

# First-line panitumumab plus irinotecan/5-fluorouracil/leucovorin treatment in patients with metastatic colorectal cancer

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## Abstract

**Purpose** Panitumumab monotherapy is approved for *KRAS* wild-type (WT) metastatic colorectal cancer (mCRC) progressing after standard chemotherapy. This study evaluated first-line panitumumab plus FOLFIRI in patients with mCRC.

**Methods** In this phase II, single-arm study, panitumumab (6 mg/kg) and FOLFIRI [irinotecan (180 mg/m<sup>2</sup>) and leucovorin (400 mg/m<sup>2</sup>) followed by a 5-fluorouracil 400 mg/m<sup>2</sup> bolus and a 2,400–3,000 mg/m<sup>2</sup> continuous infusion] were administered every 14 days until progression. Data were analysed descriptively overall and by tumour *KRAS* status.

**Results** *KRAS* data were available for 145/154 (94%) patients: 59% *KRAS* WT and 41% mutant (MT); mean follow-up was 39.5 versus 35.8 weeks, respectively. Objective responses occurred in 49% of patients: 56% versus 38% in the *KRAS* WT versus MT groups [(18% difference (95% CI 1–35%); odds ratio 2.1 (95% CI 1.0–4.4)]; median duration of response was 13.0 versus 7.4 months. More patients in the WT group underwent R0 resection (8% vs. 5%); median progression-free survival also favoured this group (8.9 vs. 7.2 months). The most common adverse events (any grade) were integument toxicities (98%), diarrhoea (79%) and stomatitis/oral mucositis (51%).

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**Conclusions** As expected, consistently favourable efficacy was observed in patients with *KRAS* WT versus MT tumours receiving first-line panitumumab plus FOLFIRI treatment.

**Keywords** Chemotherapy · Fully human monoclonal antibody · Metastatic colorectal cancer · Panitumumab

## Introduction

5-fluorouracil (5-FU)-based chemotherapy provides the mainstay of treatment for patients with metastatic colorectal cancer (mCRC). Combinations of infusional 5-FU, leucovorin, and oxaliplatin (FOLFOX), and infusional 5-FU, leucovorin and irinotecan (FOLFIRI) are considered standard treatments for mCRC (Fuchs et al. 2007; Tournigand et al. 2004). Adding novel, targeted agents to these combinations has further improved patient outcomes (Hurwitz et al. 2004; Van Cutsem et al. 2009). In the case of infusional chemotherapy backbones, data have been promising for epidermal growth factor receptor (EGFR)-targeted antibodies.

EGFR signalling is implicated in the pathogenesis of CRC and other cancers of epithelial origin (Kari et al. 2003). Analyses from several studies have demonstrated that tumours with mutated (MT) *KRAS* status are resistant to anti-EGFR therapy (Amado et al. 2008; Benvenuti et al. 2007; Van Cutsem et al. 2009; Di Fiore et al. 2007; De Roock et al. 2008; Freeman et al. 2008). Consequently, EGFR inhibitors should only be used in patients with tumours expressing wild-type (WT) *KRAS* (European Medicines Agency 2009a, b; Dolgin 2009). Panitumumab is a fully human EGFR-targeted monoclonal antibody (Cohenuram and Saif 2007) that is approved in the USA as monotherapy for mCRC with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy regimens (Amgen Inc. 2010), and in Europe for patients with EGFR-expressing mCRC of WT *KRAS* status independent of prior therapy (Amgen Ltd 2009). Phase III trials have recently demonstrated that first-line panitumumab plus FOLFOX (Douillard et al. 2010) and second-line panitumumab plus FOLFIRI treatments are effective and have acceptable safety (Peeters et al. 2010) in patients with *KRAS* WT mCRC. Based on these data, panitumumab has recently been recommended in Europe for use in combination with chemotherapy in the first- and second-line settings (European Medicines Agency 2011).

Here we report a single-arm, multicentre, phase II study evaluating the efficacy and safety of first-line panitumumab plus FOLFIRI treatment for patients with mCRC (NCT00508404). At the time of study initiation, the value

of tumour *KRAS* status was not known. After the importance of this biomarker was demonstrated in patients receiving anti-EGFR therapies (Amado et al. 2008; Di Fiore et al. 2007) the protocol was amended to evaluate outcomes by tumour *KRAS* status. The study was fully enrolled at the time of this amendment.

