 2013). Median OS times with panitumumab and cetuximab treatment were 10.2 months and 9.9 months, respectively (HR = 0.94; 95% CI = 0.82–1.07; P = 0.0002; Fig. 2A). The retention rate was 1.11, indicating that panitumumab treatment preserved 111% of the cetuximab OS benefit. The non-inferiority test was positive (Z-score = −3.58; P = 0.0002), consistent with the primary analysis results. OS was similar between treatment arms across most patient subgroups (Fig. 2B).

3.2.2. Progression-free survival

At the time of the final analysis, 486 patients (97%) treated with panitumumab and 490 (98%) patients treated with cetuximab had had a PFS event. Median PFS was 4.2 months in the panitumumab arm and 4.4 months in the cetuximab arm (HR = 0.98; 95% CI = 0.87–1.12; Fig. 2C). PFS was similar between treatment arms for all patient subgroups analysed (Fig. 2D).

Table 1
Baseline demographic and clinical characteristics.

Characteristic	Panitumumab (n = 499)	Cetuximab (n = 500)
Men	315 (63.1)	318 (63.6)
White	266 (53.3)	258 (51.6)
Median (range) age, y	61.0 (19–86)	60.5 (20–89)
Region		
North America/Western Europe/Australia	154 (30.9)	156 (31.2)
Rest of world	345 (69.1)	344 (68.8)
ECOG PS		
0	154 (30.9)	163 (32.6)
1	303 (60.7)	297 (59.4)
2	42 (8.4)	40 (8.0)
Prior radiotherapy	131 (26.3)	128 (25.6)
Prior bevacizumab	126 (25.3)	132 (26.4)
Refractory to oxaliplatin or irinotecan[a]	495 (99.2)	496 (99.2)
Location of primary tumour		
Colon	292 (58.5)	326 (65.2)
Rectum	207 (41.5)	174 (34.8)
Sites of metastatic disease		
Liver only	52 (10.4)	50 (10.0)
Other sites ± liver	447 (89.6)	450 (90.0)

Data are expressed as n (%) unless otherwise noted.
ECOG PS = Eastern Cooperative Oncology Group Performance Status.
[a] Failure of a prior regimen containing irinotecan for metastatic disease and a prior regimen containing oxaliplatin for metastatic disease was an eligibility requirement for enrolment in ASPECCT. Oxaliplatin and irinotecan may have been administered sequentially or in combination.

3.2.3. Objective response rate

ORR (95% CI) was 22.0% (18.4%–26.0%) in the panitumumab arm and 19.8% (16.3%–23.6%) in the cetuximab arm (odds ratio = 1.15; 95% CI = 0.83–1.58; Table A2). Two patients (0.4%) in the panitumumab arm and zero patients (0%) in the cetuximab arm had a complete response.

3.3. Safety

The safety analysis included 496 patients in the panitumumab arm and 503 patients in the cetuximab arm. The overall incidence of treatment-emergent AEs was similar between patients treated with panitumumab and cetuximab for AEs of any grade (98%, 98%), serious AEs (30%, 34%), grade 3 AEs (37%, 32%) and grade 4 AEs (8%, 5%). The incidence of fatal AEs was the same as in the primary analysis: 29 patients (6%) in the panitumumab arm and 50 patients (10%) in the cetuximab arm.

Adverse events that occurred in ≥10% of patients in either treatment arm are summarised in Table 2. The incidence of grade 3/4 hypomagnesaemia was greater among patients who received panitumumab (7%) versus cetuximab (3%). Six patients (1.2%) in the panitumumab arm and two (0.4%) in the cetuximab arm discontinued treatment because of hypomagnesaemia. Furthermore, 25 patients (5%) in the panitumumab arm and 14 patients (3%) in the cetuximab arm underwent dose modifications for hypomagnesaemia. Grade 3/4 infusion reactions occurred in 1 (0.2%) in the panitumumab arm and 9 (1.8%) patients in the cetuximab arm.

