

# Panitumumab: the evidence for its use in the treatment of metastatic colorectal cancer

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**Abstract:** Panitumumab is the first fully human monoclonal antibody to Epidermal Growth Factor Receptor (EGFR) to enter clinical trials for the treatment of solid tumors. The anti-tumor activity of panitumumab has been tested *in vitro* and *in vivo*, and inhibition of tumor growth has been observed in numerous cancer models, particularly lung, kidney and colorectal (CRC). Preclinical and clinical studies have established a role for panitumumab in metastatic colorectal cancer (mCRC) refractory to multiple chemotherapeutic regimens. Based on these encouraging findings, panitumumab was approved by the US Food and Drug Administration for the treatment of patients with epidermal growth factor receptor-expressing mCRC refractory to fluoropyrimidine-, oxaliplatin-, and/or irinotecan-containing chemotherapeutic regimens. The improvement in progression free survival (PFS) and response rate (RR) produced by panitumumab monotherapy was significantly greater in patients with non mutated (wild-type) K-RAS than in those with mutant K-RAS. Therefore implementing routine K-RAS screening and limiting the use of EGFR inhibitors to patients with wild-type K-RAS appears the better strategy for select only the patients who could benefit from the therapy with panitumumab and also may have the potential for cost savings. The purpose of this review was to evaluate the patient-related, disease-related and economic-related evidence for the use of panitumumab in the treatment of metastatic colorectal cancer in clinical practice.

**Keywords:** colorectal cancer, EGFR; K-RAS, panitumumab

## Core Evidence clinical impact summary for [Panitumumab for metastatic colorectal cancer]

Outcome measure	Evidence	Implications
<b>Disease-oriented evidence</b>		
Phase I-II studies	Panitumumab was well tolerated, and no human anti-human antibody formation or infusion-related reactions were observed. Moreover, the use of panitumumab increased overall response rate and seemed to improve PFS and OS.	Panitumumab was evaluated in phase III trials in patients with relapsed or refractory metastatic CRC.
Phase III	Panitumumab significantly improved overall response rate, PFR and OS in mCRC pretreated patients.	Panitumumab monotherapy received FDA approval for the treatment of metastatic colorectal cancer with disease progression while receiving or after receiving fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy regimens.

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Patient-oriented evidence		
K-RAS	Clinical efficacy of panitumumab therapy is restricted to patients with wild-type K-RAS tumors. There was no evidence of benefit in patients with mutated K-RAS tumors.	K-RAS genotyping of tumors should be strongly considered to select patients being treated with panitumumab.
Skin Toxicity	The development of skin toxicity during panitumumab monotherapy has been significantly linked with higher response rate and longer survival.	Skin toxicity cannot be used to select patients and it could be useful in the clinical practice to identify patients who may derive greater benefit from panitumumab treatment.
Economic evidence		
Role of K-RAS testing in clinical practice.	Screening could cost several thousand dollars per patient and still result in a lower overall cost of care, based on very conservative estimates of the cost reduction associated with treatment avoidance in patients with K-RAS mutations.	Implementing routine K-RAS screening and limiting the use of EGFR inhibitors to patients with wild-type K-RAS actually appears the better strategy for selecting only the patients who could benefit from the therapy with panitumumab and also may have the potential for cost savings.

## Introduction

The most recent improvements in the treatment of mCRC have derived from the development of targeted therapy toward cell surface receptors and their associated intracellular second-messenger systems. Targeted therapy against tumors is an attractive therapeutic strategy in the treatment of human malignancies, complementing currently available chemotherapeutic agents and avoiding overlapping toxicities, as well as potentially improving clinical response rates and patient survival.

Recently, EGFR has been validated as a therapeutic target in several human tumors, including colorectal cancer (CRC).