## Methods

### Patients

Eligible patients were  $\geq 18$  years of age, with histologically or cytologically confirmed, radiologically measurable mCRC, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. All disease sites must have been evaluated  $\leq 28$  days prior to enrolment and tissue from the primary or metastatic site had to be available. EGFR expression was not required for study entry. Patients who had received prior systemic therapy (including anti-EGFR therapy) for mCRC (except adjuvant fluoropyrimidine-based chemotherapy given  $\geq 6$  months prior to enrolment) were excluded. Radiotherapy  $\leq 14$  days prior to enrolment was not permitted and patients must have recovered from all radiotherapy-related toxicities. Patients with untreated and symptomatic central nervous system metastases or significant cardiovascular disease were excluded. The study protocol was approved by the relevant independent ethics committees and the study was conducted in accordance with International Conference on Harmonization of Good Clinical Practice regulations/guidelines. All patients provided signed, informed consent before any study-related procedures were performed.

### Study design and treatment schedule

Panitumumab and FOLFIRI were administered once every 14 days until disease progression, unacceptable toxicity, or withdrawal of consent. If FOLFIRI or panitumumab were withdrawn or withheld due to toxicity, the other agent was continued. On Day 1 of the first cycle, panitumumab (6 mg/kg) was administered as a  $60 \pm 15$  min intravenous (IV) infusion, just prior to chemotherapy; if this was well tolerated, subsequent infusions could be administered over  $30 \pm 10$  min. No panitumumab-specific premedication was required. FOLFIRI [irinotecan ( $180 \text{ mg/m}^2$ ) IV over  $90 \pm 15$  min and leucovorin ( $400 \text{ mg/m}^2$ ) IV over  $120 \pm 15$  min (sequentially/in parallel), followed by a 5-FU  $400 \text{ mg/m}^2$  bolus and a 5-FU  $2,400\text{--}3,000 \text{ mg/m}^2$  continuous IV infusion over  $46 \pm 2$  h] was also administered on Day 1 of each cycle. One cycle was defined as the 14-day period following initiation of study treatment.

## Efficacy analyses

Response was assessed using modified Response Evaluation Criteria in Solid Tumors (Therasse et al. 2000) (mRECIST v1.0). Patients were evaluated every 8 weeks until Week 48, and every 3 months thereafter until disease progression. All responses were confirmed  $\geq 4$  weeks after response was first noted. Objective response (OR) rate was the primary efficacy endpoint. Secondary efficacy endpoints included: disease control rate; duration of response (DoR); progression-free survival (PFS); time to progression (TTP); duration of stable disease (DoSD); and time to treatment failure (TTF). The incidence of complete (R0) metastatic resection was also reported.

## Tolerability analyses

The incidence and severity of adverse events (AEs) were measured throughout the study and graded using National Cancer Institute Common Toxicity Criteria version 3.0 (NCI CTCAE v3.0; National Cancer Institute Cancer Therapy Evaluation Program [CTEP] 2005), except for selected skin toxicities (nail changes, erythema, pruritus, acneiform rash, rash/desquamation, and ulceration) that were graded using a modified version of the CTC v3.0 (Online Resource 1; National Cancer Institute Cancer Therapy Evaluation Program [CTEP] 2006). AEs of particular interest were predefined and included those known to be associated with EGFR inhibitors and/or FOLFIRI. A safety follow-up visit was scheduled for 8 weeks after treatment completion.

## KRAS analyses

DNA was extracted from patients' pre-treatment tumour samples to evaluate *KRAS* mutation status and define the efficacy population for analysis purposes. *KRAS* testing was performed centrally at HistoGeneX in Belgium using the research-use only DxS kit that utilises allele-specific, real-time polymerase chain reaction to detect seven of the most common *KRAS* mutations. This kit detects  $\sim 1\%$  of MT DNA in a background of WT genomic DNA.

