Au *et al.*[44]

Design	Participants	Arms	Outcomes
Study design: Supplementary study to parallel open-label RCT **Country:** Australia and Canada **No. of centres:** Unknown **Funding:** Amgen, Bristol-Myers Squibb, Merck Serono **Notes:** This is a supplementary paper to Jonker *et al.*[37]	**Number randomised:** 572 **Inclusion criteria:** Advanced, pretreated, EFGR-detectable, histologically proven metastatic colorectal cancer for which no other standard anticancer therapies were available. All had prior chemotherapy and all experienced treatment failure or were considered unsuitable for treatment with both irinotecan and oxaliplatin **Therapy common to all participants:** Best supportive care **Sample attrition/dropout:** Compliance with HRQoL questionnaire – cetuximab (93.7–60.8%), BSC (94.4–35.4%)	**Arm no. 1** **Name:** Cetuximab plus best supportive care ***n*:** 287 **Drug:** Cetuximab **Starting daily dose:** 400 mg/m^2 intravenously over 2 hours **Dosage details:** 250 mg/m^2 intravenously weekly **Arm no. 2** **Name:** best supportive care ***n*:** 285 **Drug:** not applicable **Starting daily dose:** not applicable **Dosage details:** not applicable	**Primary outcome measure:** Overall survival **Secondary outcome measure(s):** Progression-free survival, response rate, safety, HRQoL **Method of assessment:** Participants attended clinic visits scheduled at baseline and weeks 4, 8, 16 and 24 and completed the self-administered EORTC QLQ-C30 Scoring was completed according to the EORTC QLQ-C30 manual and linear transformation was used to standardise raw scores to range between 0 and 100 Higher scores correspond to better HRQoL in functional scales and global health status and to worse HRQoL in symptom scores Missing items in a scale were handled using the methods outlined in the scoring manual

Baseline characteristics

	CET + BSC			BSC			
	n	**Estimate**	**Mean**	***n***	**Estimate**	**Mean**	***p*-value**
	Refers to Jonker *et al.*[37] for full characteristics; stated as balanced between arms						
Age (years), median	63						

BSC, best supportive care; CET, cetuximab.

Results

	CET + BSC			BSC			
	n	Estimate	Mean	*n*	Estimate	Mean	*p*-value
Study medication: duration of treatment	Until disease progression or toxicity						
Compliance with HRQoL assessments							
Received at baseline	287	93.7%		285	94.4%		
Received at 4 weeks	266	86.5%		270	68.5%		
Received at 8 weeks	239	81.2%		238	63.9%		
Received at 16 weeks	197	67%		172	46.5%		
Received at 24 weeks	158	60.8%		113	35.4%		
EORTC QLQ-C30 scale by assessment time (mean change scores)							
Week 8 physical function							
Overall	185		–3.9 (SD 15.6)	147		–8.6 (SD 20.4)	0.046
KRAS WT	90		–0.69 (SD 13.59)	62		–7.15 (SD 20.26)	0.11
KRAS mutant	48		–6.53 (SD 16.30)	46		–12.9 (SD 21.56)	0.14
Week 8 global health status							
Overall	185		–0.5 (SD 20.4)	149		–7.1 (SD 22.4)	0.008
KRAS WT	88		3.22 (SD 19.63)	63		–7.67 (SD 21.34)	0.0016
KRAS mutant	48		–4.69 (SD 20.48)	47		–9.57 (SD 24.63)	0.53
Week 16 physical function							
Overall	125		–5.9 (SD 17.7)	76		–12.5 (SD 21.6)	0.027
KRAS WT	69		–3.43 (SD 17.93)	36		–13.8 (SD 21.47)	0.0078
KRAS mutant	27		–9.51 (SD 19.45)	22		–9.47 (SD 22.85)	0.72
Week 16 global health status							
Overall	128		–3.6 (SD 22.6)	75		–15.2 (SD 25.8)	< 0.001
KRAS WT	70		–0.24 (SD 21.19)	36		–18.1 (SD 27.64)	< 0.001
KRAS mutant	28		–9.52 (SD 19.60)	21		–13.9 (SD 26.79)	0.62
Week 8 global health status, ≥ 10-point decrease		23.2%			38.3%		0.004
Week 16 global health status, ≥ 10-point decrease		31.3%			49.3%		0.069
Week 8 physical function, ≥ 10-point decrease		24.9%			34.7%		0.051
Week 16 physical function, ≥ 10-point decrease		30.4%			43.4%		0.069
Week 8 physical function, ≥ 10-point decrease							
KRAS WT		17.8%					
KRAS mutant		31.3%					0.09
Week 16 physical function, ≥ 10-point decrease							
KRAS WT		21.7%					
KRAS mutant		40.7%					0.08
Median time (months) for physical function to decrease by 10 points		5.4			3.7		0.022

	CET + BSC			BSC			
	n	Estimate	Mean	*n*	Estimate	Mean	*p*-value
Median time (months) for global health scale to decrease by 10 points		5.4			3.7		0.062
Mean change scores of other scales and domains							
8 weeks							
Role function			–5			–12.7	0.02
Fatigue			8.2			1.2	0.002
Nausea			6.2			0.7	0.007
Pain			8.4			–0.9	<0.001
Dyspnoea			7.8			0.7	0.005
Sleep			4.3			–1.6	0.03
Financial impact			2.0			–4.5	<0.001
16 weeks							
Role function			–7.5			–23.8	<0.001
Social function			–3.9			–11.3	0.04
Fatigue			15.8			2.3	<0.001
Nausea			11.3			0.9	<0.001
Pain			13.6			1.1	0.007
Dyspnoea			23.0			1.6	<0.001
Appetite			13.3			–1.8	<0.001
Constipation			11.4			0.5	0.02
Overall HRQoL response (improvements at least one time point)							
Pain		47%				27%	0.001
Fatigue		41%				31%	0.04
Nausea		22%				16%	0.01
Dyspnoea		22%				13%	0.04
Financial impact		23%				14%	0.003
Global health scale							
KRAS WT		40%					
KRAS mutant		19%					0.01
Sleep							
KRAS WT		36%					
KRAS mutant		23%					0.03

BSC, best supportive care; CET, cetuximab; SD, standard deviation.

Methodological issues

Randomisation and allocation

Eligible patients were randomly assigned on a 1:1 basis to receive cetuximab plus best supportive care or best supportive care alone.

Data analysis

Primary HRQoL analysis was defined prospectively as a comparison of the change of scores from baseline to 8 or 16 weeks for the physical function and global health status scales respectively (Wilcoxon's test).

Secondary HRQoL analyses, defined prospectively, included comparisons of the proportions of patients with worsened physical function and global health status at 8 and 16 weeks using Fisher's exact test and the time to deterioration in physical function and global health status scales using the log-rank test.

HRQoL – improved (increase in 10 units), worsened (decrease in 10 units) or remained stable (change < 10 units). The chi-squared test was used to compare the distributions of HRQoL response categories between arms.

HRQoL outcomes were analysed by *KRAS* status. Correlation between HRQoL response and objective tumour response was also sought.

Power calculation

Not reported; see Jonker and colleagues.[37]

Conflicts of interest

Lead author and seven colleagues declare consultancy fees.

Quality appraisal

1. Was the assignment to the treatment groups really random? Not reported
2. Was the treatment allocation concealed? No
3. Were the groups similar at baseline in terms of prognostic factors? Reported – yes
4. Were the eligibility criteria specified? Adequate
5. Were outcome assessors blinded to the treatment allocation? Unclear; however, the *KRAS* analysis was blinded
6. Was the care provider blinded? No
7. Was the patient blinded? No
8. Were the point estimates and measure of variability presented for the primary outcome measure? Adequate
9. Did the analyses include an ITT analysis? Reported – yes
10. Were withdrawals and dropouts completely described? Adequate

Jonker *et al.*[37]

Design	Participants	Arms	Outcomes
Study design: Parallel, open-label RCT **Country:** Australia and Canada **No. of centres:** Unknown **Funding:** Not reported **Length of follow-up:** 14.6 months	**Number randomised:** 572 **Inclusion criteria:** Advanced colorectal cancer expressing EGFR that was detectable by immunohistochemical methods in a central reference laboratory. The patients had either been treated with a fluoropyrimidine, irinotecan and oxaliplatin with no response to treatment (as defined by unacceptable adverse events or progression of the tumour within 6 months of completion of treatment) or had contraindications to treatment with these drugs. The patients had disease that could be measured or otherwise evaluated; an ECOG performance status of 0–2; adequate bone marrow, kidney and liver function; and no serious concurrent illness **Exclusion criteria:** Patients were ineligible if they had received any agent that targets the EGFR pathway or treatment with a murine monoclonal antibody. Previous bevacizumab treatment was permitted but not required **Therapy common to all participants:** Best supportive care	**Arm no. 1** **Name:** Cetuximab plus best supportive care ***n*:** 287 **Drug:** Cetuximab **Starting daily dose:** Intravenously as an initial dose of 400 mg/m^2 of body surface area, administered over 120 minutes **Dosage details:** Weekly maintenance infusion of 250 mg/m^2, administered over 60 minutes **Arm no. 2** **Name:** Best supportive care ***n*:** 285 **Drug:** N/A **Starting daily dose:** N/A **Dosage details:** Measures designed to provide palliation of symptoms and improve quality of life	**Primary outcome measure:** Overall survival, defined as time from randmisation until death from any cause **Secondary outcome measure(s):** Progression-free survival, defined as time from randomisation until the first objective observation of disease progression or death from any cause Response rates, defined according to the modified RECIST QoL, assessed by mean changes in scores of physical function and global health status at 8 and 16 weeks **Method of assessment:** All patients were assessed every 4 weeks. Telephone monitoring was conducted until death for patients unable to attend the clinic. Chest radiographs and cross-sectional imaging were performed at baseline and every 8 weeks in both study groups until tumour progression occurred Quality of life was assessed using the EORTC QLQ-C30 at baseline and at 4, 8, 16 and 24 weeks after randomisation

Baseline characteristics

	CET + BSC			BSC			
Demographics	***n***	**Estimate**	**%**	***n***	**Estimate**	**%**	***p*-value**
Age (years)	287	63[a]	28.6–88.1[b]	285	63.6[a]	28.7–85.9[b]	
Sex (*n* male)	287	186	64.8	285	182	63.9	
ECOG status							
0	287	72	25.1	285	64	22.5	
1	287	148	51.6	285	154	54.0	
2	287	67	23.3	285	67	23.5	
Site of primary cancer							
Colon only	287	171	59.6	285	161	56.5	
Rectum only	287	63	22.0	285	70	24.6	
Colon and rectum	287	53	18.5	285	54	18.9	
Any previous radiotherapy	287	103	35.9	285	99	34.7	
Previous chemotherapy							
Adjuvant therapy	287	108	37.6	285	103	36.1	
No. of regimens							
1 or 2	287	50	17.4	285	54	18.9	
3	287	109	38.0	285	108	37.9	
4	287	87	30.3	285	72	25.3	
≥5	287	41	14.3	285	51	17.9	

Demographics	CET + BSC			BSC			*p*-value
	n	Estimate	%	*n*	Estimate	%	
Thymidylate synthase inhibitor	287	287	100	285	285	100	
Irinotecan	287	277	96.5	285	273	95.8	
Oxaliplatin	287	281	97.9	285	278	97.5	
Sites of disease							
Liver	287	230	80.1	285	233	81.8	
Lung	287	188	65.5	285	180	63.2	
Lymph nodes	287	130	45.3	285	117	41.1	
Peritoneal cavity	287	45	15.7	285	41	14.4	
No. of sites of disease							
1	287	40	13.9	285	53	18.6	
2	287	84	29.3	285	69	24.2	
3	287	84	29.3	285	89	31.2	
≥4	287	79	27.5	285	74	26.0	

BSC, best supportive care; CET, cetuximab.
a Median.
b Range.

