Study	Jonker *et al.*[37]	Van Cutsem *et al.*[7]	Van Cutsem *et al.*[38]
Participants	**Inclusion criteria:** Advanced colorectal cancer expressing EGFR detectable by immunohistochemical methods; previous treatment with either fluoropyrimidine, irinotecan or oxaliplatin with no response to treatment or contraindications to treatment with these drugs; disease that could be measured or evaluated, ECOG performance status of 0–2 with 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	**Inclusion criteria:** Age ≥ 18 years; 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 ≥ 65 mg/m^2 per week and oxaliplatin ≥ 30 mg/m^2 per week); ECOG performance status of 0–2; two or three prior chemotherapy regimens for metastatic colorectal cancer; 1% EGFR-positive membrane staining in primary or metastatic tumour cells **Exclusion criteria:** Symptomatic brain metastases, interstitial pneumonitis or pulmonary fibrosis; systematic chemotherapy or radiotherapy within 30 days before random assignment; prior anti-EFGR agents	**Inclusion criteria:** As for Van Cutsem *et al.*[7] **Exclusion criteria:** As for Van Cutsem *et al.*[7]
Interventions	**Cetuximab + BSC:** Given intravenously as an initial dose of 400 mg/m^2 of body surface area, administered over 120 minutes, followed by a weekly maintenance infusion of 250 mg/m^2, administered over 60 minutes **BSC:** Measures designed to provide palliation of symptoms and improve quality of life	**Panitumumab + BSC:** 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 **BSC:** Defined as the best palliative care excluding antineoplastic agents	**Panitumumab + BSC:** As for Van Cutsem *et al.*[7]
Study objectives	To demonstrate the effect of cetuximab on survival or QoL in patients with advanced colorectal cancer	To evaluate the effect of panitumumab monotherapy in patients with chemorefactory metastatic colorectal cancer	To demonstrate the efficacy and safety of cetuximab for survival or QoL in patients with advanced colorectal cancer
Outcomes	**Primary:** Overall survival, defined as time from randomisation until death from any cause **Secondary:** Progression-free survival, defined as time from randomisation until the first objective observation of disease progression or death from any cause	**Primary:** Progression-free survival by blinded central radiology assessment, calculated from day of random assignment until radiological progression or death **Secondary:** 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	**Primary:** Safety, including incidence of grade 3/4 adverse and treatment-related events, skin-related events and antibody formation **Secondary:** 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

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Analysis	All patients who underwent randomisation were included in the efficacy analyses on the basis of the group to which they were assigned Time-to-event variables were summarised with the use of Kaplan–Meier plots Primary comparisons were made using 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 scores was defined a priori as a decline of ≥10 points from baseline It was estimated a priori that 445 deaths would provide a statistical power of 90% and a two-sided alpha of 5% to detect an absolute increase of 9.6% in 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) Safety analysis was conducted on an on-treatment basis, contrasting patients who had at least one dose of cetuximab (including those who crossed over) with patients assigned to supportive care alone, and omitting patients who withdrew consent before any intervention	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 in the primary analysis and 4% test of overall survival were prespecified conditional on a significant progression-free survival difference. The 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 the 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 The study had 90% power for a two-sided test at the 1% significance level given a hazard ratio (panitumumab relative to BSC) 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	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 time 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 were 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 The sample size was limited to the patients enrolled in the BSC 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

BSC, best supportive care; ORR, overall response rate.