## Statistical analyses

An OR rate of 40% is commonly achievable in mCRC patients receiving first-line treatment with FOLFIRI alone (Saltz et al. 2000), therefore, a sample size of 150 patients (from  $\sim 40$  centres) was selected to enable estimation of a 45% OR rate for panitumumab plus FOLFIRI, with a 95% confidence interval (CI) of 37–53%. Given the documented significance of *KRAS* mutation status on the efficacy of EGFR-targeted therapies (Amado et al. 2008; Van Cutsem et al. 2009), the study protocol was amended in August

2008 to permit investigation of the effect of *KRAS* status on outcome. Based on historical data (Amado et al. 2008), the prevalence of WT and MT *KRAS* was assumed to be 55 and 45%, respectively; therefore, approximately 75 patients versus 60 patients would have WT versus MT tumour *KRAS* status (assuming 90% of patients had *KRAS*-evaluable samples). An OR rate of 35% in the MT *KRAS* subset and of  $\sim 53\%$  in the WT *KRAS* subset would provide an odds ratio of 2.1 (95% CI 1.1–4.3) if 135 patients had evaluable *KRAS* status and the expected prevalence of WT versus MT were to be observed.

Study endpoints were analysed in the full analysis set and by tumour *KRAS* status. Data were analysed using descriptive statistics including point estimates, 95% CI, and Kaplan–Meier plots. Modelling techniques (e.g. logistic regression or Cox proportional hazards modelling) were used to explore the relationship between covariates and outcome. The full (overall) analysis set included enrolled patients providing informed consent who received  $\geq 1$  panitumumab dose and who had either evaluable or unevaluable tumour *KRAS* status. Similarly, the *KRAS* safety analysis set comprised all patients who received  $\geq 1$  dose of panitumumab and had evaluable *KRAS* data; the full safety analysis set included patients with unevaluable *KRAS* status. Only patients with measurable disease at baseline were included in the response analysis. The data cut-off for the primary analysis was  $\sim 12$  months after the last patient was enrolled.

## Results

### Patients

Between 9 May 2007 and 18 June 2008, 154 patients were enrolled at 36 study centres in Austria, Belgium, France, Germany, and Sweden. Overall, most patients were men (68%) and almost all were Caucasian (97%) (Table 1). Median age was 64.0 years and 11% were  $\geq 75$  years of age. The most frequently reported sites of metastases were the liver (76%), lung parenchyma (20%), and lymph nodes (12%). Most patients had  $>1$  site of metastases (54%); 34% had liver-only metastases. There were 145 patients (94%) with *KRAS*-evaluable samples: 86 patients (59%) had *KRAS* WT tumours. Most characteristics were similar between *KRAS* groups, although slightly higher proportions with *KRAS* MT tumours had colon cancer (66% vs. 58%), were female (46% vs. 22%), and were  $\geq 75$  years of age (17% vs. 7%) [data not shown].

### Treatment

Overall, the mean [standard deviation (SD)] administered panitumumab dose was 5.8 (0.5) mg/kg, the mean (SD)

**Table 1** Baseline patient demographics and disease characteristics

	Panitumumab plus FOLFIRI	
	Overall ( <i>n</i> = 154)	<i>KRAS</i> WT ( <i>n</i> = 86)
Sex, <i>n</i> (%) male	105 (68)	67 (78)
Median age (range), years	64.0 (21–84)	63.5 (21–84)
Age group, <i>n</i> (%)		
<65 years	79 (51)	45 (52)
≥65 years	75 (49)	41 (48)
<75 years	137 (89)	80 (93)
≥75 years	17 (11)	6 (7)
Caucasian race, <i>n</i> (%)	150 (97)	83 (97)
Primary diagnosis, <i>n</i> (%)		
Colon cancer	92 (60)	50 (58)
Rectal cancer	62 (40)	36 (42)
ECOG performance status, <i>n</i> (%)		
0	90 (58)	46 (53)
1	56 (36)	36 (42)
2	7 (5)	3 (3)
3	1 (1) <sup>a</sup>	1 (1) <sup>a</sup>
Prior adjuvant therapy, <i>n</i> (%)	30 (19)	15 (17)
Number of metastatic sites, <i>n</i> (%)		
1	71 (46)	37 (43)
2	47 (31)	26 (30)
≥3	36 (23)	23 (27)
Sites of metastatic disease, <i>n</i> (%)		
Liver only	52 (34)	31 (36)
Liver plus other sites	69 (45)	41 (48)
Other sites only	33 (21)	14 (16)