Results

	CET + BSC			BSC			*p*-value
	n	Estimate	%	*n*	Estimate	%	
ITT population							
Study medication: duration of treatment			8 weeks				
Overall survival	287	0.77[a]					0.005
ECOG performance status of 0 or 1		0.72[b]					
ECOG performance status of 2		0.89[c]					
<65 years		0.77[d]					
>65 years		0.75[e]					
Female		0.69[f]					
Male		0.80[g]					
Median survival (months)	287	6.1		285	4.6		
No rash		2.6					
Grade 1 rash		4.8					
Grade 2 rash		8.4					0.001[h]
Progression-free survival		0.68[i]					
Response rate							
Partial response	287	23	8.0	285	0	0	<0.001
Stable disease	287	90	31.4	285	31	10.9	<0.001
Proportion of patients alive at 6 months	287		50	285		33	
Proportion of patients alive at 12 months	287		21	285		16	

	CET + BSC			BSC			
	n	Estimate	%	*n*	Estimate	%	*p*-value
Deterioration in physical function at 8 weeks	287	–3.9		285	–8.6		< 0.05
Deterioration in physical function at 16 weeks	287	–5.9		285	–12.5		0.03
Deterioration in global health scale at 8 weeks	287	–0.5		285	–7.1		0.008
Deterioration in global health scale at 16 weeks	287	–3.6		285	–15.2		< 0.001
Safety population							
Any adverse event	288	226	78.5	274	162	59.1	
Oedema	288	15	5	274	16	5.8	
Fatigue	288	95	33.0	274	71	25.9	
Anorexia	288	24	8.3	274	16	5.8	
Constipation	288	10	3.5	274	16	5.8	
Nausea	288	16	5.6	274	15	5.5	
Vomiting	288	16	5.6	274	15	5.5	
Non-neutropenic infection	288	37	12.8	274	15	5.5	
Confusion	288	16	5.6	274	6	2.2	
Abdominal pain	288	38	13.2	274	43	15.7	
Other pain	288	43	14.9	274	20	7.3	
Dyspnoea	288	47	16.3	274	34	12.4	
Rash	288	34	11.8	274	1	0.4	
Infusion reaction – grade 1	288	30	10.4	274	0	0	
Infusion reaction – grade 2	288	16	5.6	274	0	0	
Infusion reaction – grade 3	288	8	2.8	274	0	0	
Infusion reaction – grade 4	288	5	1.7	274	0	0	
Rash – grade 1	288	114	39.6	274	32	11.7	
Rash – grade 2	288	107	37.2	274	11	4.0	
Rash – grade 3	288	34	11.8	274	1	0.4	
Rash – grade 4	288	0	0	274	0	0	
Hypomagnesaemia – grade 1[j]	288	95	36.7	274	29	14.6	
Hypomagnesaemia – grade 2[j]	288	28	10.8	274	1	0.4	
Hypomagnesaemia – grade 3[j]	288	7	2.7	274	0	0	
Hypomagnesaemia – grade 4[j]	288	8	3.1	274	0	0	

BSC, best supportive care; CET, cetuximab.
a Hazard ratio for disease progression (95% CI 0.64 to 0.92).
b Hazard ratio for disease progression (95% CI 0.58 to 0.89).
c Hazard ratio for disease progression (95% CI 0.62 to 1.27).
d Hazard ratio for disease progression (95% CI 0.61 to 0.98).
e Hazard ratio for disease progression (95% CI 0.56 to 1.0).
f Hazard ratio for disease progression (95% CI 0.50 to 0.94).
g Hazard ratio for disease progression (95% CI 0.63 to 1.01).
h *p*-value for rashes.
i Hazard ratio for disease progression (95% CI 0.57 to 0.80).
j The results for hypomagnesemia are based on 259 patients in the cetuximab group and 198 patients in the supportive-care group.

Methodological issues

Randomisation and allocation

Eligible patients were stratified according to centre and ECOG performance status and randomly assigned in a 1 : 1 ratio. Randomisation was peformed by the National Cancer Institute of Canada Clinical Trials Group central office with the use of a minimisation method that dynamically balanced patients according to stratification factors.

Data analysis

Time-to-event variables were summarised with the use of Kaplan–Meier plots.

Primary comparisons of the treatment groups were made with the use of the stratified log-rank test. Hazard ratios with 95% CIs were calculated from stratified Cox regression models with treatment group as the single factor. Deterioration in QoL score was defined a priori as a decline of ≥ 10 points from baseline.

All *p*-values were two-sided.

Power calculation

It was estimated a priori that 445 deaths would provide a statistaical power of 90% and a two-sided alpha of 5% to detect an absolute increase of 9.6% in the 1-year overall survival from the predicted 1-year overall survival of 14.1% in the group assigned to supportive care alone (hazard ratio 0.74).

Conflicts of interest

Two authors are employees of the National Cancer Institute of Canada Clinical Trials Group and received funding from Bristol-Myers Squibb and Amgen. Two authors received research grants from Bristol-Myers Squibb and one author received consulting fees from Amgen. One author is an employee of and owns equity in Bristol-Myers Squibb.

Quality appraisal

1. Was the assignment to the treatment groups really random? Reported – yes
2. Was the treatment allocation concealed? No
3. Were the groups similar at baseline in terms of prognostic factors? Reported – yes
4. Were the eligibility criteria specified? Reported – yes
5. Were outcome assessors blinded to the treatment allocation? No
6. Was the care provider blinded? No
7. Was the patient blinded? No
8. Were the point estimates and measure of variability presented for the primary outcome measure? Adequate
9. Did the analyses include an ITT analysis? Reported – yes
10. Were withdrawals and dropouts completely described? Reported – yes

Karapetis *et al.*[45]

Design

Study design: Retrospective *KRAS* analysis of parallel, open-label RCT

Country: Australia and Canada

No. of centres: Unknown

Funding: National Cancer Institute of Canada, ImClone Systems and Bristol-Myers Squibb

Length of follow-up: Not reported

Notes: Cetuximab therapy was continued until the disease progressed or until the patient could not tolerate the toxic effects

Participants

Number randomised: 572

Inclusion criteria: Not fully reported in this paper, only states that no patients had received previous therapy directed against EGFR. Refer to Jonker *et al.*[37] for main trial

Exclusion criteria: Not reported

Therapy common to all participants: Best supportive care

Arms

Arm no. 1

Name: Cetuximab plus best supportive care

***n*:** 287

Drug: Cetuximab

Starting daily dose: Intravenously as an initial dose of 400 mg/m^2 of body surface area, administered over 120 minutes

Dosage details: Weekly maintenance infusion of 250 mg/m^2, administered over 60 minutes

Arm no. 2

Name: Best supportive care

***n*:** 285

Drug: N/A

Starting daily dose: N/A

Dosage details: Measures designed to provide palliation of symptoms and improve quality of life

Outcomes

Primary outcome measure: Overall survival, defined as time from randomisation until death from any cause

Secondary outcome measure(s): Progression-free survival, defined as time from randomisation until the first objective observation of disease progression or death from any cause

Response rates, defined according to the modified RECIST

QoL, assessed by mean changes in scores of physical function and global health status at 8 and 16 weeks

Method of assessment: Patients were evaluated for tumour response or progression every 8 weeks by radiological imaging

Assays of tissue samples for *KRAS* mutations were performed in a blinded fashion

N/A, not applicable.

Baseline characteristics

	All			*KRAS* mutant			*KRAS* WT			
Demographics	***n***	**Estimate**	**%**	***n***	**Estimate**	**%**	***n***	**Estimate**	**%**	***p*-value**
Age	572	63.2[a]		164	62.0[b]		230	63.5[c]		0.57
< 65 years	572	335	58.6	164	99	60.4	230	133	57.8	
≥ 65 years	572	237	41.4	164	65	39.6	230	97	42.2	
Sex										0.20
Female	572	204	35.7	164	63	38.4	230	74	32.2	
Male	572	368	64.3	164	101	61.6	230	156	67.8	
ECOG performance status										
0	572	136	23.8	164	34	20.7	230	56	24.3	0.70
1	572	302	52.8	164	94	57.3	230	127	55.2	
2	572	134	23.4	164	36	22.0	230	47	20.4	
Site of primary cancer										
Colon only	572	332	58.0	164	108	65.9	230	137	59.6	0.41
Rectum only	572	133	23.3	164	32	19.5	230	50	21.7	
Colon and rectum	572	107	18.7	164	24	14.6	230	43	18.7	
Any previous radiotherapy	572	202	35.3	164	50	30.5	230	77	33.5	0.53

	All			*KRAS* mutant			*KRAS* WT			
Demographics	***n***	**Estimate**	**%**	***n***	**Estimate**	**%**	***n***	**Estimate**	**%**	***p*-value**
Previous chemotherapy										
Adjuvant therapy	572	211	36.9	164	57	34.8	230	83	36.1	0.79
No. of regimens										
1 or 2	572	104	18.2	164	27	16.5	230	46	20.0	0.70
3	572	217	37.9	164	69	42.1	230	86	37.4	
4	572	159	27.8	164	46	28.0	230	63	27.4	
≥5	572	92	16.1	164	22	13.4	230	35	15.2	
Thymidylate synthase inhibitor	572	572	100	164	164	100	230	230	100	
Irinotecan	572	550	96.2	164	161	98.2	230	219	95.2	0.12
Oxaliplatin	572	559	97.7	164	163	99.4	230	222	96.5	0.06
Sites of disease										
Liver	572	463	80.9	164	129	78.7	230	189	82.2	0.38
Lung	572	368	64.3	164	98	59.8	230	144	62.6	0.57
Lymph nodes	572	247	43.2	164	64	39.0	230	103	44.8	0.25
Peritoneal cavity	572	86	15.0	164	23	14.0	230	38	16.5	0.50
No. of sites of disease										
1	572	93	16.3	164	27	16.5	230	40	17.4	0.27
2	572	153	26.7	164	45	27.4	230	63	27.4	
3	572	173	30.2	164	42	25.6	230	75	32.6	
≥4	572	153	26.7	164	50	30.5	230	52	22.6	
Treatment										
Cetuximab plus BSC	572	287	50.2	164	81	49.4	230	117	50.9	0.77
BSC	572	285	49.8	164	83	50.6	230	113	49.1	

BSC, best supportive care.
a Median (range 28.6–88.1 years).
b Median (range 37.4–88.1 years).
c Median (range 28.6–85.9 years).

Results

	CET + BSC			BSC			
	n	Estimate	%	*n*	Estimate	%	*p*-value
ITT population							
Study medication: duration of treatment							
KRAS assessed	287	198	69.0	285	196	68.8	
Overall survival							
KRAS mutant	198	0.98[a]		196			
KRAS WT	198	0.55[b]		196			
1-year survival rate – mutant	198			196		13.2	
1-year survival rate – WT	198			196		20.1	
Median overall survival (months)							
KRAS mutant	198	4.5		196	4.6		
KRAS WT	198	9.5		196	4.8		
Progression-free survival							
KRAS mutant	198	0.99[c]					
KRAS WT	198	0.4[d]					
KRAS mutant, median PFS (months)	198	1.8		196	1.8		
KRAS WT, median PFS (months)	198	3.7		196	1.9		
Response rate							
KRAS mutant	198			196		0	
KRAS WT	198			196		0	
Global health scale at 8 weeks, mean change							
KRAS mutant	198	–4.7		196	–9.6		
KRAS WT	198	3.2		196	–7.7		
Difference WT	198	10.9[e]					0.002
Global health scale at 16 weeks, mean change							
KRAS mutant	198	–9.5		196	–13.9		
KRAS WT	198	–0.2		196	–18.1		
Difference WT	198	17.9[f]					< 0.001
Safety population	No safety data presented; refer to Jonker *et al.*[37]						

BSC, best supportive care; CET, cetuximab; PFS, progression-free survival.

a Hazard ratio for disease progression (95% CI 0.70 to 1.37).

b Hazard ratio for disease progression (95% CI 0.41 to 0.74).

c Hazard ratio for disease progression (95% CI 0.73 to 1.35).

d Hazard ratio for disease progression (95% CI 0.30 to 0.54).

e 95% CI 4.2 to 17.6.

f 95% CI 7.6 to 28.2.