3.4. Outcomes by prior bevacizumab therapy

In total, 126 patients (25%) in the panitumumab arm and 132 patients (26%) in the cetuximab arm received prior bevacizumab therapy. Baseline characteristics were similar between treatment arms (Table A3). OS outcomes appeared more favourable for patients treated with panitumumab versus cetuximab (median, 11.3 months versus 9.8 months; HR = 0.75; 95% CI = 0.58–0.97; Figs. 2B and 3A). After adjustment for baseline covariates including ECOG performance status, number of metastatic sites and baseline LDH, the OS HR was 0.65 (95% CI = 0.49–0.85) with panitumumab versus cetuximab. Post-progression antitumour therapy was similar between patients previously treated with bevacizumab who received panitumumab (47%) and cetuximab (52%). Median PFS was 4.7 months in the panitumumab arm versus 3.2 months in the cetuximab arm (HR = 0.85; 95% CI = 0.66–1.08; Figs. 2D and 3B).

For patients who had not previously received bevacizumab (panitumumab, n = 373; cetuximab, n = 368), median OS (10.0 months versus 9.9 months; HR = 1.04, 95% CI = 0.89–1.21) and PFS (3.8 months

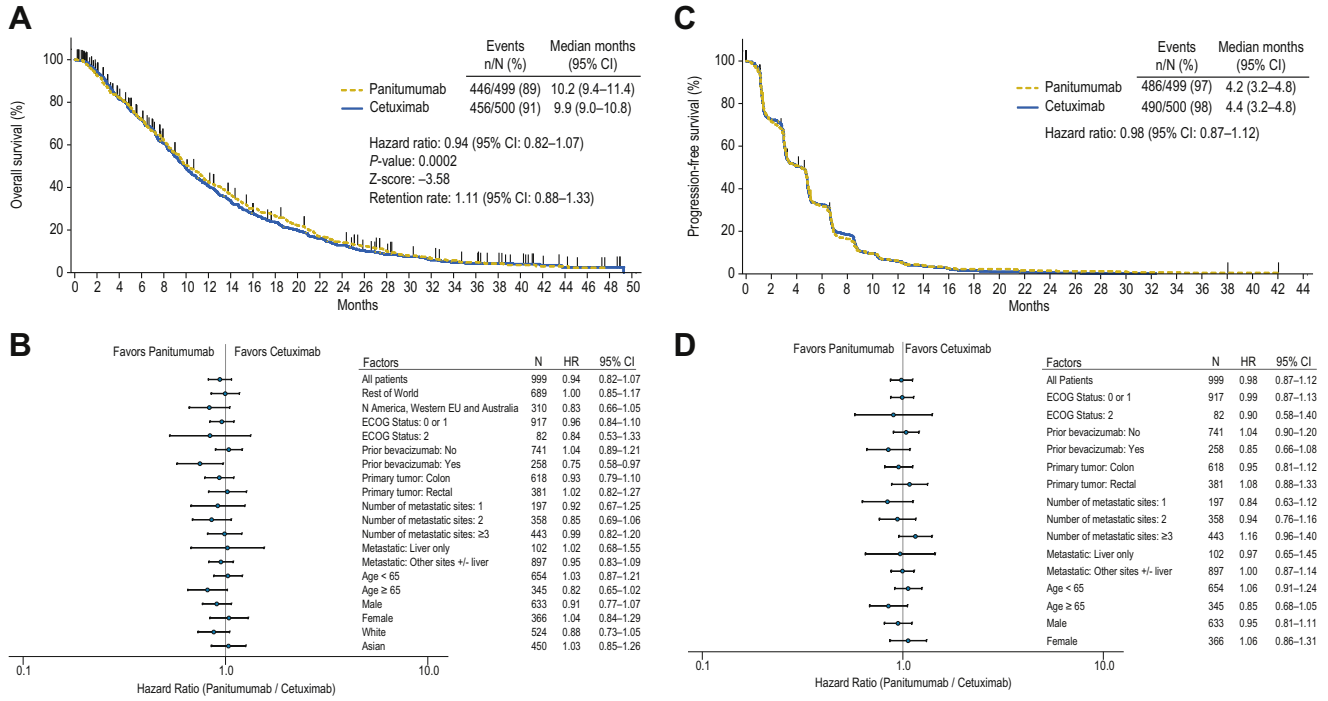

Fig. 2. Overall survival by treatment arm (A) and for subgroup analysis (B). Progression-free survival by treatment arm (C) and for subset analysis (D).

versus 4.7 months; HR = 1.04, 95% CI = 0.90–1.20) were similar (Fig. A1A, A1B).