WT wild type

<sup>a</sup> Patient had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 at screening, thus inclusion criteria were satisfied

cumulative dose was 70.1 (40.4) mg/kg, and the median number of panitumumab cycles delivered was 12.2 (range 1–35). The mean (SD) cumulative panitumumab dose (77.0 (43.2) vs. 62.2 (34.6) mg/kg) and number of panitumumab cycles delivered [13.2 (7.5) vs. 10.9 (6.1)] were higher in the *KRAS* WT group versus the MT group. Overall, the mean (SD) relative dose intensity for irinotecan was 83.4 (12.9) and for the 5-FU bolus was 84.3 (12.9). Overall, the median number of chemotherapy cycles delivered was 12.0 (range 1–35). The cumulative chemotherapy dose delivered (any component) was also higher in the *KRAS* WT group than in the MT group.

Of 154 patients who enrolled in the study, 147 (95%) discontinued panitumumab treatment (94% *KRAS* WT vs. 98% MT); the most common reason was radiographic disease progression [53 patients, 36% (31% *KRAS* WT vs. 45% MT)]. A total of 149 patients (97%) discontinued FOLFIRI (95% *KRAS* WT vs. 100% MT); radiographic

**Table 2** Best overall response

	Panitumumab plus FOLFIRI	
	Overall ( <i>n</i> = 152) <sup>a</sup>	<i>KRAS</i> WT ( <i>n</i> = 85)
Best overall response, <i>n</i> (%)		
Complete response	3 (2)	2 (2)
Partial response	72 (47)	46 (54)
Stable disease	63 (41)	29 (34)
Disease progression	10 (7)	6 (7)
Unevaluable	1 (1)	0 (0)
Not done	3 (2)	2 (2)
Objective response rate, % (95% CI)	49 (41–58)	56 (45–67)

CI confidence interval, WT wild type

<sup>a</sup> Only patients with measurable disease at baseline according to Response Evaluation Criteria in Solid Tumours (RECIST) were included

disease progression was again the most common reason [50 patients, 34% (26% *KRAS* WT vs. 44% MT)]. Overall, the median time to withdrawal from all treatment was 6.0 months (95% CI 5.7–6.6) and was 6.9 months (95% CI 6.2–7.6) in the *KRAS* WT versus 5.8 months (95% CI 5.3–6.8) in the *KRAS* MT group.

Six patients (7%) in the *KRAS* WT group, 1 patient (2%) in the MT group, and 1 patient (11%) with unevaluable *KRAS* tumour status were still receiving ≥1 element of their treatment at time of analysis.

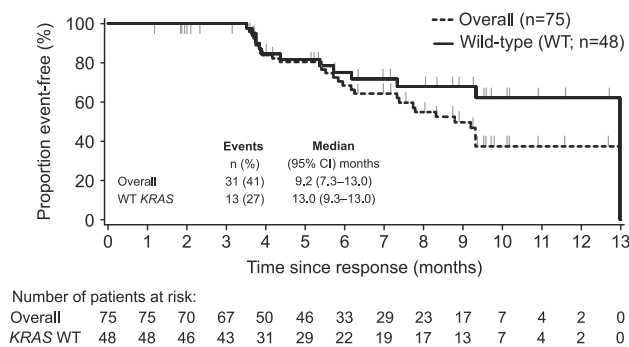
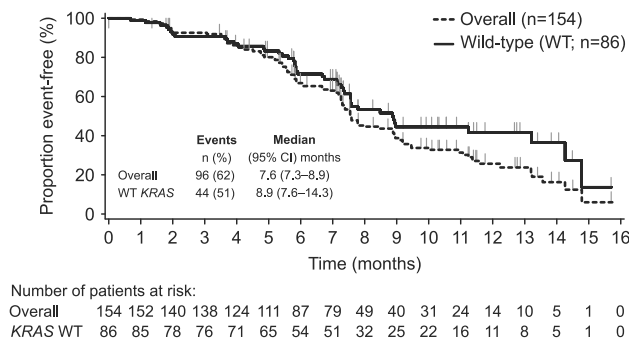
## Efficacy

### Objective response, duration of response, and resection rates

Mean (SD) follow-up time was 37.7 (15.7) weeks overall: 39.5 (16.7) weeks in the *KRAS* WT group and 35.8 (14.4) weeks in the MT group. Two patients had immeasurable disease at baseline and were excluded from the response analysis.