In fact, overexpression or dysregulation of EGFR has been reported in several solid tumors and it is associated with tumor cell proliferation, invasion, distant metastasis, angiogenesis, antiapoptosis, and resistance to chemotherapy or radiation therapy. In CRC, EGFR is overexpressed in 60%–80% of tumors, and the extent of EGFR expression has been shown to positively correlate with a poor prognosis.<sup>1,2</sup>

The EGFR-targeted monoclonal antibodies block the interaction between a ligand and the extracellular binding domain of EGFR, inhibiting both phosphorylation and activation of EGFR-associated kinases (such as epidermal growth factor (EGF), transforming growth factor- $\alpha$  (TGF- $\alpha$ )), causing internalization of the receptor, inhibition of cellular growth, induction of apoptosis, and decreased production of

growth factors (such as proinflammatory cytokines, vascular endothelial growth factor (VEGF)).<sup>3,4</sup>

Both monoclonal antibodies and small molecules inhibitors of the tyrosine-kinase of EGFR have been evaluated in the treatment of solid tumors, including CRC, non-small cell lung cancer, squamous cell carcinoma of the head and neck.<sup>5</sup> Currently, two monoclonal antibodies targeting the EGFR, cetuximab and panitumumab, are commercially available for the treatment of mCRC.

## Panitumumab

Panitumumab, formerly known as ABX-EGF, is a fully human IgG2 monoclonal antibody targeting EGFR and developed using XenoMouse (Abgenix, Fremont, CA, USA) technology. *In vitro*, panitumumab has been found to have high binding affinity to EGFR, competitively blocking binding of EGF and TGF- $\alpha$  to the receptor and leading to internalization of the receptor-antibody complex. This prevents ligand-induced EGFR-tyrosine autophosphorylation and subsequent activation of key downstream signaling molecules involved in carcinogenesis. This leads to antitumor effects by promoting apoptosis and inhibiting cell proliferation, growth and angiogenesis.<sup>6,7</sup>

Since it is the first fully human monoclonal antibody, the risk of hypersensitivity reactions with panitumumab is reduced, and this may be important for long-term administration.<sup>8</sup>

Table 1 Summary of clinical trials regarding panitumumab

Study/ reference	Number of patients	Tumor types	Dosing	EGFR expression	Results
<b>Phase I trials</b>					
Figlin et al <sup>12</sup>	43	Advanced renal, prostate, NSCLC, pancreatic, esophageal, CRC	0.01–2.5 mg/kg weekly	NR	SD = 1 (esophageal) SD = 1 (colorectal) MR = 1 (prostate) PR = 5 (CRC) SD = 18 MR = 1 (prostate)
Weiner et al <sup>13</sup>	96	Advanced CRC, lung, pancreatic, prostate, renal, esophageal/gastroesophageal and anal cancer	0.01–5 mg/kg weekly 6 mg/kg every 2 weeks 9 mg/kg every 3 weeks	I+ EGFR expression in $\geq 10\%$ of tumor cells	
<b>Phase II trials</b>					
Malik et al <sup>14</sup>	148	Metastatic CRC	2.5 mg/kg weekly	Cohort A: 2+ or 3+ in $\geq 10\%$ cells  Cohort B: sum of 1+, 2+, 3+ in $\geq 10\%$ cells, but sum of 2+, 3+ in $< 10\%$ of cells $\geq 10\%$ EGFR expression in tumor cells	PR (n = 11) TTP = 3.4 mo OS = 10 mo PR (n = 4) TTP = 2.1 mo OS = 9.4 mo PR = 3 SD = 8 PD = 19
Berlin et al <sup>15</sup>	39	Metastatic CRC		low (1%–9% cells) negative ( $< 1\%$ cells) low + negative	PR = 1 PR = 2 SD = 7
Hecht et al <sup>16</sup>	23	Metastatic CRC	6 mg/kg every 2 weeks	EGFR expression positive in $\geq 10\%$ cells	Part 1: PR = 9 SD = 5 Part 2: PR = 8 SD = 11
Hecht et al <sup>17</sup>	Part 1: 19  Part 2: 23	Metastatic CRC	Part 1: 2.5 mg/kg weekly combined with IFL  Part 2: 2.5 mg/kg weekly combined with FOLFIRI		
<b>Phase III trials</b>					
Van Cutsem et al <sup>18</sup>	463	Metastatic CRC	Arm A: panitumumab 6 mg/kg every 2 weeks  Arm B: no panitumumab, BSC only	EGFR expression in $\geq 1\%$ tumor cells	Arm A: PR = 22 SD = 62 Median PFS = 8 weeks Arm B: PR = 0 SD = 23 Median PFS = 7, 3 weeks PR = 19 SD = 58 CR = 1 Median PFS = 9, 4 weeks
Van Cutsem et al <sup>19</sup>	176	Metastatic CRC	6 mg/kg every 2 weeks	EGFR expression in $\geq 1\%$ tumor cells	