3.5. Outcomes by skin toxicity severity

In total, 496 patients in the panitumumab arm and 503 patients in the cetuximab arm were included in the skin toxicity analysis. Baseline demographics and clinical characteristics were generally similar between patients with worst-grade 2–4 and worst-grade ≤1 skin toxicity (Table A4). Median (range) time to first (any grade) skin toxicity was 10 (1–213) days with panitumumab treatment and 11 (1–367) days with cetuximab treatment. Median time to resolution after the last dose of panitumumab or cetuximab was 37 days and 36 days, respectively.

Patients in the panitumumab arm with worst-grade 2–4 skin toxicity versus those with worst-grade ≤1 skin toxicity had longer median OS (14.0 versus 7.0 months; HR = 0.47; 95% CI = 0.39–0.57; Fig. 4A) and PFS (5.1 versus 2.9 months; Fig. A2A). Median duration of panitumumab treatment was 22 weeks for patients with worst-grade 2–4 skin toxicity and 8 weeks for patients with worst-grade ≤1 skin toxicity. Similarly, patients in the cetuximab arm with worst-grade 2–4 skin toxicity versus those with worst-grade ≤1 skin toxicity also had longer median OS (12.6 versus 7.9 months; HR = 0.57; 95% CI = 0.47–0.69; Fig. 4B) and PFS (4.9 versus 3.0 months; Fig. A2B). Median duration of cetuximab treatment was 22 weeks for patients with worst-grade 2–4 skin toxicity and 13 weeks for patients with worst-grade ≤1 skin toxicity.

3.6. Outcomes by hypomagnesaemia development

Overall, 496 patients in the panitumumab arm and 503 patients in the cetuximab arm with prior oxaliplatin and irinotecan exposure were included in the hypomagnesaemia analysis. Baseline demographics and clinical characteristics were generally similar between patients with hypomagnesaemia versus patients without hypomagnesaemia in both treatment arms (Table A5). Median (range) time to first hypomagnesaemia onset (any grade) was 83 (1–1130) days with panitumumab treatment and 57 (1–452) days with cetuximab treatment.

In the panitumumab arm, similar median OS times were observed in patients with hypomagnesaemia at week 5 versus those without (12.0 versus 11.3 months; HR = 1.20; 95% CI = 0.83–1.73; Fig. A3A), and in patients with ≥20% decrease in magnesium levels at week 5 versus those with <20% decrease (10.8 versus 11.3 months; HR = 1.18; 95% CI = 0.87–1.61; Fig. A3B). Patients in the cetuximab arm with hypomagnesaemia at week 5 had worse median OS (8.1 versus 10.5 months; HR = 1.67; 95% CI = 1.08–2.56; Fig. A4A) versus those without hypomagnesaemia. Additionally, patients with ≥20% decrease in magnesium levels from baseline at week 5 versus those with <20% decrease also had worse median OS (7.3 versus

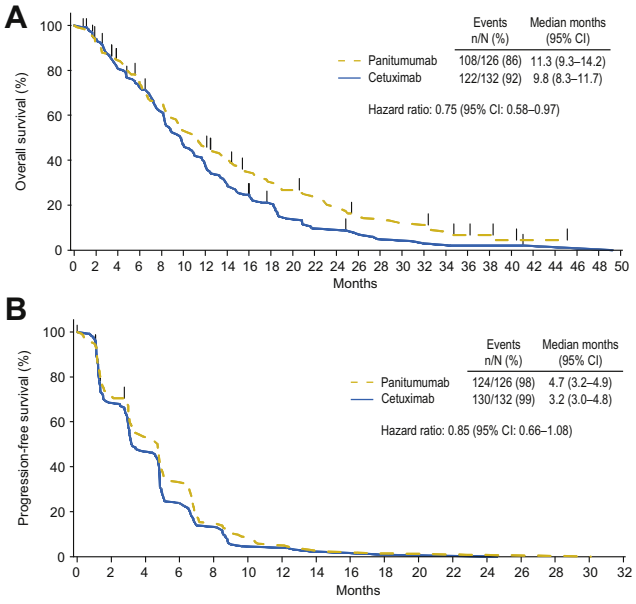

Fig. 3. Kaplan–Meier curves for overall survival (A) and progression-free survival (B) for patients with prior bevacizumab treatment.