Methodological issues

Randomisation and allocation

Not applicable as a retrospective study; see Jonker and colleagues[37] for main study.

Data analysis

All randomly assigned patients for whom data on *KRAS* mutation status were available were included in the analysis.

Survival was summarised with the use of Kaplan–Meier curves and the difference in survival between treatment groups compared with the use of the log-rank test, with hazard ratios and 95% CIs calculated from a Cox regression model with a single covariate.

To assess whether or not *KRAS* was an independant prognostic factor for patients receiving supportive care, a multivariate Cox regression model was fitted to data for patients receiving supportive care alone. The Cox regression model, with treatment, *KRAS* mutation status and their interaction as covariates, was used to assess the interaction between treatment and *KRAS* status.

All reported *p*-values are two-sided and were not adjusted for multiple testing.

For QoL, Wilcoxon's tests were used to compare the treatment arms with respect to the mean change from baseline in scores on the global QoL scale. A difference of more than 10 points was considered to indicate clinical significance.

Power calculation

Not reported.

Conflicts of interest

Two authors received consulting fees from Merck Serono, two authors received consulting fees from Bristol-Myers Squibb, two authors were employed by the National Cancer Institute of Canada Clinical Trials Group and funded by Bristol-Myers Squibb and Amgen, one author received consulting fees from ImClone and two authors received research grants from Amgen, Merck Serono, Bristol-Myers Squibb and Alphapharm.

Quality appraisal

1. Was the assignment to the treatment groups really random? Not applicable
2. Was the treatment allocation concealed? No
3. Were the groups similar at baseline in terms of prognostic factors? Reported – yes
4. Were the eligibility criteria specified? Reported – yes
5. Were outcome assessors blinded to the treatment allocation? Partial
6. Was the care provider blinded? No
7. Was the patient blinded? No
8. Were the point estimates and measure of variability presented for the primary outcome measure? Adequate
9. Did the analyses include an ITT analysis? Reported – yes
10. Were withdrawals and dropouts completely described? Reported – yes

Peeters *et al.*[52]

Design	Participants	Arms	Outcomes
Study design: Supplementary study to open-label, Phase III RCT. See Van Cutsem *et al.*[7] **Country:** Not reported **No. of centres:** Unknown **Funding:** Not reported **Length of follow-up:** Median follow-up time for all patients was 29 months (range 24–38 months) and for 39 surviving patients it was 28 months (range 24–26 months)	**Number randomised:** 463 **Inclusion criteria:** Pathological diagnosis of metastatic colorectal adenocarcinoma, ECOG performance status of 0–2, radiological documentation of disease progression during or within 6 months after the last administration of fluoropyrimidine, irinotecan and oxaliplatin, two or three prior chemotherapy regimens, EGFR membrane staining on ≥ 1% tumour cells by immunohistochemistry at a central laboratory, adequate haematological, renal and hepatic function and no symptomatic brain metastases **Exclusion criteria:** Not reported **Therapy common to all participants:** Best supportive care	**Arm no. 1** **Name:** Panitumumab plus best supportive care ***n*:** 231 **Drug:** Panitumumab **Dosage details:** Panitumumab 6.0 mg/kg twice a week plus BSC **Arm no. 2** **Name:** Best supportive care ***n*:** 232 **Drug:** N/A **Starting daily dose:** N/A **Dosage details:** N/A	**Primary outcome measure:** Progression-free survival, defined as the time from randomisation to the earliest radiological disease progression per modified RECIST by blinded central review or death, with censoring at the last complete tumour assessment **Secondary outcome measure(s):** Overall survival time and best overall objective response by central radiology, safety (including skin toxicity severity), patient-reported skin toxicity, disease-related symptoms and HRQoL **Method of assessment:** Blinded central radiological tumour assessment using modified RECIST at specified time points from weeks 8 to 48 and every 3 months thereafter until disease progression. Responses were confirmed no less than 4 weeks after the response criteria were first met. At the discretion of the investigator, patients could be evaluated for radiographic tumour assessment after developing symptoms consistent with disease progression Patient-reported outcome assessments were obtained at baseline and every 2 weeks or monthly during the treatment phase of the study and at the 30-day safety follow-up visit. Patient-reported skin toxicity was measured using the modified Dermatology Life Quality Index (mDLQI); colorectal cancer symptoms were measured using the NCCN FCSI; HRQoL was measured using the EQ-5D and the EORTC QLQ-C30 global health status/QOL scale

N/A, not applicable.

Baseline characteristics

No characteristics reported; see main paper by Van Cutsem and colleagues.[7]

Results

	PAN + BSC			BSC			
	n	Estimate	%	*n*	Estimate	%	*p*-value
Number of completed questionnaires							
mDLQI week 4	208	189		184	128		
mDLQI week 8	208	112		184	47		
mDLQI week 12	208	91		184	12		
mDLQI week 16	208	66		184	6		
EQ-5D week 4	208	189		184	129		
EQ-5D week 8	208	112		184	46		
EQ-5D week 12	208	92		184	13		
EQ-5D week 16	208	66		184	7		
FCSI subscale week 4	208	190		184	130		
FCSI subscale week 8	208	113		184	47		
FCSI subscale week 12	208	91		184	13		

	PAN + BSC			BSC			
	n	Estimate	%	*n*	Estimate	%	*p*-value
FCSI subscale week 16	208	66		184	7		
Progression-free survival							
Onset of grade 2 or above skin toxicity	363	0.71					0.0230
Onset of grade 2 or above skin toxicity in 2 months, all patients	363	0.63					0.0126
Skin toxicity grades 2–4 vs grade 1	182	0.63[a]					0.0063
Skin toxicity grades 2–4 WT	110	0.75[b]					
Grade 2-onset skin toxicity, any time, all patients	182	0.71[c]					0.0230
Grade 2-onset skin toxicity, 0–1 months, all patients	182	0.27[d]					0.0476
Grade 2-onset skin toxicity, 1–2 months, all patients,	182	0.69[e]					0.0575
Grade 2-onset skin toxicity, 2–3 months, all patients	182	0.69[f]					0.4205
Grade 2-onset skin toxicity, >3 months, all patients	110	1.02[g]					0.9628
Grade 2-onset skin toxicity, any time, WT	110	0.75[h]					0.2021
Grade 2-onset skin toxicity, 0–2 months, WT	110	0.55[i]					0.0453
Grade 2-onset skin toxicity, >2 months, WT	110	1.12[j]					0.7589
Grade 2-onset skin toxicity, any time, mutant	72	0.83[k]					0.4635
Grade 2-onset skin toxicity, 0–2 months, mutant	72	0.84[l]					0.5049
Grade 2-onset skin toxicity, >2 months, mutant	72	0.79[m]					0.7111
Overall survival							
Skin toxicity grades 2–4 vs grade 1	182	0.6[n]					0.0033
Skin toxicity grade 2 or above, all patients	182	0.63[o]					0.0034
Grade 2 onset skin toxicity, 0–2 months, all patients	182	0.45[p]					0.0480
Grade 2 onset skin toxicity, 2–4 months, all patients,	182	0.42[q]					0.0139
Grade 2 onset skin toxicity, 4–6 months, all patients	182	0.97[r]					0.9276
Grade 2 onset skin toxicity, 6 months, all patients	182	0.71[s]					0.1394

	PAN + BSC			BSC			
	n	Estimate	%	*n*	Estimate	%	*p*-value
Grade 2 onset skin toxicity, 0–4 months, all patients	182	0.43[t]					0.0017
Grade 2 onset skin toxicity, >4 months, all patients	182	0.77[u]					0.1965
Grade 2 onset skin toxicity, any time, WT	110	0.58[v]					0.0252
Grade 2 onset skin toxicity, 0–4 months, WT	110	0.45[w]					0.0569
Grade 2 onset skin toxicity, >4 months, WT	110	0.66[x]					0.1628
Grade 2 onset skin toxicity, any time, mutant	72	0.85[y]					0.5318
Grade 2 onset skin toxicity, 0–4 months, mutant	72	0.44[z]					0.0406
Grade 2 onset skin toxicity, >4 months, mutant	72	1.3[aa]					0.4349
Safety population							
Skin toxicity grade 1 and above	229	209	91				
Skin toxicity grades 2–4	229	158	69				
Skin toxicity grade 1	288	51	17.7				

BSC, best supportive care; CET, cetuximab.

a Hazard ratio for disease progression (95% CI 0.45 to 0.88).
b Hazard ratio for disease progression (95% CI 0.49 to 1.17).
c Hazard ratio for disease progression (95% CI 0.53 to 0.95).
d Hazard ratio for disease progression (95% CI 0.08 to 0.99).
e Hazard ratio for disease progression (95% CI 0.47 to 1.01).
f Hazard ratio for disease progression (95% CI 0.28 to 1.71).
g Hazard ratio for disease progression (95% CI 0.53 to 1.95).
h Hazard ratio for disease progression (95% CI 0.49 to 1.17).
i Hazard ratio for disease progression (95% CI 0.31 to 0.99).
j Hazard ratio for disease progression (95% CI 0.55 to 2.25).
k Hazard ratio for disease progression (95% CI 0.51 to 1.36).
l Hazard ratio for disease progression (95% CI 0.50 to 1.40).
m Hazard ratio for disease progression (95% CI 0.22 to 2.78).
n Hazard ratio for disease progression (95% CI 0.43 to 0.85).
o Hazard ratio for disease progression (95% CI 0.46 to 0.86).
p Hazard ratio for disease progression (95% CI 0.21 to 0.99).
q Hazard ratio for disease progression (95% CI 0.21 to 0.84).
r Hazard ratio for disease progression (95% CI 0.45 to 2.08).
s Hazard ratio for disease progression (95% CI 0.45 to 1.12).
t Hazard ratio for disease progression (95% CI 0.26 to 0.73).
u Hazard ratio for disease progression (95% CI 0.52 to 1.14).
v Hazard ratio for disease progression (95% CI 0.36 to 0.94).
w Hazard ratio for disease progression (95% CI 0.20 to 1.02).
x Hazard ratio for disease progression (95% CI 0.37 to 1.18).
y Hazard ratio for disease progression (95% CI 0.52 to 1.41).
z Hazard ratio for disease progression (95% CI 0.20 to 0.97).
aa Hazard ratio for disease progression (95% CI 0.68 to 2.49).

Methodological issues

Randomisation and allocation

Not reported.

Data analysis

Patients were stratified by ECOG score (0–1 vs 2) and geographical region (Western Europe vs Central and Eastern Europe vs the rest of the world).

The primary analysis of patient-reported outcomes used analysis of covariance to estimate 95% CIs for the least squares adjusted means within and between the panitumumab and BSC groups for the time-adjusted area under the curve for the mDLQI, FCSI and EQ-5D scales.

To account for lead-time bias and under-reporting of skin toxicity because of early treatment discontinuation, a landmark approach was used that limited the analysis to patients having at least grade 1 skin toxicity with a progression-free survival time of at least 28 days.

Patients were excluded if they had no post-baseline assessments.

For progression-free survival and overall survival analyses, a Cox proportional hazards model was used to examine the relationship between severity of skin toxicity and time to event.

Pearson correlation coefficients were used to examine the association between patient-reported skin toxicity and median post-baseline patient-reported outcomes. Kruskal–Wallis and Terpstra–Jonckheere tests were used to examine general and ordered associations between severity of skin toxicity and the minimum post-baseline mDLQI score.