Overall, 75 patients (49%; 95% CI 41–58%) had an OR; median DoR was 8.8 months (95% CI 7.3–13.0) (Table 2; Fig. 1). A higher proportion of patients in the *KRAS* WT group (56%; 95% CI 45–67%) than in the MT group (38%; 95% CI 26–52%) had an OR. The difference in OR rates [18% (95% CI 1–35%)] and the odds ratio [2.1 (95% CI 1.0–4.4)] favoured the *KRAS* WT group. Median DoR was also longer in these patients [13.0 months (95% CI 9.3–13.0) versus 7.4 months (95% CI 5.4–8.8), respectively].

A higher proportion of patients in the *KRAS* MT group (52%) had stable disease compared with patients in the WT group (34%). Overall, the median DoSD was 5.9 months (95% CI 5.6–7.3). The hazard ratio (HR) comparing DoSD

**Fig. 1** Duration of response**Fig. 2** Progression-free survival

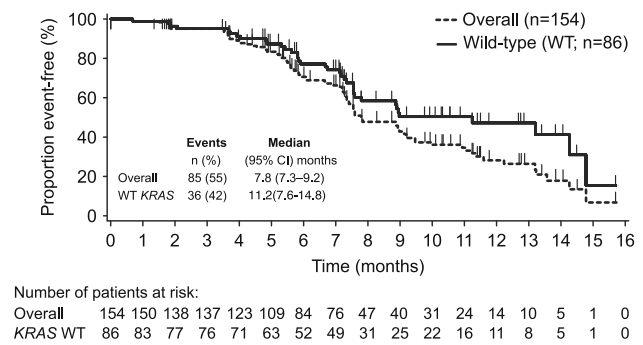
in the *KRAS* WT and MT groups was 0.8 (95% CI 0.4–1.4). There was little difference between *KRAS* groups in disease control rate [91% vs. 90%; 1% difference; 95% CI –10 to 13% (unadjusted odds ratio 1.1; 95% CI 0.3–3.9)].

Overall, 11 patients (7%; 95% CI 4–12%) had a R0 resection. In the *KRAS* WT group, 7 patients (8%; 95% CI 3–16%) had a R0 resection compared with 3 patients in the *KRAS* MT group (5%; 95% CI 1–14%). The majority of patients had a R0 resection of liver metastases (*KRAS* WT:  $n = 6$  vs. MT:  $n = 1$ ). In patients with liver-only metastases at baseline ( $n = 52$ ), R0 resections were performed in 8 patients (15%) overall and 6/31 patients (19%) versus 1/16 patients (6%) in the *KRAS* WT and MT groups, respectively.

#### Progression-free survival, time to progression, and time to treatment failure

Overall, 96 patients (62%) progressed or died (*KRAS* WT:  $n = 44$  [51%]; MT: 48 [81%]); median PFS was 7.6 months (95% CI 7.3–8.9) (Fig. 2). PFS was longer for patients with *KRAS* WT tumours [8.9 months (95% CI 7.6–14.3)] compared with those with MT tumours [7.2 months (95% CI 5.6–7.8)]. The estimated HR was 0.5 (95% CI 0.3–0.7) indicating a lower average event rate and longer time to progression or death for patients with *KRAS* WT tumours.

Overall, 85 patients (55%) had disease progression [*KRAS* WT:  $n = 36$  (42%); MT: 45 (76%)] median TTP

**Fig. 3** Time to disease progression

was 7.8 months (95% CI 7.3–9.2) (Fig. 3). Median TTP was 11.2 months (95% CI 7.6–14.8) in the *KRAS* WT versus 7.3 months (95% CI 5.7–8.9) in the MT group; results from the Cox proportional hazards model for TTP favoured the *KRAS* WT group (HR 0.4; 95% CI 0.3–0.6).

Of the 154 patients enrolled, 146 (95%) ended the treatment phase; the median TTF was 6.2 months (95% CI 5.8–6.9). Similar proportions in the *KRAS* WT and MT groups ended the treatment phase; however, median TTF was longer in the *KRAS* WT group (6.9 months; 95% CI 6.2–7.6) than in the MT group (5.8 months; 95% CI 5.3–6.8).