(Continued)

Table 1 (Continued)

Study/ reference	Number of patients	Tumor types	Dosing	EGFR expression	Results
Hecht et al <sup>20</sup>	1053	Metastatic CRC (first-line treatment)	This trial evaluated panitumumab (6 mg/kg every 2 weeks) added to bevacizumab and chemotherapy (oxaliplatin- or irinotecan-based)	NR	Median PFS was 10.0 and 11.4 months for the panitumumab and control arms, respectively. Median survival was 19.4 months and 24.5 months for the panitumumab and control arms, respectively. The addition of panitumumab to bevacizumab and oxaliplatin- or irinotecan-based chemotherapy results in increased toxicity and decreased PFS.
Douillard et al <sup>21</sup>	1183	Metastatic CRC (first-line treatment)	Arm 1: FOLFOX + panitumumab 6 mg/kg every 2 weeks Arm 2: FOLFOX alone	NR at entry	PFS in Wild-Type K-RAS pts: Arm 1: 9, 6 months Arm 2: 8 months PFS in Mutated K-RAS pts: Arm 1: 7, 3 months Arm 2: 8, 8 months
Peeters et al <sup>22</sup>	1186	Metastatic CRC (second-line treatment)	Arm 1: FOLFIRI + panitumumab 6 mg/kg every 2 weeks Arm 2: FOLFIRI alone	NR at entry	PFS in Wild-Type K-RAS pts: Arm 1: 5, 9 months Arm 2: 3, 9 months PFS in Mutated K-RAS pts: Arm 1: 5 months Arm 2: 4, 9 months

**Abbreviations:** CR, complete response; FOLFIRI, fluorouracil, leucovorin, irinotecan (infusional); PR, partial response; IFL, irinotecan, fluorouracil, leucovorin (bolus); MR, minor response; FOLFOX, fluorouracil, leucovorin, oxaliplatin (infusional); SD, stable disease; NSCLC, non-small-cell lung cancer; PD, progressive disease; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; NR, not required; PFS, progression-free survival; TTP, time to progression.

Panitumumab induces cell-cycle arrest in the G0–G1 interphase, whereas cetuximab causes arrest in the G1 phase. Unlike cetuximab, panitumumab does not induce antibody-dependent cellular cytotoxicity.<sup>9,10</sup>

Panitumumab was initially studied as a single agent in previously treated patients with metastatic colorectal cancer and showed promising antitumor responses and minimal adverse effects, offering an alternative to cetuximab as a second- or third-line treatment option for patients with metastatic colorectal cancer who have failed prior therapies.

## Disease-oriented evidence

### Phase I and II studies

Panitumumab has been evaluated in clinical trials both as monotherapy and in combination with other agents for the treatment of solid tumors, including colorectal and kidney cancer (Table 1).<sup>11</sup>

A phase I trial by Figlin et al<sup>12</sup> using doses ranging from 0.1 mg/kg up to 2.5 mg/kg was performed in 43 patients with several tumor types (renal = 10; prostate = 3; non-small-cell lung cancer = 7; pancreatic = 3; esophageal = 3 and CRC = 7). Patients received up to 4 weekly doses, and those experiencing response or stable disease (SD) were eligible to continue to receive treatment every other week for 6 additional months or until disease progression. Biologic activity was seen even with low doses, including one patient with esophageal cancer treated with the lowest dose that had SD for 7 months. A partial response (PR) of 10 months was seen in one patient with CRC treated with 2.5 mg/kg. The incidence of skin rash in patients receiving 2.0 or 2.5 mg/kg approached 100%. Overall, panitumumab was well tolerated and no allergic reactions, infusion-related or serious adverse events were observed.