Time to onset of the first grade 2 or higher skin toxicity was modelled as a time-dependent covariate in separate Cox models for progression-free survival and overall survival among all randomised patients, with indicators for their randomisation factors. Time to onset was examined at any time and in 1- to 2-month increments with a piecewise model. Months were calculated by multiplying the number of days by 12 and dividing by 364.25.

All *p*-values were two-sided.

Power calculation

Not reported.

Conflicts of interest

One author has financial interests in Amgen and Merck Serono, one author receives research funding from Amgen, one author is on the advisory board of Amgen and three authors are employed by and own stock in Amgen.

Quality appraisal

1. Was the assignment to the treatment groups really random? Unknown
2. Was the treatment allocation concealed? No
3. Were the groups similar at baseline in terms of prognostic factors? Unknown
4. Were the eligibility criteria specified? Reported – yes
5. Were outcome assessors blinded to the treatment allocation? Partial
6. Was the care provider blinded? No
7. Was the patient blinded? No
8. Were the point estimates and measure of variability presented for the primary outcome measure? Reported – yes
9. Did the analyses include an ITT analysis? Reported – yes
10. Were withdrawals and dropouts completely described? Adequate

Siena *et al.*[53]

Design	Participants	Arms	Outcomes
Study design: Supplementary study to parallel, open-label RCT **Country:** Unknown **No. of centres:** Unknown **Funding:** Amgen **Length of follow-up:** Median follow-up time for survival for all patients was 72 weeks (range 52–113 weeks) **Notes:** This is a supplementary paper to Van Cutsem *et al.*[7]	**Number randomised:** 463 **Inclusion criteria:** Inclusion criteria were pathological diagnosis of metastatic colorectal adenocarcinoma, radiological documentation of disease progression during or within 6 months following the last administration of fluoropyrimidine, irinotecan and oxaliplatin, prior exposure of prespecified doses of irinotecan and oxaliplatin and two or three prior chemotherapy regimens **Exclusion criteria:** Not reported **Therapy common to all participants:** Best supportive care	**Arm no. 1** **Name:** Panitumumab plus best supportive care ***n*:** 231 **Drug:** Panitumumab **Starting daily dose:** Not reported **Dosage details:** Not reported **Arm no. 2** **Name:** Best supportive care ***n*:** 232 **Drug:** N/A **Starting daily dose:** N/A **Dosage details:** N/A	**Primary outcome measure:** Progression-free survival **Secondary outcome measure(s):** Best objective response, overall survival and patient-reported outcomes **Method of assessment:** Objective tumour response was assessed by blinded central radiology review using modified RECIST criteria at specified time points from week 8 to week 48 and every 3 months thereafter until disease progression. Responses were confirmed no less than 4 weeks after response criteria were first met Tumour response, including stable disease, was evaluated at the first scheduled assessment (week 8) Patient-reported outcome assessments were taken at baseline and every 2 weeks or monthly during the treatment phase of the study and at the 30-day safety follow-up visit. Colorectal cancer symptomatology was measured using the NCCN FCSI and HRQoL was measured using the EQ-5D, the EQ-5D VAS and two global health items from the EORTC QLQ-C30 (range between 0 and 100) Missing items in a scale were handled by the methods outlined in the scoring manual

N/A, not reported.

Baseline characteristics

	PAN + BSC			BSC			
	n	Estimate	Mean	*n*	Estimate	Mean	*p*-value
	Not reported; refers to Van Cutsem *et al.*[7] for full characteristics						

BSC, best supportive care; PAN, panitumumab.

Results

	PAN + BSC			BSC			
	n	Estimate	%	*n*	Estimate	%	*p*-value
Completion of PRO							
PRO all enrolled analysis set	231	207		232	184		
PRO all enrolled analysis set and alive at week 8, EQ-5D	231	179		232	164		
Patients completing EQ-5D							
Week 4	231	189		232	129		
Week 8	231	111		232	47		
Week 12	231	91		232	14		

	PAN + BSC			BSC			
	n	Estimate	%	*n*	Estimate	%	*p*-value
Week 16	231	62		232	7		
PRO all enrolled analysis set and alive at week 8, FCSI	231	181		232	166		
Patients completing FCSI							
Week 4	231	190		232	130		
Week 8	231	112		232	48		
Week 12	231	90		232	14		
Week 16	231	62		232	7		
Progression-free survival							
PAN vs BSC	463	0.63[a]					< 0.001
Response rate							
Partial response	231	22	10	232	0	0	
Stable disease	231	62	27	232	23	10	
Time to death (months)							
Overall, median	231	7.6					
With PD at week 8, median	231	3.6					
Alive at week 8 without PD, median				231	8.6		
Alive at week 8 with PD, median				231	4.3		
Safety population							
No data reported							

BSC, best supportive care; PAN, panitumumab; PD, progressive disease; PRO, patient-reported outcome.
a Hazard ratio for disease progression (95% CI 0.52 to 0.77).

Methodological issues

Randomisation and allocation

Not reported.

Data analysis

To assess whether or not the treatment differences in progression-free survival were due to patients with an objective response, a post hoc sensitivity analysis of progression-free survival that removed responding patients in the panitumumab group was conducted to evaluate the contribution of non-responding patients to the treatment effect with panitumumab. The objective was to evaluate the association between progression-free survival and colorectal cancer symptoms, HRQoL and overall survival.

The *t*-tests and least squares estimates were calculated for differences in patient-reported outcome measures, controlling for baseline score by progression status as of week 8.

For overall survival within each treatment group, survival was examined among patients surviving to at least week 8. A Cox regression model was used to examine the correlation between time to radiological progression and time to death.

Patients who died without radiological progression were censored at their last radiological assessment of time to progression.

Power calculation
Not reported; see Van Cutsem and colleagues.[7]

Conflicts of interest
Not reported.

Quality appraisal

1. Was the assignment to the treatment groups really random? Not reported
2. Was the treatment allocation concealed? No
3. Were the groups similar at baseline in terms of prognostic factors? Unclear
4. Were the eligibility criteria specified? Adequate
5. Were outcome assessors blinded to the treatment allocation? Reported – yes
6. Was the care provider blinded? No
7. Was the patient blinded? No
8. Were the point estimates and measure of variability presented for the primary outcome measure? Adequate
9. Did the analyses include an ITT analysis? Unclear
10. Were withdrawals and dropouts completely described? Reported – yes

Van Cutsem *et al.*[7]

Design	Participants	Arms	Outcomes
Study design: Parallel, open-label RCT **Country:** Unknown **No. of centres:** Unknown **Funding:** Amgen **Length of follow-up:** All patients were followed up for survival approximately every 3 months for up to 2 years after random assignment. The median follow-up time after crossover from best supportive care was 61 weeks (range 18 to 103 weeks)	**Number randomised:** 463 **Inclusion criteria:** Pathological diagnosis of metastatic colorectal adenocarcinoma and radiological documentation of disease progression during or within 6 months following the last administration of fluoropyrimidine, irinotecan and oxaliplatin; dose intensity of irinotecan $\geq 65\,mg/m^2$ per week and of oxaliplatin $\geq 30\,mg/m^2$ per week were required; >18 years; ECOG status 0–2; two or three prior chemotherapy regimens for metastatic colorectal cancer; and 1% EGFR-positive membrane staining in primary or metastaic tumour cells by immunohistochemistry prospectively read centrally (after amendment – 10% in original protocol) **Exclusion criteria:** Symptomatic brain metastases, interstitial pneumonitis or pulmonary fibrosis, systematic chemotherapy or radiotherapy within 30 days before random assignment and prior anti-EFGR agents **Therapy common to all participants:** Best supportive care	**Arm no. 1** **Name:** Panitumumab plus best supportive care ***n*:** 231 **Drug:** Panitumumab **Dosage details:** Panitumumab was administered using a 60-minute intravenous infusion at 6 mg/kg once every 2 weeks until patients progressed or unacceptable toxicity developed. Premedication was not required **Arm no. 2** **Name:** Best supportive care ***n*:** 232 **Drug:** N/A **Starting daily dose:** N/A **Dosage details:** N/A	**Primary outcome measure:** Progression-free survival by blinded central radiology assessment, calculated from day of random assignment until radiological progression or death **Secondary outcome measure(s):** Objective response, overall survival and safety. Best objective response by blinded central review and overall survival time. Overall survival was calculated from the day of random assignment until death, censoring patients at the last day known to be alive. All patients were followed up for survival every 3 months for up to 2 years after random assignment. Best supportive care patients determined by the investigator to have disease progression were eligible to receive panitumumab under a separate study. The crossover evidence was based on prior evidence of activity with panitumumab and cetuximab **Method of assessment:** Objective tumour response was evaluated by central radiology review using modified RECIST at weeks 8, 12, 16, 24, 32, 40 and 48 and every 3 months thereafter until disease progression, and confirmed no less than 4 weeks after the criteria for response were first met. At the discretion of the investigator, patients could be evaluated for radiographic tumour assessment after developing symptoms consistent with disease progression

N/A,not applicable.

Baseline characteristics

	PAN + BSC			BSC		
Demographics	***n***	**Estimate**	**%**	***n***	**Estimate**	**%**
Sex						
Male	231	146	63	232	148	64
Female	231	85	37	232	84	36
Race/ethnicity						
White	231	229	99	232	228	98
Other	231	2	1	232	4	2
Age (years)						
Median		62			63	
Minimum		27			27	
Maximum		82			83	
Primary diagnosis						
Colon cancer	231	153	66	232	157	68
Rectal cancer	231	78	34	232	75	32
ECOG performance status						
0	231	107	46	232	80	34
1	231	94	41	232	115	50
2	231	29	13	232	35	15
3	231	1	0	232	2	1
Cells with EGFR membrane staining						
1% to < 10%	231	57	25	232	57	25
10–100%	231	172	74	232	174	75
Intensity of EGFR staining						
3+ (strong)	231	47	20	232	41	18
2+ (moderate)	231	122	53	232	113	49
1+ (weak)	231	60	26	232	78	34
0	231	0	0	232	0	0
Previous adjuvant chemotherapy	231	86	37	232	78	34
Previous lines of chemotherapy						
2	231	230	100	232	232	100
3	231	84	36	232	88	38

BSC, best supportive care; PAN, panitumumab.