Table 2
Adverse events of interest occurring in ≥10% of patients.

AEs, n (%)	Panitumumab (n = 496)		Cetuximab (n = 503)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Rash	249 (50.2)	25 (5.0)	257 (51.1)	18 (3.6)
Dermatitis acneiform	140 (28.2)	17 (3.4)	136 (27.0)	14 (2.8)
Hypomagnesaemia	137 (27.6)	35 (7.0)	91 (18.1)	14 (2.8)
Diarrhoea	92 (18.5)	10 (2.0)	89 (17.7)	9 (1.8)
Dry skin	83 (16.7)	1 (0.2)	79 (15.7)	0 (0)
Pruritus	83 (16.7)	4 (0.8)	89 (17.7)	1 (0.2)
Fatigue	75 (15.1)	14 (2.8)	89 (17.7)	18 (3.6)
Decreased appetite	70 (14.1)	3 (0.6)	78 (15.5)	7 (1.4)
Nausea	68 (13.7)	4 (0.8)	58 (11.5)	7 (1.4)
Abdominal pain	63 (12.7)	19 (3.8)	83 (16.5)	14 (2.8)
Vomiting	59 (11.9)	9 (1.8)	52 (10.3)	7 (1.4)
Paronychia	58 (11.7)	11 (2.2)	75 (14.9)	9 (1.8)
Acne	52 (10.5)	3 (0.6)	69 (13.7)	5 (1.0)
Constipation	41 (8.3)	1 (0.2)	74 (14.7)	3 (0.6)
Pyrexia	31 (6.3)	2 (0.4)	59 (11.7)	4 (0.8)
Other AEs, n (%)				
Skin toxicity[a]	431 (86.9)	63 (12.7)	440 (87.5)	48 (9.5)
Infusion reactions	14 (2.8)	1 (0.2)	63 (12.5)	9 (1.8)

AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities.
[a] Skin toxicity included multiple terms from the skin and subcutaneous tissue disorders system organ class per MedDRA v15.0.

10.8 months; HR = 2.16; 95% CI = 1.52–3.08; Fig. A4B).

In the panitumumab arm, patients with hypomagnesaemia at any point during the study had longer median OS versus those without hypomagnesaemia (13.6 versus 8.7 months; HR = 0.63; 95% CI = 0.51–0.78; Fig. 5A). Median duration of treatment was 28 weeks in patients with hypomagnesaemia and 11 weeks in patients without hypomagnesaemia in the panitumumab arm. In the cetuximab arm, patients with hypomagnesaemia at any point during the study also had longer median OS versus those without hypomagnesaemia (12.6 versus 9.3 months; HR = 0.71; 95% CI = 0.56–0.90; Fig. 5B). PFS was also longer in patients with hypomagnesaemia in both treatment arms (Fig. A5A, A5B). Median duration of treatment was 27 weeks in patients with hypomagnesaemia and 14 weeks in patients without hypomagnesaemia in the cetuximab arm.

In the panitumumab arm, patients with worst-grade 2–4 hypomagnesaemia had a similar median OS to those with worst-grade 1 hypomagnesaemia (13.6 versus 13.9 months; HR = 1.12; 95% CI = 0.78–1.60). In the cetuximab arm, patients with worst-grade 2–4 hypomagnesaemia had a shorter median OS versus those with worst-grade 1 hypomagnesaemia (10.3 versus 12.6 months; HR = 1.31; 95% CI = 0.83–2.05).

4. Discussion

In the previously published primary analysis, ASPECCT met its primary end-point of non-inferiority for OS. In this final analysis, panitumumab remained non-inferior to cetuximab for OS: panitumumab retained 111% (95% CI = 88%–133%) of the OS benefit of cetuximab over BSC in patients with chemotherapy-refractory wild-type *KRAS* exon 2 mCRC. PFS and ORR remained similar between arms.