Weiner et al<sup>13</sup> updated these data in with another phase I trial. 96 patients were enrolled and treated (CRC = 39, lung = 14, pancreatic = 3, prostate = 21, renal = 15, esophageal = 3 and anal cancer = 1). Sequential cohorts were enrolled to receive four infusions of panitumumab monotherapy at different dose levels ranging from 0.01 to 5.0 mg/kg once per week, 6.0 mg/kg every 2 weeks and 9.0 mg/kg every 3 weeks. Grade 3 or 4 related adverse events were noted in 10% of patients, with grade 3 skin-related effects being the most frequent (7% of patients). No maximally tolerated dose was reached and no infusion-related reactions were observed. Furthermore, five of the 39 CRC patients achieved a PR.

After the favourable response rate observed among patients with CRC participating in these studies, panitumumab

was evaluated in phase II trials in patients with relapsed or refractory metastatic CRC (Table 1).

One study included patients who had failed therapy with a fluoropyrimidine (with or without leucovorin) and either irinotecan or oxaliplatin, or both.<sup>14</sup> Assessment based on level of EGFR expression was also carried out and patients were enrolled into 2 cohorts. Patient cohorts were determined by levels of EGFR expression. Cohort A (n = 105) consisted of patients with 2+ or 3+ EGFR over-expression in  $\geq 10\%$  of tumor cells. Cohort B (n = 43) included patients with the sum of 1+, 2+, and 3+ EGFR staining found in  $\geq 10\%$  of tumor cells, but with the sum of 2+ and 3+ in  $< 10\%$  of tumor cells. Patients received panitumumab 2.5 mg/kg weekly for 8 weekly cycles. Overall, 15 PR were reported: 11 (10%) in cohort A and 4 (9%) in cohort B. Median time to disease progression and median survival were 3.4 months and 10 months, respectively, for cohort A, and 2.1 months and 9.4 months, respectively, for cohort B.

In another phase II trial performed by Berlin et al<sup>15</sup> panitumumab monotherapy was evaluated in patients with mCRC failing at least two previous regimens with a fluoropyrimidine, irinotecan, and oxaliplatin. Panitumumab was administered at 6 mg/kg intravenously every 2 weeks until disease progression occurred. Primary endpoints were: objective RR; response duration; PFS; and survival time. The secondary endpoint was tolerability. Assessment based on level of EGFR expression was also carried out, and all patients were required to have EGFR staining of  $\geq 10\%$  tumor cells on immunohistochemistry (IHC).

An interim analysis in May 2005 included 39 patients eligible for efficacy evaluation following  $\geq 20$  weeks of treatment and 91 patients available for tolerability analysis after receiving at least 1 dose of panitumumab. At week 16, 3 (8%) patients had PR, 8 patients (21%) achieved SD, and 19 patients (49%) experienced disease progression. Nine patients (22%) were not assessable. Integument toxicities included skin (96%), nail (30%), cheilitis (7%), and hair (5%). Eye toxicity occurred in 85% of patients; diarrhea, in 27% (3 with grade 3); and hypomagnesemia, in 12% (3 with grade 3 or grade 4). Grade 3 hypersensitivity reaction occurred in 1 patient and resolved with treatment. This study plans a total enrollment of 300 patients.<sup>15</sup>

Moreover, the results of another study showed, in patients with low or negative EGFR staining, a response rate of approximately 5%.<sup>16</sup>

Panitumumab was also evaluated in combination with fluorouracil/leucovorin and irinotecan (IFL or FOLFIRI

regimens) for first-line treatment of metastatic colorectal cancer. Part 1 of the study included patients who received panitumumab with IFL ( $n = 19$ ), and part 2 included patients who received panitumumab with FOLFIRI ( $n = 24$ ). Eligibility criteria included no prior chemotherapy and EGFR positivity ( $\geq 10\%$ ). Panitumumab was administered weekly at a dose of 2.5 mg/kg over one hour. Due to unacceptable toxicity in part 1 (58% grade 3 or grade 4 diarrhea), the study was modified to evaluate panitumumab in combination with FOLFIRI (part 2).