Results

	PAN + BSC			BSC			
	n	Estimate	Mean	*n*	Estimate	Mean	*p*-value
Duration of treatment	Until disease progression or toxicity						
Progression-free survival							
PAN vs BSC	463	0.54[a]					<0.0001
Male	294	0.57[b]					
Female	169	0.51[c]					
Age <65 years	276	0.51[d]					
Age 65+ years	187	0.60[e]					
Primary cancer: colon	310	0.55[f]					
Primary cancer: rectal	153	0.53[g]					
ECOG performance status 0–1	396	0.56[h]					
ECOG performance status 2–3	67	0.46[i]					
Previous regimens: 2	290	0.63[j]					
Previous regimens: 3	149	0.39[k]					
Metastasis sites: 1–2	322	0.49[l]					
Metastasis sites: 3–5	139	0.67[m]					
Intensity of EGFR staining: 1+	138	0.62[n]					
Intensity of EGFR staining: 2+	235	0.51[o]					
Intensity of EGFR staining: 3+	88	0.58[p]					
Cells with EGFR staining: 1 to <10%	114	0.47[q]					
Cells with EGFR staining: 10–100%	346	0.57[r]					
Time (weeks), median	231	8[s]		232	7.3[t]		
Time (weeks), mean	231	13.08[u]		232	8.5[v]		
Associated with skin toxicity, grades 2–4 vs grade 1	231	0.62[w]					
Overall survival							
PAN vs BSC	436	1[x]					
Deaths	231	186		232	194		
Associated with skin toxicity, grades 2–4 vs grade 1	231	0.59[y]					
Objective response	231	22		232	0		
Median time to response (weeks)	231	7.9[z]					
Median duration of response (weeks)	231	17[aa]					
Safety population							
All grades							
Patients with at least one adverse event	229	229		234	202		
Erythema	229	146		234	2		
Dermatitis acneiform	229	142		234	2		
Pruritis	229	130		234	5		
Skin exfoliation	229	56		234	0		
Fatigue	229	55		234	34		
Paronychia	229	55		234	0		
Abdominal pain	229	53		234	39		
Anorexia	229	50		234	43		
Nausea	229	50		234	36		
Diarrhoea	229	48		234	26		
Rash	229	46		234	2		

	PAN + BSC			BSC			
	n	Estimate	Mean	*n*	Estimate	Mean	*p*-value
Skin fissures	229	45		234	1		
Constipation	229	44		234	21		
Vomiting	229	42		234	28		
Dyspnoea	229	33		234	31		
Pyrexia	229	33		234	29		
Asthenia	229	33		234	27		
Cough	229	31		234	17		
Back pain	229	24		234	16		
Oedema	229	24		234	13		
General physical health deterioration	229	23		234	8		
Grade 3							
Patients with at least one adverse event	229	75		234	41		
Erythema	229	12		234	0		
Dermatitis acneiform	229	17		234	0		
Pruritis	229	5		234	0		
Skin exfoliation	229	5		234	0		
Fatigue	229	10		234	7		
Paronychia	229	3		234	0		
Abdominal pain	229	17		234	8		
Anorexia	229	7		234	5		
Nausea	229	2		234	1		
Diarrhoea	229	3		234	0		
Rash	229	2		234	0		
Skin fissures	229	2		234	0		
Constipation	229	6		234	2		
Vomiting	229	5		234	2		
Dyspnoea	229	9		234	8		
Pyrexia	229	0		234	4		
Asthenia	229	6		234	5		
Cough	229	1		234	0		
Back pain	229	4		234	0		
Oedema	229	2		234	1		
General physical health deterioration	229	11		234	2		
Grade 4							
Patients with at least one adverse event	229	4		234	2		
Erythema	229	0		234	0		
Dermatitis acneiform	229	0		234	0		
Pruritis	229	0		234	0		
Skin exfoliation	229	0		234	0		
Fatigue	229	0		234	0		
Paronychia	229	0		234	0		
Abdominal pain	229	0		234	1		
Anorexia	229	1		234	0		
Nausea	229	0		234	0		
Diarrhoea	229	0		234	0		
Rash	229	0		234	0		

	PAN + BSC			BSC			
	n	Estimate	Mean	*n*	Estimate	Mean	*p*-value
Skin fissures	229	0		234	0		
Constipation	229	0		234	0		
Vomiting	229	0		234	0		
Dyspnoea	229	2		234	0		
Pyrexia	229	0		234	0		
Asthenia	229	1		234	0		
Cough	229	0		234	0		
Back pain	229	0		234	0		
Oedema	229	0		234	0		
General physical health deterioration	229	5		234	1		

BSC, best supportive care; PAN, panitumumab; SD, standard deviation.
a Hazard ratio for disease progression (95% CI 0.44 to 0.66).
b Hazard ratio for disease progression (95% CI 0.44 to 0.73).
c Hazard ratio for disease progression (95% CI 0.36 to 0.71).
d Hazard ratio for disease progression (95% CI 0.40 to 0.67).
e Hazard ratio for disease progression (95% CI 0.43 to 0.83).
f Hazard ratio for disease progression (95% CI 0.43 to 0.70).
g Hazard ratio for disease progression (95% CI 0.37 to 0.75).
h Hazard ratio for disease progression (95% CI 0.45 to 0.69).
i Hazard ratio for disease progression (95% CI 0.27 to 0.81).
j Hazard ratio for disease progression (95% CI 0.49 to 0.81).
k Hazard ratio for disease progression (95% CI 0.26 to 0.57).
l Hazard ratio for disease progression (95% CI 0.38 to 0.63).
m Hazard ratio for disease progression (95% CI 0.47 to 0.95).
n Hazard ratio for disease progression (95% CI 0.42 to 0.91).
o Hazard ratio for disease progression (95% CI 0.39 to 0.67).
p Hazard ratio for disease progression (95% CI 0.37 to 0.90).
q Hazard ratio for disease progression (95% CI 0.31 to 0.71).
r Hazard ratio for disease progression (95% CI 0.46 to 0.72).
s 95% CI 7.9 to 8.4.
t 95% CI 7.1 to 7.7.
u SD 0.8.
v SD 0.5.
w Hazard ratio for disease progression (95% CI 0.46 to 0.72).
x Hazard ratio for disease progression (95% CI 0.82 to 1.22).
y Hazard ratio for disease progression (95% CI 0.42 to 0.85).
z Hazard ratio for disease progression (95% CI 6.7 to 15.6).
aa Hazard ratio for disease progression (95% CI 7.9 to 76.7).

Methodological issues

Randomisation and allocation

Patients were randomly assigned in a 1 : 1 ratio to receive panitumumab plus best supportive care or best supportive care alone. Randomisation was stratified by ECOG performance status (0 or 1 vs 2) and region (Western Europe vs Central and Eastern Europe vs the rest of the world).

Data analysis

The primary analysis included all patients randomly assigned. Progression-free survival was analysed at the 5% significance level using a log-rank test stratified by baseline ECOG performance status and region. A 1% test of objective response at the primary analysis and 4% test of overall survival were prespecified conditional on a significant progression-free survival difference. The primary analysis of overall survival and an update of objective response rates and duration of response were conducted after a minimum of 12 months' follow-up. Kaplan–Meier methodology was used to estimate progression-free survival, overall survival and time to and duration of response, including 95% CIs for event-free rates and difference in rates. The 65%

CIs for time-to-event quartiles were calculated according to Brookmeye and Crowley.[90] Hazard ratios for progression-free survival and overall survival were estimated using a Cox proportional hazards regression model adjusted for the randomisation factors.

Power calculation

The study had 90% power for a two-sided 1% significance level test given a hazard ratio (panitumumab relative to best supportive care) of 0.67. The sample size goal was 430 patients, with an event goal of 362 patients with progressive disease by central review or death.

Conflicts of interest

Two authors were employed by Amgen, two authors were consultants for Amgen, Merck and Roche and two authors received research funding from Amgen and GlaxoSmithKline.

Quality appraisal

1. Was the assignment to the treatment groups really random? Unclear – not reported whether or not randomisation was performed centrally
2. Was the treatment allocation concealed? No
3. Were the groups similar at baseline in terms of prognostic factors? Adequate
4. Were the eligibility criteria specified? Reported – yes
5. Were outcome assessors blinded to the treatment allocation? Reported – yes
6. Was the care provider blinded? No
7. Was the patient blinded? No
8. Were the point estimates and measure of variability presented for the primary outcome measure? Reported – yes
9. Did the analyses include an ITT analysis? Reported – yes
10. Were withdrawals and dropouts completely described? Partial

Van Cutsem *et al*.[38]

Design	Participants	Arms	Outcomes
Study design: Open-label single-arm study – supplementary to main trial reported by Van Cutsem *et al*.[7] **Country:** Unknown **No. of centres:** Unknown **Funding:** Amgen **Length of follow-up:** Patients who discontinued the extension study were to complete a safety follow-up visit 4 weeks after the last panitumumab infusion. Patients were followed for survival approximately every 3 months for up to 2 years from the randomisation phase of the Phase III study	**Number randomised:** N/A **Inclusion criteria:** Patients who had radiographically documented disease progression while receiving best supportive care in the Phase III study Patients were required to complete the last assessement in the Phase III study not more than 3 months before enrolment in the extension study and in the interim could not have received systemic chemotherapy, radiotherapy, investigational agents or antitumour therapies including approved antitumour small molecules and biologics Patients were required to have adequate renal and hepatic function and an ECOG performance status of 0, 1 or 2 at entry into the extension study. EGFR membrane expression in ≥ 1% of tumour cells was an eligibility criterion for the Phase III study **Exclusion criteria:** During this interval patients could not have had a myocardial infarction, interstitial pneumonitis or pulmonary fibrosis. Brain metastases, if present, were to be controlled and asymptomatic **Therapy common to all participants:** Best supportive care	**Arm no: 1** **Name:** Panitumumab plus best supportive care ***n*:** 231 **Drug:** Panitumumab **Dosage details:** Panitumumab was administered using a 60-minute intravenous infusion of 6 mg/kg once every 2 weeks until patients progressed or unacceptable toxicity developed. Premedication was not required	**Primary outcome measure:** Safety, including incidence of grade 3/4 adverse and treatment-related events, skin-related events and antibody formation **Secondary outcome measure(s):** Although no secondary end points were prespecified in the protocol, the efficacy of panitumumab monotherapy was explored by assessing progression-free survival, ORR, time to and duration of response, duration of stable disease and survival using the local investigators' assessment of radiographic images **Method of assessment:** Primary – Safety assessments were carried out every 2 weeks and at the safety follow-up visit 4 weeks after the last panitumumab infusion. Adverse events were graded using the NCI-CTC version 2.0 with the exception of selected dermatological toxic effects (erythema, rash, desquamation and ulceration), which were graded using the NCI-CTC version 3.0 with modifications Secondary – Patients were evaluated for tumour response every 8 weeks from the first dose of panitumumab and at the time of suspected disease progression according to a modified version of RECIST. Stable disease was first evaluated at the first scheduled assessment (week 8). Disease control rate was defined as the sum of the objective response and stable disease rates. Tumour responses were confirmed no less than 4 weeks after the criteria for response were first met. Patients with no response confirmation were considered non-responders

Baseline characteristics

	PAN + BSC		
Demographics	***n***	**Estimate**	**%**
Sex			
Male	176	111	63
Race			
White or Caucasian	176	175	99
Japanese	176	1	1
Age (years)			
Median	176	62[a]	
≥ 65 years	176	67	38
Primary diagnosis			
Colon cancer	176	113	64
Rectal cancer	176	63	36
Number of prior chemotherapy regimens			
Median	176	2[b]	
Number of prior chemotherapy lines			
1–2	176	114	65
≥ 3	176	62	35
Duration of BSC in the Phase III study (weeks)			
0–2	176	16	9
3–6	176	45	26
7–10	176	89	51
11–20	176	21	12
20–47	176	5	3
Percentage of tumour cells with membrane EGFR staining			
< 1%	176	1	1
1–9%	176	45	26
10–20%	176	53	30
21–35%	176	19	11
> 35%	176	58	33
ECOG performance status			
0	176	53	30
1	176	85	48
2	176	38	22

BSC, best supportive care; PAN, panitumumab; ORR, overall response rate.
a Range 32–83 years.
b Range 2–6 years.