The reported safety profiles for the panitumumab and cetuximab treatment arms were consistent with those

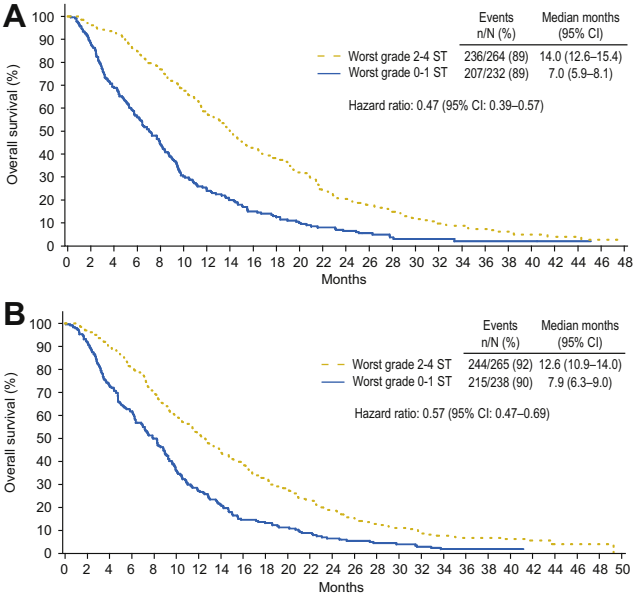

Fig. 4. Kaplan–Meier curves for overall survival by worst skin toxicity for patients treated with panitumumab (A) and cetuximab (B). ST = skin toxicity.

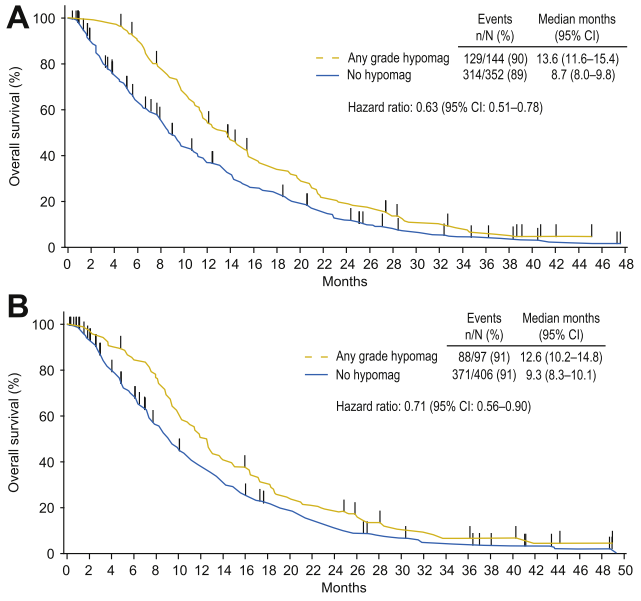

Fig. 5. Kaplan–Meier curves for overall survival by presence or absence of hypomagnesaemia for patients treated with panitumumab (A) and cetuximab (B).

previously described [1,4,5]. No new toxicities or safety signals were identified in either arm. The rates of grade ≥3 on-target AEs of interest were similar between the panitumumab and cetuximab treatment arms for skin toxicity (13%, 10%) and slightly higher with panitumumab for hypomagnesaemia (7%, 3%). The overall rate of infusion reactions was lower in the panitumumab arm (2.8%, 12.5%), with grade ≥3 reactions occurring in one patient treated with panitumumab and nine patients treated with cetuximab.

Patients with hypomagnesaemia at any point during ASPECCT had longer median OS versus those without hypomagnesaemia for both panitumumab and cetuximab arms, consistent with a previous analysis [16]. However, in a landmark analysis at week 5, median OS in the panitumumab arm for patients with hypomagnesaemia was similar to those without (12.0 versus 11.3 months; HR = 1.20) and for patients with ≥20% reduction in magnesium levels from baseline versus those with <20% reduction (10.8 versus 11.3 months; HR = 1.18). In the cetuximab arm, median OS time was shorter for those with hypomagnesaemia than for those without (8.1 versus 10.5 months; HR = 1.67), and for patients with ≥20% reduction in magnesium at week 5 versus <20% reduction (7.3 versus 10.8 months; HR = 2.16). The cetuximab results were consistent with results from a 28-day analysis reported from the cetuximab monotherapy CO.17 trial [17], but in contrast to those reported in retrospective analyses of patients treated with cetuximab in combination with either irinotecan [18] or oxaliplatin [19].