No complete responses were observed. The investigators reported 9 (47%) patients with PR and 5 (26%) with SD for part 1 of the study. Among patients enrolled in part 2, there were 8 (33%) with PR and 11 (46%) with SD. Median PFS was 5.6 months and 10.9 months for parts 1 and 2, respectively. Median survival for patients enrolled in part 1 was 16.8 months. Survival data were not available for patients enrolled in part 2; however, 23 out of 24 patients were alive at the time of analysis.<sup>17</sup>

### Phase III studies

Based on the encouraging clinical outcomes of the above mentioned phase II trials, a pivotal, randomized, controlled phase III trial conducted in Europe, Australia, and Canada was performed, in order to compare panitumumab 6 mg/kg intravenously every 2 weeks plus best supportive care (BSC) versus best supportive care alone. The aim of this study was to show the significant difference in PFS. A total of 463 patients were enrolled ( $n = 231$  receiving panitumumab plus BSC and  $n = 232$  receiving BSC alone). Eligible patients had metastatic colorectal cancer ( $\geq 1\%$  EGFR-positive tumor cells) and documented progressive disease during treatment or within 6 months of completing treatment with a fluoropyrimidine, irinotecan, and oxaliplatin.

Patients in the best supportive care group experiencing progressive disease could receive panitumumab in a cross-over study. This study was designed to be able to detect a 33% difference in PFS, but the results far exceeded this with a risk reduction of 46%, statistically significant with  $P < 0.000000001$ . The overall response rate was 36% versus 10% (control) with a median duration of response of 17 weeks in the control arm. At 6 months, PFS was 18% versus 5% and this difference was maintained at 8 months: 10% versus 4%. Although no difference has been noted in overall survival, this is likely to have been confounded by the fact that 75% of those on the best supportive care arm crossed over to panitumumab with impressive results. Of the

174 patients who crossed over to the treatment arm, there was a 9% PR and 32% with SD.

The most common toxicities reported were skin toxicities, hypomagnesemia, and diarrhoea. Skin reaction occurred in 90% of patients receiving panitumumab and consistent with other reports, an association between severe rash and greater clinical efficacy was observed. As expected with fully human antibodies, panitumumab had a low frequency of infusion-related reactions and no antibody formation. An open-label extension study showed similar results for those patients initially receiving best supportive care who later received panitumumab therapy. Based on these results, panitumumab monotherapy received FDA approval for the treatment of metastatic colorectal cancer with disease progression while receiving or after receiving fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy regimens.<sup>18,19</sup>

The role of panitumumab in combination with anti-angiogenic drugs has also been explored in a randomized phase III study (Panitumumab Advanced Colorectal Cancer Evaluation, (PACCE)). In this trial patients with mCRC were randomly assigned for first-line treatment within each chemotherapy cohort (823 patients oxaliplatin- and 230 irinotecan-based) to bevacizumab and chemotherapy with or without panitumumab 6 mg/kg every 2 weeks. Most patients received oxaliplatin-based chemotherapy. The primary end-point was PFS within the oxaliplatin cohort. The results of the study were negative, as the combination of panitumumab with bevacizumab and chemotherapy resulted in a decrease of PFS and in excessive toxicity, particularly diarrhoea, infections and pulmonary embolism. The results were consistent in both the oxaliplatin and irinotecan cohorts. Moreover, as demonstrated previously, the triple combination did not provide additional benefit in the K-RAS wild-type population treated with panitumumab.<sup>20</sup>

Recently, two large, randomized, phase III trials, were presented at 2009 Joint ECCO/ESMO Multidisciplinary Congress in Berlin, Germany.<sup>21,22</sup>

The PRIME trial was a multicenter, randomized, phase III study performed by Douillard et al<sup>21</sup> in order to analyze the safety and efficacy of first-line treatment with panitumumab plus FOLFOX versus FOLFOX alone in mCRC according to K-RAS status.