#### Tolerability

Overall, the most frequently reported clinically significant AEs (any grade) were integument toxicities (98%); the most common were skin (97%), eye and hair (38% each), and nail (32%) toxicities. Other frequently reported clinically significant AEs were diarrhoea (79%), stomatitis/oral mucositis (51%), vascular toxicity (32%), and hypomagnesaemia (21%). Overall, the most frequently reported grade  $\geq 3$  AEs were diarrhoea (24%), neutropenia (18%), acne and rash (10% each), pulmonary embolism (8%), and paronychia (6%). Incidences of grade 3/4 AEs of particular interest are shown in Table 3. No infusion reactions were reported as AEs; however, 13% of patients overall experienced symptoms meeting the CTCAE definition of possible infusion reactions, most of which were mild or moderate (1 patient had a grade 3 reaction).

Overall, 84 patients (55%) had serious AEs, 43 serious AEs (28%) were considered treatment related. By *KRAS* group, the most frequently reported serious, treatment-related AEs were diarrhoea (15% *KRAS* WT, 8% MT), vomiting (3% *KRAS* WT, 2% MT), neutropenia (2% *KRAS* WT, 3% MT), and dehydration, fatigue, and pulmonary embolism (2% *KRAS* WT, 2% MT for each AE). Overall, 13 patients (8%) had fatal AEs; there were 7 (8%) fatal AEs in the *KRAS* WT group compared with 6 (10%) in the MT group. The fatal AEs in the *KRAS* WT group were death (unknown cause), haematemesis, hepatic failure, intestinal

**Table 3** Grade 3/4 adverse events (AEs) of interest by Medical Dictionary for Regulatory Activities (MedDRA) term, irrespective of causality

Event, n (%)	Panitumumab plus FOLFIRI	
	Overall (n = 154)	<i>KRAS</i> WT (n = 86)
Any grade 3/4 AE of interest	97 (63)	63 (73)
Integument toxicity	55 (36)	29 (34)
Skin toxicity	48 (31)	25 (29)
Diarrhoea	37 (24)	20 (23)
Vascular toxicity	27 (18)	15 (17)
Nail toxicity	16 (10)	9 (10)
Stomatitis/oral mucositis	12 (8)	6 (7)
Hypomagnesaemia	6 (4)	4 (5)
Cardiac toxicity	4 (3)	4 (5)
Eye toxicity	4 (3)	2 (2)
Hair toxicity	4 (3)	1 (1)
Pulmonary toxicity	4 (3)	1 (1)
Hypocalcemia	2 (1)	0 (0)
Cheilitis	0 (0)	0 (0)
Infusion-related reaction <sup>a</sup>	0 (0)	0 (0)

WT wild type

<sup>a</sup> Infusion reactions reported as an AE; 1 grade 3 infusion reaction occurred in the *KRAS* WT group that met the Common Toxicity Criteria for Adverse Events (CTCAE) definition

obstruction, multi-organ failure, rectal haemorrhage, and septic shock; in the *KRAS* MT group the fatal AEs were mCRC (2 patients), death (unknown cause), general health deterioration, subileus, and vena cava thrombosis.

Overall, 29% of patients had AEs leading to discontinuation of any study drug; 20% had treatment-related AEs leading to discontinuation of any study drug. A higher proportion of patients in the *KRAS* MT (29%) versus WT (22%) groups had AEs leading to panitumumab discontinuation; the most frequently reported were skin-related toxicities [e.g rash (5%), acne (2%), paronychia (2%), and folliculitis (1%)]. Similar proportions of patients in the *KRAS* WT (21%) versus MT (20%) groups had AEs leading to chemotherapy discontinuation; AEs included diarrhoea (3%), paronychia (3%), and acne, catheter-related infection, fatigue, pulmonary embolism, and stomatitis (all 1%).