Results

	PAN + BSC		
	n	Estimate	%
Duration of treatment	Until disease progression or toxicity		
Best objective response			
Complete response	176	1	0.6
Partial response	176	19	11
Stable disease	176	58	33
Disease progression	176	65	37
Unevaluable[a]	176	4	2
No radiological scan available	176	29	16
Disease control	176	78	44
Time to response (weeks)			
Median (range)	176	8	7–25
Duration of response (weeks)[b]			
Median (range)	176	16	8–35
Duration of stable disease (weeks)			
Median (range)	176	16	7–63
Progression-free survival time (weeks)[c]			
Median (95% CI)	176	9.4	8.0 to 13.4
Overall survival time (months)[d]			
Median (95% CI)	176	6.3	5.1 to 6.8
Safety			
All grades			
Patients with at least one adverse event[e]	176	162	92
Erythema	176	112	64
Acne	176	104	59
Pruritus	176	101	57
Rash	176	93	53
Other skin manifestations	176	65	37
Paronychia and other nail disorders	176	50	28
Skin exfoliation	176	22	13
Diarrhoea	176	15	9
Conjunctivitis	176	10	6
Nausea	176	8	5
Grade 3			
Patients with at least one adverse event	176	29	16
Erythema	176	8	5
Acne	176	11	6
Pruritus	176	2	1
Rash	176	8	5
Other skin manifestations	176	4	2

	PAN + BSC		
	n	Estimate	%
Paronychia and other nail disorders	176	3	2
Skin exfoliation	176	1	1
Diarrhoea	176	1	1
Conjunctivitis	176	1	1
Nausea	176	0	0
Grade 4			
Patients with at least one adverse event	176	3	2
Erythema	176	1	1
Acne	176	0	0
Pruritus	176	0	0
Rash	176	0	0
Other skin manifestations	176	0	0
Paronychia and other nail disorders	176	0	0
Skin exfoliation	176	0	0
Diarrhoea	176	0	0
Conjunctivitis	176	0	0
Nausea	176	0	0

BSC, best supportive care; PAN, panitumumab.
a Patients who had only one assessment.
b For the 20 responders.
c At the time of study completion, 158 (90%) patients had disease progression or had died of any cause.
d 145 (82%) patients died.
e There were no grade 5 treatment-related adverse events.

Methodological issues

Randomisation and allocation

Not applicable as this was a single-arm study.

Data analysis

The primary analyses of safety and efficacy outcomes included all enrolled patients who received at least one dose of panitumumab.

Time to response was calculated as the period from enrolment date to the first objective response. Duration of response was calculated only for the responders as the period from the first objective response to the first observation of disease progression or death due to disease progression.

Duration of stable disease was calculated as the period from enrolment date to the first observation of disease progression or death due to disease progression; only patients who had at least one scan of stable disease as their best response were included.

Progression-free survival time was calculated as the period from enrolment date to the first observation of disease progression or death.

Overall survival time was calculated as the period from enrolment to death.

Descriptive statistics were calculated for the incidence of objective response (with two-sided 95% CIs), adverse events, laboratory values, changes in vital signs and antibody measurements. Time-to-event outcomes were analysed using Kaplan–Meier methods. For the analyses on overall survival, a minimum of 12 months of follow-up was included.

Among patients with skin toxicity, the relationship between severity of skin toxicity and overall survival was evaluated using a Cox regression model adjusted for the Phase III randomisation factors, ECOG score and geographical region. Patients were included in the analysis if they were progression free for at least 28 days to allow the worst severity of skin toxicity to manifest.

Power calculation

The sample size was limited to the patients enrolled in the best supportive care arm of the Phase III study who met the eligibility criteria (planned $n = 200$). Assuming a true event rate of 1%, the probability of at least one patient experiencing a given adverse event was 87% for a sample size of 200.

Conflicts of interest

None reported.

Quality appraisal

1. Was the assignment to the treatment groups really random? Not applicable – single-arm extension study
2. Was the treatment allocation concealed? No
3. Were the groups similar at baseline in terms of prognostic factors? Not applicable
4. Were the eligibility criteria specified? Reported – yes
5. Were outcome assessors blinded to the treatment allocation? Unknown
6. Was the care provider blinded? No
7. Was the patient blinded? No
8. Were the point estimates and measure of variability presented for the primary outcome measure? Adequate
9. Did the analyses include an ITT analysis? Reported – yes
10. Were withdrawals and dropouts completely described? Reported – yes

Amado *et al.*[32]

Design	Participants	Arms	Outcomes
Study design: Supplementary study to parallel, open-label RCT **Country:** Unknown **No. of centres:** Unknown **Funding:** Amgen **Length of follow-up:** Median follow-up time for remaining 36 patients was 14.1 months	**Number randomised:** 463 **Inclusion criteria:** Patients with metastatic colorectal cancer with EGFR expression in ≥1% of tumour cells (assessed by immunohistochemistry) and documented evidence of disease progression after failure of fluoropyrimidines and prespecified exposure to oxaliplatin and irinotecan **Exclusion criteria:** Not reported **Therapy common to all participants:** Best supportive care	**Arm no. 1** **Name:** Panitumumab plus best supportive care ***n*:** 208 **Drug:** Panitumumab **Dosage details:** Panitumumab was administered using a 60-minute intravenous infusion at 6 mg/kg once every 2 weeks **Arm no. 2** **Name:** Best supportive care ***n*:** 219 **Drug:** N/A **Starting daily dose:** N/A **Dosage details:** N/A	**Primary outcome measure:** Progression-free survival, defined as the interval from random assignment to radiological progression or death **Secondary outcome measure(s):** Objective response rate, overall survival and safety **Method of assessment:** Tumour status was assessed radiographically every 4–8 weeks from week 8 until disease progression assessed by blinded central review using the RECIST A best response of stable disease was determined at or after week 8 after random assignment Mutant *KRAS* status was detected using a validated kit that identifies seven mutations in codons 12 and 13 using allele-specific real-time polymerase chain reaction. *KRAS* analysis was performed blinded. A central laboratory validated the assay for analytical and diagnostic performance, established acceptance criteria and included appropriate quality controls for each assay

N/A, not applicable.

Baseline characteristics

	PAN + BSC			BSC			
Demographics	***n***	**Estimate**	**%**	***n***	**Estimate**	**%**	***p*-value**
Mutant							
Sex							
Male	84	47	56	100	64	64	
Race/ethnicity							
White	84	84	100	100	97	97	
Age (years)							
Median		62			62		
Minimum		27			27		
Maximum		79			83		
Primary diagnosis							
Colon cancer	84	53	63	100	65	65	
Rectal cancer	84	31	37	100	35	35	
ECOG performance status							
0	84	43	51	100	37	37	
1	84	28	33	100	47	47	
≥2	84	13	15	100	16	16	

	PAN + BSC			BSC			
Demographics	***n***	**Estimate**	**%**	***n***	**Estimate**	**%**	***p*-value**
Cells with EGFR membrane staining							
1% to <10%	84	20	24	100	23	23	
10–100%	84	63	75	100	77	77	
Intensity of EGFR staining							
3+ (strong)	84	17	20	100	17	17	
2+ (moderate)	84	42	50	100	51	51	
1+ (weak)	84	24	29	100	32	32	
0	84	1	1	100	0	0	
Prior adjuvant chemotherapy	84	27	32	100	40	40	
Prior lines of chemotherapy							
2	84	54	64	100	74	74	
3	84	23	27	100	24	24	
WT							
Sex							
Male	124	83	67	119	76	64	
Race/ethnicity							
White	124	122	98	119	118	99	
Age (years)							
Median		62.5			63.0		
Minimum		29			32		
Maximum		82			81		
Primary diagnosis							
Colon cancer	124	86	69	119	82	69	
Rectal cancer	124	38	31	119	37	31	
ECOG performance status							
0	124	53	43	119	40	34	
1	124	56	45	119	62	52	
≥2	124	15	12	119	17	14	
Cells with EGFR membrane staining							
1% to <10%	124	31	25	119	29	24	
10–100%	124	93	75	119	89	75	
Intensity of EGFR staining							
3+ (strong)	124	25	20	119	22	18	
2+ (moderate)	124	69	56	119	58	49	
1+ (weak)	124	30	24	119	39	33	
0	124	0	0	119	0	0	
Prior adjuvant chemotherapy	124	50	40	119	32	27	
Prior lines of chemotherapy							
2	124	79	64	119	63	53	
3	124	41	33	119	49	41	

BSC, best supportive care; PAN, panitumumab.

Results

	PAN + BSC			BSC			
	n	Estimate	Mean	*n*	Estimate	Mean	*p*-value
Duration of treatment	Until disease progression or toxicity						
Progression-free survival (weeks)							
KRAS assessable, median	208	0.59[a]	8	219		7.3	
WT, median	124	0.45[b]	12.3	119		7.3	
Mutant, median	84	0.99[c]	7.4	100		7.3	
Crossover, WT, median	90	0.32[d]	16.4				
Crossover, mutant, median	77		7.9				
WT progression-free survival (subset analysis)							
PAN vs BSC	243	0.45[e]					
Male	159	0.42[f]					
Female	84	0.46[g]					
Age < 65 years	141	0.42[h]					
Age 65+ years	102	0.47[i]					
Primary diagnosis: colon cancer	168	0.47[j]					
Primary diagnosis: rectal cancer	75	0.36[k]					
ECOG performance status: 0–1	211	0.47[l]					
ECOG performance status: 2–3	32	0.35[m]					
Prior regimens: 2	142	0.54[n]					
Prior regimens: 3	90	0.28[o]					
Prior regimens: 3+	100	0.27[p]					
Metastasis sites: 1–2	172	0.42[q]					
Metastasis sites: 3–5	69	0.52[r]					
EGFR staining intensity: 1+	69	0.30[s]					
EGFR staining intensity: 2+	127	0.49[t]					
EGFR staining intensity: 3+	47	0.34[u]					
Cells with EGFR staining: 1 to < 10%	60	0.33[v]					
Cells with EGFR staining: 10–35%	101	0.41[w]					
Cells with EGFR staining: > 35%	81	0.37[x]					
Overall survival							
KRAS assessable, deaths	208	186		219	205		
WT, median (months)	124	107	8.1	119	110	7.6	
Mutant, median (months)	84	79	4.9	100	95	4.4	
Response rate							
KRAS *assessable*							
Stable disease, (%)	208	25		219	10		
Disease progression (%)	208	50		219	68		
Response rate				219	0		
Crossover							
Response rate	167	20					
Stable disease	167	55					

	PAN + BSC			BSC			
	n	Estimate	Mean	*n*	Estimate	Mean	*p*-value
WT							
Partial response	124	17					
Stable disease	124	42		119	14		
Response rate							
Median time to response (weeks)	124		7.9[y]				
Median duration of response (weeks)	124		19.7[z]				
Mutant							
Stable disease	84	10		100	8		
Safety population							
Combined arm							
KRAS assessable, treatment-related grade 3 adverse events	427	20					
WT integument-related events	243	25					
Mutant integument-related events	184	13					
WT grade 4 integument-related events	243	0					
Mutant grade 4 integument-related events	184	1					
Separate arm							
Adverse event, mutant	84	100		100	84		
Adverse event, WT	124	100		119	90		
Diarrhoea, all grades, WT	124	24					
Diarrhoea, all grades, mutant	84	19					
Diarrhoea, grade 3, WT	124	2					
Diarrhoea, grade 3, mutant	84	1					

BSC, best supportive care; PAN, panitumumab.
a Hazard ratio for disease progression (95% CI 0.48 to 0.72).
b Hazard ratio for disease progression (95% CI 0.34 to 0.59).
c Hazard ratio for disease progression (95% CI 0.73 to 1.36).
d Hazard ratio for disease progression (95% CI 0.22 to 0.45).
e Hazard ratio for disease progression (95% CI 0.34 to 0.59).
f Hazard ratio for disease progression (95% CI 0.30 to 0.59).
g Hazard ratio for disease progression (95% CI 0.29 to 0.73).
h Hazard ratio for disease progression (95% CI 0.29 to 0.60).
i Hazard ratio for disease progression (95% CI 0.31 to 0.73).
j Hazard ratio for disease progression (95% CI 0.34 to 0.65).
k Hazard ratio for disease progression (95% CI 0.21 to 0.61).
l Hazard ratio for disease progression (95% CI 0.35 to 0.62).
m Hazard ratio for disease progression (95% CI 0.15 to 0.82).
n Hazard ratio for disease progression (95% CI 0.38 to 0.76).
o Hazard ratio for disease progression (95% CI 0.17 to 0.47).
p Hazard ratio for disease progression (95% CI 0.17 to 0.44).
q Hazard ratio for disease progression (95% CI 0.30 to 0.59).
r Hazard ratio for disease progression (95% CI 0.30 to 0.89).
s Hazard ratio for disease progression (95% CI 0.16 to 0.56).
t Hazard ratio for disease progression (95% CI 0.31 to 0.75).
u Hazard ratio for disease progression (95% CI 0.20 to 0.58).
v Hazard ratio for disease progression (95% CI 0.18 to 0.63).
w Hazard ratio for disease progression (95% CI 0.28 to 0.60).
x Hazard ratio for disease progression (95% CI 0.18 to 0.75).
y Range 7.0–15.6 weeks.
z Range 7.9–88.7 weeks.