Patients were randomized 1:1 to receive 6 mg/kg of panitumumab plus FOLFOX every 2 weeks (Arm 1) versus FOLFOX alone (Arm 2). The primary endpoint was PFS. The study randomized a total of 1183 patients, with 593 in Arm 1 and 590 in Arm 2. K-RAS results were obtained for 93% of patients: 60% were K-RAS wild-type and 40% were

Table 2 Summary of clinical trials regarding panitumumab

Protocol IDs	Title	Design	Status	Trial description
CTRU-PICCOLO-MO-05-7289	Phase III Randomized Study of Irinotecan Hydrochloride With Versus Without Panitumumab or Cyclosporine in Patients With Fluorouracil-Resistant Advanced or Metastatic Colorectal Cancer	Phase III, Randomized	Active	Arm I: Patients receive irinotecan on day 1. Arm II: Patients receive irinotecan on day 1 and oral cyclosporine three times a day on days 1–3. Arm III: Patients receive panitumumab followed by irinotecan on day 1. Single-agent panitumumab may be continued during breaks in chemotherapy treatment. The primary objective of this study is to compare the effect of panitumumab versus cetuximab on overall survival (OS) for chemorefractory metastatic colorectal cancer (mCRC) among subjects with wild-type Kirsten rat Sarcoma-2 virus (KRAS) tumors.
20080763	ASPECTT: A Study of Panitumumab Efficacy and Safety Compared to Cetuximab in Subjects With KRAS Wild-Type Metastatic Colorectal Cancer	Phase III, Randomized	Active	Arm 1: FOLFIRI + Panitumumab Arm 2: FOLFIRI + Bevacizumab
20060141	SPRITT – Second-Line Panitumumab Irinotecan Treatment Trial	Phase II, Randomized	Active	Arm I: erlotinib once daily on days 1–14, panitumumab on day 1, and irinotecan on day 1. Treatment repeats every 2 weeks in the absence of disease progression or unacceptable toxicity.
NU-0714	Phase II Randomized Study of Erlotinib Hydrochloride and Panitumumab With Versus Without Irinotecan Hydrochloride as Second-Line Therapy in Patients With Metastatic Colorectal Cancer	Phase II, Randomized	Active	Arm I: erlotinib once daily on days 1–14 and panitumumab on day 1. Treatment repeats every 2 weeks in the absence of disease progression or unacceptable toxicity. Upon disease progression, patients receive irinotecan hydrochloride as in Arm I. Arm II: Patients receive erlotinib and panitumumab as in Arm II.
20070509	PEAK: A Phase 2 Study of Panitumumab Plus mFOLFOX6 vs Bevacizumab Plus mFOLFOX6 for First Line Treatment of Metastatic Colorectal Cancer Subjects With Wild-Type KRAS Tumors	Phase II	Active	The primary objective of this study is to estimate the treatment effect on progression-free survival (PFS) of panitumumab relative to bevacizumab in combination with mFOLFOX6 chemotherapy as first-line therapy in subjects with tumors expressing wild-type KRAS, unresectable mCRC.
08-287	Panitumumab in Cetuximab Refractory KRAS Wild-Type Colorectal Cancer	Phase II	Active	The purpose of this research study is to learn whether panitumumab helps treat colorectal cancer in participants who have not responded to treatment with cetuximab.
TTD-08-04	Safety and Efficacy Study of FOLFOX4 + Panitumumab vs FOLFIRI + Panitumumab in Subjects WT KRAS Colorectal Cancer and Liver-only Metastases	Phase II	Active	The purpose of the study is to evaluate the efficacy and safety of the combination of Panitumumab with FOLFOX4 Chemotherapy or Panitumumab with FOLFIRI Chemotherapy in Subjects with Wild-Type KRAS Colorectal Cancer and liver-only Metastases.
BrUOG-CR-218	Panitumumab and Bevacizumab Maintenance After First-Line FOLFOX-Bevacizumab for Patients With Advanced Colorectal Cancer With Wild-Type Ras	Phase II	Active	Bevacizumab given at 7.5 mg/kg every 3 weeks until disease progression. Panitumumab given at 9 mg/kg every 3 weeks until disease progression. Primary Objective: To determine the safety of every 3 week panitumumab and bevacizumab as maintenance therapy for patients with metastatic colorectal cancer.