## Discussion

This is the first study to investigate the effect of tumour *KRAS* status on response to first-line panitumumab plus FOLFIRI treatment. As seen in recent phase III mCRC studies (Douillard et al. 2010; Peeters et al. 2010), panitumumab efficacy appears to be limited to patients with

*KRAS* WT tumours. As expected, outcomes for patients with *KRAS* MT mCRC were less favourable. However, without a concurrent control group, we cannot definitively determine if this additional efficacy is due to panitumumab. Nonetheless, these results are consistent with those from the CRYSTAL trial where the likelihood of OR significantly improved with cetuximab–FOLFIRI versus FOLFIRI alone ( $P = 0.004$ ) (Van Cutsem et al. 2009). Patients with *KRAS* WT status receiving cetuximab–FOLFIRI were also more likely to respond than those with MT status in this trial (59% vs. 36%;  $P = 0.03$ ). Although cross-trial comparisons are difficult, efficacy outcomes in this study are consistent with those previously reported for cetuximab in combination with irinotecan- (Van Cutsem et al. 2009) or oxaliplatin-based chemotherapy in the first-line setting (Bokemeyer et al. 2009). In the present study, the OR rate in the *KRAS* MT group (38%) is comparable with that for patients treated with FOLFIRI alone [39% (Saltz et al. 2000) and 35% (Douillard et al. 2000) with bolus or infusional 5-FU, respectively], in line with previous reports that there is no benefit of adding panitumumab to FOLFIRI in this population. On the other hand, and in contrast to when combined with FOLFOX (Douillard et al. 2010), EGFR antibodies plus FOLFIRI do not produce inferior outcomes in patients with *KRAS* MT tumours. However, the predictive versus prognostic value of *KRAS* cannot be distinguished in this study. The R0 resection rate (7%) in this study is similar to that reported for cetuximab plus FOLFIRI in the first-line setting (6%) (Van Cutsem et al. 2009). As expected, R0 resections were more common in patients with liver-only metastases at baseline (15% overall; 19% in the *KRAS* WT group). Demographics and baseline disease characteristics in the present study were as expected and representative of a first-line mCRC population. Of note, the *KRAS* ascertainment rate was 94% and distribution of *KRAS* status was in line with previous reports (Lièvre et al. 2006; Di Fiore et al. 2007; Santini et al. 2008; Amado et al. 2008; Yen et al. 2009; Douillard et al. 2010; Peeters et al. 2010).

Safety data from the present study were as expected for an anti-EGFR inhibitor plus irinotecan-based chemotherapy in this setting (Van Cutsem et al. 2009). Diarrhoea is often associated with panitumumab and chemotherapy treatment and overall, was the most frequently reported grade 3/4 AE in this study, although it was generally manageable. Other common grade 3/4 AEs in the *KRAS* WT group included neutropenia, acne, rash, pulmonary embolism, and paronychia. Skin toxicities are a common side effect of anti-EGFR therapy (Segaert and Van Cutsem 2005) and the incidence of skin toxicities in this study appear similar to previous reports for EGFR inhibitors in mCRC (Cunningham et al. 2004; Saltz et al. 2004; Koo et al. 2007; Sobrero et al. 2008; Bokemeyer et al. 2009; Raoul et al.

2009; Van Cutsem et al. 2009; Douillard et al. 2010; Peeters et al. 2010). However, cross-trial comparisons can be hindered by different ways of reporting such AEs and by the use of different CTC grading criteria (modified v3.0 in the present study vs. v2.0 in previous reports). Overall, 5% of patients discontinued the study due to an AE; no notable differences were observed between *KRAS* groups. In line with previous panitumumab studies (Douillard et al. 2010; Peeters et al. 2010; Van Cutsem et al. 2007), infusion reactions were rare, likely due to the fully human structure of this antibody therapy.

In conclusion, panitumumab plus FOLFIRI was an effective first-line treatment for patients with *KRAS* WT mCRC. The efficacy and safety of panitumumab was similar to that observed with cetuximab plus irinotecan-based chemotherapy in the first-line setting. Panitumumab plus FOLFIRI may, therefore, represent a useful option for the first-line treatment of patients with *KRAS* WT mCRC. Further analyses to determine the effect of other potential biomarkers (BRAF, NRAS, PIK3CA and PTEN) on OR are ongoing.

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**Conflict of interest** CHK has acted as a consultant/advisor to Amgen Ltd, Merck KG Darmstadt & Roche Ltd; HL has acted as a consultant/advisor for Amgen Ltd & Roche Ltd; RH, JT & MK have received honoraria from Amgen Ltd, JT has also received research funding and MK has also acted as an advisor for this company; EG & LDC are employees of Amgen Ltd and also own shares in this company.

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