Methodological issues

Randomisation and allocation

Refer to Van Cutsem *et al.*[7]

Data analysis

All analyses were prespecified in a statistical analysis plan before *KRAS* mutation assessment.

A quantitative interaction test at a two-sided 5% level was used to compare the progression-free survival log-hazard ratio (hazard ratio panitumumab relative to best supportive care) from a Cox model with covariates for the randomisation factors between the WT and mutant *KRAS* groups.

Kaplan–Meier methods were used to estimate progression-free survival and overall survival. Conditional on a significant interaction test, sequential testing at a 5% level of progression-free survival, followed by overall survival and overall response rate, were planned within the WT group between panitumumab and BSC.

A log-rank test was used for progression-free survival, a Wilcoxon's test for overall survival and a generalised Cochran–Mantel–Haenszel test for response rate, each stratified by the randomisation factors.

Power calculation

Based on an assessable sample size of 380 patients and assuming 60% WT prevalence, power was estimated at > 99% if the hazard ratio was 1.0 in the mutant group and at 87% if the hazard ratio was 0.8 in the mutant group, assuming an overall hazard ratio of 0.54 among all patients.

Conflicts of interest

The majority of authors are employed by Amgen and have stock ownership.

Quality appraisal

1. Was the assignment to the treatment groups really random? Unknown
2. Was the treatment allocation concealed? No
3. Were the groups similar at baseline in terms of prognostic factors? Adequate
4. Were the eligibility criteria specified? Partial
5. Were outcome assessors blinded to the treatment allocation? Reported – yes
6. Was the care provider blinded? No
7. Was the patient blinded? No
8. Were the point estimates and measure of variability presented for the primary outcome measure? Reported – yes
9. Did the analyses include an ITT analysis? Reported – yes
10. Were withdrawals and dropouts completely described? Reported – yes

Asmis *et al.*[43]

Design	Participants	Arms	Outcomes
Study design: Supplementary study to parallel open label RCT **Country:** Unknown **No. of centres:** Unknown **Funding:** Unknown **Length of follow-up:** Not reported	**Number randomised:** 572 **Inclusion criteria:** Patients with metastatic colorectal cancer with EGFR immunohistochemically detectable **Exclusion criteria:** Not reported **Therapy common to all participants:** Best supportive care	**Arm no. 1** **Name:** Cetuximab plus best supportive care ***n*:** 287 **Drug:** Cetuximab **Starting dose:** 400 mg/m^2 **Dosage details:** Weekly dose of 250 mg/m^2 **Arm no. 2** **Name:** Best supportive care ***n*:** 285 **Drug:** N/A **Starting daily dose:** N/A **Dosage details:** N/A	**Primary outcome measure**: Main trial – overall survival, defined as time from randomisation until death from any cause **Secondary outcome measure(s):** Main trial – progression-free survival, defined as time from randomisation until the first objective observation of disease progression or death from any cause; response rates, defined according to the modified RECIST; QoL, assessed by mean changes in scores of physical function and global health status at 8 and 16 weeks. This study – relationship between age, comorbidity and performance status in predicting outcome **Method of assessment:** A CCI score was determined for each patient by two physician reviewers. After co-operative scoring of an initial cohort of 20 patient charts to establish internal consistency, the remainder of the patient charts were scored independently with scoring discrepancies resolved by consensus. Previous diagnosis of venous thromboembolism was also specifically recorded by reviewers

N/A, not applicable.

Baseline characteristics

	Age < 65 years			Age ≥ 65 years			
Demographics	***n***	**Estimate**	**%**	**n**	**Estimate**	**%**	***p*-value[a]**
Sex							
Male	335	203	60.6	237	72	30.4	0.03
Female	335	132	39.4	237	165	69.6	
ECOG performance status							
0	335	79	23.6	237	57	24.1	0.84
1	335	180	53.7	237	122	51.5	
2	335	76	22.7	237	58	24.5	
Body mass index (kg/m^2)							0.29
Median (range)	335	26.1	15.6–42.5	237	25.3	15.6–45.0	
Low (< 20)	335	33	9.9	237	25	10.5	
Normal (20–25)	335	101	30.1	237	85	35.9	
High (> 25)	335	201	60.0	237	127	53.6	
Site of primary disease							0.15
Colon only	335	189	56.4	237	143	60.3	
Rectum only	335	83	24.8	237	50	21.1	
Colon and rectum	335	63	18.8	237	44	18.6	
Time from initial diagnosis to randomisation (years)							0.07
Median (range)	335	2.2	0.5–15.7	237	2.5	0–14.7	
≥ 2	335	181	54.0	237	146	61.6	
< 2	335	154	46	237	91	38.4	

	Age < 65 years			Age ≥ 65 years			
Demographics	***n***	**Estimate**	**%**	**n**	**Estimate**	**%**	***p*-value[a]**
Lactate dehydrogenase							0.37
≤ upper normal limit	335	83	24.8	237	51	21.5	
> upper normal limit	335	235	70.1	237	175	73.8	
Alkaline phosphate							0.93
≤ upper normal limit	335	93	27.8	237	66	27.8	
> upper normal limit	335	241	71.9	237	168	70.9	
Haemoglobin							0.07
CTC grade 0	335	122	36.4	237	69	29.1	
CTC grade ≥ 1	335	213	63.6	237	168	70.9	
Serum creatinine							0.06
CTC grade 0	335	309	92.2	237	208	87.8	
CTC grade ≥ 1	335	25	7.5	237	29	12.2	
Number of previous chemotherapy drug classes							0.005
≤ 2	335	9	2.7	237	19	8.0	
> 2	335	326	97.3	237	218	92.0	
Comorbidity score							0.002
0	335	268	80.0	237	162	68.4	
≥ 1	335	67	20.0	237	75	31.6	
Venous thromboembolism							0.95
No	335	303	90.4	237	214	90.3	
Yes	335	32	9.6	237	23	9.7	
KRAS status							0.68
WT	335	133	39.7	237	97	40.9	
Mutant	335	99	29.6	237	65	27.4	
Treatment							0.15
BSC only	335	158	47.2	237	127	53.6	
Cetuximab plus BSC	335	177	52.8	237	110	46.4	
Duration of treatment (weeks)							0.47
Median (range)	335	8	1–46.3	237	8.1	1–60	
Cumulative dose (mg/m^2)							0.47
Median (range)	335	2155	390.8–10,331	237	2202	395.8–15,216	

BSC, best supportive care; CTC, common toxicity criteria.
a From Fisher's exact test.

	Comorbidity score 0			Comorbidity score ≥ 1			
Demographics	***n***	**Estimate**	**%**	***n***	**Estimate**	**%**	***p*-value[a]**
Sex							0.06
Male	430	267	62.1	142	41	28.9	
Female	430	163	37.9	142	101	71.1	
ECOG performance status							0.80
0	430	105	24.4	142	31	21.8	
1	430	224	52.1	142	78	54.9	
2	430	101	23.5	142	33	23.2	
Body mass index (kg/m^2)							0.21
Median (range)	430	25.4	15.6–42.0	142	26.2	16.4–45.0	
Low (< 20)	430	41	9.5	142	17	12.0	
Normal (20–25)	430	148	34.4	142	38	26.8	
High (> 25)	430	241	56.0	142	87	61.3	
Site of primary disease							0.46
Colon only	430	244	56.7	142	88	62.0	
Rectum only	430	101	23.5	142	32	22.5	
Colon and rectum	430	85	19.8	142	22	15.5	
Time from initial diagnosis to randomisation (years)							1.0
Median (range)	430	2.3	0.5–15.7	142	2.2	0–10.9	
≥ 2	430	246	57.2	142	81	57.0	
< 2	430	184	42.8	142	61	43.0	
Lactate dehydrogenase							0.91
≤ upper normal limit	430	100	23.3	142	34	23.9	
> upper normal limit	430	308	71.6	142	102	71.8	
Alkaline phosphate							0.59
≤ upper normal limit	430	117	27.2	142	42	29.6	
> upper normal limit	430	310	72.1	142	99	69.7	
Haemoglobin							0.22
CTC grade 0	430	150	34.9	142	41	28.9	
CTC grade ≥ 1	430	280	65.1	142	101	71.1	
Serum creatinine							0.41
CTC grade 0	430	391	90.9	142	126	88.7	
CTC grade ≥ 1	430	38	8.8	142	16	11.3	
Number of previous chemotherapy drug classes							1.0
≤ 2	430	21	4.9	142	7	4.9	
> 2	430	409	95.1	142	135	95.1	
Age (years)							0.002
Median (range)	430	62.0	28.6–88.1	142	65.8	35.5–85.2	
< 65	430	268	62.3	142	67	47.2	
≥ 65	430	162	37.7	142	75	52.8	

Demographics	Comorbidity score 0			Comorbidity score ≥ 1			*p*-value[a]
	n	Estimate	%	*n*	Estimate	%	
Venous thromboembolism							0.44
No	430	391	90.9	142	126	88.7	
Yes	430	39	9.1	142	16	11.3	
KRAS status							0.29
WT	430	168	39.1	142	62	43.7	
Mutant	430	128	29.8	142	36	25.4	
Missing	430	134	31.2	142	44	31.0	
Treatment							0.12
BSC only	430	206	47.9	142	79	55.6	
Cetuximab plus BSC	430	224	52.1	142	63	44.4	
Duration of treatment (weeks)							0.06
Median (range)	430	8	1–60	142	16	1–55.9	
Cumulative dose (mg/m^2)							0.06
Median (range)	430	2152	391–15,216	142	3508	396–12,650	

BSC, best supportive care.
a From Fisher's exact test.