It is unclear why patients treated with cetuximab who developed hypomagnesaemia early may have different outcomes compared with patients treated with panitumumab, and why differences exist between studies. Although no clear biologic explanation has been identified, based on analyses from previous studies it has been hypothesised that the predictive value of hypomagnesaemia varies for different lines of treatment (perhaps as a consequence of combination with chemotherapy) [19,20]. In Vincenzi *et al.* (2011) and Stintzing *et al.* (2013), patients were treated with cetuximab and irinotecan and cetuximab and oxaliplatin, respectively, whereas in ASPECCT and the CO.17 trial, patients were heavily pretreated and received cetuximab as a monotherapy; the latter two analyses also excluded patients who had died within 5 weeks (this analysis) or 28 days (Vickers *et al.*, 2013) of randomisation. These patients may not have had sufficient time on therapy to develop hypomagnesaemia and their inclusion in the analysis by Vincenzi *et al.* (2011) may have confounded the results. Interaction with varying chemotherapy agents may have also confounded the results.

For patients who received panitumumab, median OS appeared moderately longer for those who had previously received bevacizumab (11.3 months) than for those who had not (10.0 months). It is possible that these differences may be the result of an association between the EGFR and vascular endothelial growth factor (VEGF) pathways; a recent study has provided clinical evidence supporting the existence of an interrelationship between the VEGF and EGFR signalling pathways [21]. It is difficult to draw definitive conclusions from ASPECCT as both arms received anti-EGFR treatment. There is an ongoing debate about the effect of prior bevacizumab exposure on patient response to anti-EGFR therapy, with varying outcomes demonstrated in different analyses [22,23]. One notable finding from this study was that median OS among patients who had previously received bevacizumab was longer for patients who received panitumumab versus those who received cetuximab (HR = 0.75; 95% CI = 0.58–0.97). Although multivariate analysis of baseline covariates was conducted (HR = 0.65; 95% CI = 0.49–0.85), this subgroup analysis was not adjusted for multiplicity, and the possibility that this finding is an artefact cannot be excluded. Presently, it is unclear what biologic mechanism might underlie such a difference in outcomes with panitumumab and cetuximab among patients who had previously received bevacizumab.

Subset analysis of outcomes by skin toxicity severity indicated that improvements in OS and PFS are associated with a higher grade of severity for patients treated with either panitumumab or cetuximab, consistent with previous studies [24–26]. However, patients with higher-grade skin toxicity had longer median duration of treatment than those with lower-grade skin toxicity. Because of this difference, it is difficult to determine

whether response improvement was linked to higher-grade skin toxicity or increased treatment exposure. Regardless of this, the proper management of skin toxicity remains important to minimise patient discomfort.

The final analysis results demonstrate that panitumumab is non-inferior to cetuximab and provides a similar OS benefit to patients with chemotherapy-refractory wild-type *KRAS* exon 2 mCRC. The observed safety profiles between treatment arms were consistent with previous studies; no new toxicities were identified. Dosing schedule and the observed incidence of infusion reactions may be considered when selecting an anti-EGFR therapy.

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Conflict of interest statement

Price has served as a consultant for Amgen Inc. and Merck. Kim has received honoraria from Amgen Inc. and Eli Lilly and has received research funding from Merck Serono, Bayer and Roche. Li has received research funding from Roche and Merck. Cascinu has served as a consultant for Lilly, Amgen Inc. and Bayer. Ruff has received honoraria and research funding from Sanofi and Amgen Inc., and has served on a speakers bureau for Roche and Amgen Inc., and has received travel expenses from Merck Serono, Roche and Novartis. Thomas has served as a consultant for Roche and Eli Lilly. Tjulandin has received research funding from AstraZeneca, has received travel expenses from Boehringer Ingelheim and Merck Serono and has served on speakers bureaus for AstraZeneca, Pfizer, Eisai and Sanofi-Aventis. Guan is an employee of, and owns stock in, Amgen Inc. Peeters has received honoraria, research funding and travel expenses from Amgen Inc and has served as a consultant and on speakers bureau for Amgen Inc. Suresh has nothing to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.08.010.

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