Results

	CET + BSC			
	n	Estimate	95% CI	*p*-value
Duration of treatment	Until disease progression or toxicity			
Overall survival (hazard ratio)				
Age ≥ 65 vs < 65 years, all patients		1.05	0.87 to 1.27	0.60
CCI score ≥ 1 vs 0, all patients		0.80	0.65 to 1.00	0.047
CCI score ≥1 versus 0		0.66	0.47 to 0.92	0.02
Presence of venous thromboembolism, all patients		1.49	1.10 to 2.02	0.009
Performance status 2 vs 0		1.92	1.34 to 2.74	< 0.0001
Median duration of treatment (weeks), CCI ≥ 1		15.6		0.006
Median duration of treatment (weeks), CCI = 0		8		
CET vs BSC, < 65 years		0.77	0.61 to 0.98	
CET vs BSC, ≥ 65 years		0.75	0.56 to 1.00	
CET vs BSC, comorbidity 0		0.80	0.65 to 0.99	0.21
CET vs BSC, comorbidity ≥ 1		0.61	0.42 to 0.90	
Age (years)				
< 65		1		0.60
≥ 65		1.05	0.87 to 1.27	
Comorbidity score				
0		1		0.047
≥ 1		0.80	0.65 to 1.00	

	CET + BSC			
	n	Estimate	95% CI	*p*-value
Venous thromboembolism				
No		1		0.009
Yes		1.49	1.10 to 2.02	
Gender				
Female		1		0.107
Male		0.85	0.70 to 1.04	
ECOG performance status				
0		1		< 0.0001
1		1.15	0.92 to 1.45	
2		2.51	1.93 to 3.27	
Body mass index (kg/m^2)				< 0.0001
Low (< 20)		1		
Normal (20–25)		0.77	0.56 to 1.05	
High (> 25)		0.54	0.40 to 0.72	
Site of primary disease				0.068
Colon only		1		
Rectum only		0.83	0.66 to 1.05	
Colon and rectum		0.82	0.64 to 1.05	
Time from initial diagnosis to randomisation (years)				< 0.0001
≥ 2		1		
< 2		1.57	1.31 to 1.90	
Lactate dehydrogenase				< 0.0001
≤ upper normal limit		1		
> upper normal limit		1.99	1.56 to 2.53	
Alkaline phosphate				
≤ upper normal limit		1		
> upper normal limit		2.16	1.73 to 2.70	< 0.001
Haemoglobin				
CTC grade 0		1		
CTC grade ≥ 1		2.02	1.64 to 2.48	
Serum creatinine				0.839
CTC grade 0		1		
CTC grade ≥ 1		1.03	0.75 to 1.42	
Number of previous chemotherapy drug classes				0.192
≤ 2		1		
> 2		1.35	0.86 to 2.11	

	CET + BSC			
	n	Estimate	95% CI	*p*-value
KRAS *status*				0.007
WT		1		
Mutant		1.36	1.09 to 1.70	
Treatment				0.004
BSC only		1		
CET + BSC		0.76	0.63 to 0.92	
Safety				
Grade 3 or worse by age group				
Age < 65 years				
Any	178	140		1.00
Oedema	178	9		1.00
Fatigue	178	53		0.157
Anorexia	178	14		0.827
Constipation	178	8		0.327
Nausea	178	11		0.609
Vomiting	178	14		0.034
Non-neutropaenic infection	178	25		0.589
Confusion	178	6		0.061
Abdominal pain	178	29		0.051
Other pain	178	31		0.173
Dyspnoea	178	20		0.005
Rash	178	20		0.711
Age > 65 years				
Any	110	86		
Oedema	110	6		
Fatigue	110	42		
Anorexia	110	10		
Constipation	110	2		
Nausea	110	5		
Vomiting	110	2		
Non-neutropaenic infection	110	12		
Confusion	110	10		
Abdominal pain	110	9		
Other pain	110	12		
Dyspnoea	110	27		
Rash	110	14		
Grade 3 or worse by comorbidity score				
Comorbidity score 0				
Any	225	176		1.000
Oedema	225	11		0.748
Fatigue	225	73		0.762
Anorexia	225	18		0.796

	CET + BSC			
	n	Estimate	95% CI	*p*-value
Constipation	225	9		0.696
Nausea	225	14		0.536
Vomiting	225	16		0.002
Non-neutropaenic infection	225	22		0.005
Confusion	225	12		0.758
Abdominal pain	225	32		0.404
Other pain	225	35		0.691
Dyspnoea	225	33		0.177
Rash	225	28		0.661
Constipation	225	9		0.696
Comorbidity score ≥ 1				
Any	63	50		
Oedema	63	4		
Fatigue	63	22		
Anorexia	63	6		
Constipation	63	1		
Nausea	63	2		
Vomiting	63	0		
Non-neutropaenic infection	63	15		
Confusion	63	4		
Abdominal pain	63	6		
Other pain	63	8		
Dyspnoea	63	14		
Rash	63	6		

BSC, best supportive care; CET, cetuximab.

Methodological issues

Randomisation and allocation

Not reported.

Data analysis

Variables of patient age and CCI score were dichotomised – age < 65 compared with ≥ 65 years and CCI score 0 compared with ≥ 1 – with higher scores indicating greater comorbidity. The chi-squared test was used to perform univariate analyses for the association between age group and baseline patient, disease and treatment characteristics. Logistic regression modeling was used to perform multivariate analyses to identify independant characteristics correlated with age. Similar analyses were carried out for the association between comorbidity group and baseline patient, disease and treatment characteristics and to identify characteristics associated with comorbidity. Univariate and multivariate analyses of overall survival and progression-free survival by age and comorbidity were carried out using log-rank tests and Cox regression models respectively. Univariate and multivariate analyses of response by age and comorbidity were carried out using Fisher's exact test and a logistical regression model respectively.

Power calculation

Not reported.

Conflicts of interest

Two authors have acted on advisory boards for Bristol-Myers Squibb, two authors have acted on advisory boards for Merck Serono and one author is employed by and owns stock in Bristol-Myers Squibb.

Quality appraisal

1. Was the assignment to the treatment groups really random? Not reported
2. Was the treatment allocation concealed? No
3. Were the groups similar at baseline in terms of prognostic factors? Adequate
4. Were the eligibility criteria specified? Partial
5. Were outcome assessors blinded to the treatment allocation? Unclear
6. Was the care provider blinded? No
7. Was the patient blinded? No
8. Were the point estimates and measure of variability presented for the primary outcome measure? Reported – yes
9. Did the analyses include an ITT analysis? Reported – yes
10. Were withdrawals and dropouts completely described? Partial

Odom *et al.*[56]

Design	Participants	Arms	Outcomes
Study design: Supplementary study to parallel, open-label RCT **Country:** Western Europe, Central Europe, Eastern Europe, Canada, Australia and New Zealand **No. of centres:** Unknown **Funding:** Amgen **Length of follow-up:** Minimum of 12 months	**Number randomised:** 463 **Inclusion criteria:** Patients with EGFR-detectable metastatic colorectal cancer and documented evidence of disease progression after failure of fluoropyrimidines and prespecified exposure to oxaliplatin and irinotecan **Exclusion criteria:** Not reported **Therapy common to all participants:** Best supportive care	**Arm no. 1** **Name:** Panitumumab plus best supportive care ***n*:** **Drug:** Panitumumab **Dosage details:** Panitumumab was administered using a 60-minute intravenous infusion at 6 mg/kg once every 2 weeks **Arm no. 2** **Name:** Best supportive care ***n*:** **Drug:** N/A **Starting daily dose:** N/A **Dosage details:** N/A	**Primary outcome measure:** Overall survival, defined as time from randomisation until death from any cause **Secondary outcome measure(s):** HRQoL **Method of assessment:** Progression assessed by central radiological review at specified time points from weeks 8 to 48, then every 3 months thereafter. *KRAS* tumour status was evaluated in a blinded fashion Colorectal cancer symptoms were assessed using the NCCN FCSI. Patients responded to each item of this questionnaire using a 5-point scale ranging from 0 to 4. The minimal clinically important difference was defined as a change in score of ≥ 3 points Overall HRQoL was measured at baseline and monthly until disease progression using the EQ-5D index. The minimal clinically important difference for the EQ-5D index has been estimated as a change in score of ≥ 0.08 points

N/A, not applicable.

Baseline characteristics

	PAN + BSC			BSC			
Demographics	***n***	**Estimate**	**%**	***n***	**Estimate**	**%**	***p*-value**
All patients							
Sex							
Men	188	123	65	175	113	65	
Women	188	65	35	175	62	35	
Race/ethnicity							
White	188	187	99	175	171	98	
Other	188	1	1	175	4	2	
Age (years), mean (SD)	188	61	10	175	62	10	
Primary diagnosis							
Colon cancer	188	126	67	175	117	67	
Rectal cancer	188	62	33	175	58	33	
ECOG performance status							
0	188	91	48	175	62	35	
1	188	76	40	175	91	52	
2	188	21	11	175	22	13	
Time since primary diagnosis (months), mean (SD)	188	31	22	175	32	21	
Time since metastatic disease (months), mean (SD)	188	21	10	175	22	11	
Baseline EQ-5D index, mean (SD)	188	0.72	0.24	175	0.68	0.25	
Baseline FSCI score, mean (SD)	188	72.7	13.69	175	71.84	14.28	

Demographics	PAN + BSC			BSC			*p*-value
	n	Estimate	%	*n*	Estimate	%	
WT							
Sex							
Men	112	79	701	96	62	645	
Women	112	33	29	96	34	35	
Race/ethnicity							
White	112	111	99	96	95	99	
Other	112	1	1	96	1	1	
Age (years), mean (SD)	112	62	10	96	62	10	
Primary diagnosis							
Colon cancer	112	78	70	96	68	71	
Rectal cancer	112	34	30	96	28	29	
ECOG performance status							
0	112	52	46	96	35	36	
1	112	50	45	96	51	53	
2	112	10	9	96	10	10	
Time since primary diagnosis (months), mean (SD)	112	33	25	96	31	20	
Time since metastatic disease (months), mean (SD)	112	22	10	96	24	13	
Baseline EQ-5D index, mean (SD)	112	0.73	0.24	96	0.68	0.23	
Baseline FSCI score, mean (SD)	112	73.21	13.05	96	71.78	13.48	
Mutant							
Sex							
Men	76	44	58	79	51	65	
Women	76	32	42	79	28	35	
Race/ethnicity							
White	76	76	100	79	76	96	
Other	76	0	0	79	3	4	
Age (years), mean (SD)	76	60	11	79	61	11	
Primary diagnosis							
Colon cancer	76	48	63	79	49	62	
Rectal cancer	76	28	37	79	30	38	
ECOG performance status							
0	76	39	51	79	27	34	
1	76	26	34	79	40	51	
2	76	11	14	79	12	15	
Time since primary diagnosis (months), mean (SD)	76	27	17	79	34	21	
Time since metastatic disease (months), mean (SD)	76	20	10	79	19	8	
Baseline EQ-5D index, mean (SD)	76	0.71	0.25	79	0.68	0.26	
Baseline FSCI score, mean (SD)	76	70.94	14.55	79	71.91	15.28	

BSC, best supportive care; PAN, panitumumab; SD, standard deviation.

Results

	PAN + BSC vs BSC		
	n	Estimate	95% CI
ITT population[a]			
EQ-5D index, early dropout[b]			
All patients	164	–0.08	–0.21 to 0.05
WT		–0.19	–0.38 to 0.01
Mutant		–0.02	–0.19 to 0.15
EQ-5D index, late dropout			
All patients	152	0.26	0.16 to 0.37
WT		0.32	0.18 to 0.45
Mutant		0.13	–0.03 to 0.29
FCSI score, early dropout[b]			
All patients	184	0.53	–3.15 to 4.20
WT		–2.21	–7.16 to 2.75
Mutant		4.27	–1.33 to 9.88
EQ-5D score, late dropout			
All patients	150	3.63	–0.05 to 7.31
WT		5.75	1.45 to 10.04
Mutant		–0.66	–7.27 to 5.95

a Least squares mean difference.
b Data up to week 9.

Methodological issues

Randomisation and allocation

Not reported.

Data analysis

The analysis set was defined as all patients in the ITT population who had at least one post-baseline FCSI score or EQ-5D index assessment and an assessed *KRAS* status. Change in score from baseline was analysed over time using linear mixed models for repeated measures. The models included explanatory variables for study treatment arm, study week and the interaction between treatment arm and study week.

Treatment-specific estimates of the average change in each outcome score from baseline along with 95% CIs were calculated for the overall cohort and for each *KRAS* subgroup using least-squares mean difference.

To evaluate the effect of study attrition on the estimates of treatment differences, a sensitivity analysis was performed using pattern-mixture models that incorporate information about missing data.

Dropout status was incorporated into pattern-mixture models of change in score from baseline for each outcome. These models included fixed effects for treatment arm, study week, dropout pattern group and interactions between these effects. The model included random effects.

Power calculation

Not reported.

Conflicts of interest

Four authors are employees and stockholders of Amgen, one author is an advisory board member for Amgen, Eli Lilly and Company, Merck, Novartis, Roche and Sanofi-Aventis and three authors received funding from Amgen.

Quality appraisal

1. Was the assignment to the treatment groups really random? Not reported
2. Was the treatment allocation concealed? No
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