mutant. Wild-type K-RAS patients had a median PFS and response rate of 9.6 months and 55% in Arm 1, and 8 months and 48% in Arm 2, respectively.

Patients with mutated K-RAS had a median PFS of 7.3 months in Arm 1 and 8.8 months in Arm 2. Moreover, response rate was improved in patients with Wild-type K-RAS tumors (55% vs 48%) and at interim analysis, OS seemed to be significantly improved in patients with Wild-type K-RAS tumors, although additional follow-up is required. Adverse events were similar across the two arms except for those that were associated with anti-EGFR therapy. Final results confirmed the importance of K-RAS as a predictive biomarker in the setting of first-line mCRC treatment with EGFR inhibitors.<sup>21</sup>

The second study, performed by Peeters et al was a randomized, phase III study that evaluated the efficacy and safety of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) versus FOLFIRI alone as second-line treatment for mCRC. Patients enrolled in the study were randomized to receive panitumumab 6 mg/kg every 2 weeks plus FOLFIRI (Arm 1) versus FOLFIRI alone (Arm 2). Patients had metastatic colorectal adenocarcinoma; documented disease progression 6 months or less after 1 prior therapy with fluoropyrimidine for mCRC, and ECOG score of 0–2. The evaluation of PFS and OS by K-RAS mutational status were the primary endpoints in the study. A total of 1186 patients were randomized (Arm 1 = 591; Arm 2 = 595). Of all patients, 1803 (91%) were evaluable for K-RAS, with 598 (55%) being wild-type and 485 (45%) mutated. PFS was longer in wild-type K-RAS patients who were in Arm 1 versus Arm 2 (5.9 vs 3.9 months), but was similar in K-RAS mutated patients (5.0 vs 4.9 months). A similar trend was seen with OS in wild-type and mutated patients when Arm 1 was compared to Arm 2 (wild-type, 14.5 vs 12.5 months; mutated, 11.8 vs 11.1 months). With regard to safety, panitumumab was well-tolerated with a manageable toxicity profile.<sup>22</sup>

## Ongoing clinical trials

The study of panitumumab in CRC proceeds in a number of ongoing clinical trials. Current studies under way are evaluating panitumumab in combination with other chemotherapeutic drugs or with novel agents that have to come into common clinical practice. These trials will further define the role of panitumumab in CRC (Table 2).<sup>23</sup>

## Patient-oriented evidence EGFR expression

Due to the mechanism of action of panitumumab, positive EGFR protein expression, as determined by

immunohistochemistry (IHC), was initially selected as an entry criterion for several studies evaluating EGFR inhibitors. In this setting, data on the use of EGFR expression as a predictive biomarker of response to panitumumab therapy, showed controversial results. Two trials revealed a positive correlation between EGFR expression and response to panitumumab. In the first, Meropol et al<sup>24</sup> enrolled 100 patients with metastatic colorectal cancer (mCRC) to evaluate panitumumab as monotherapy after failure of treatment with fluoropyrimidine plus irinotecan or oxaliplatin or both. Patients were eligible if  $\geq 10\%$  of the tumor cells had EGFR overexpression of 2+ or 3+ by IHC. 13% of patients had a PR, and their tumor cells had 3+ EGFR expression; 39% of patients had a SD. Furthermore, panitumumab monotherapy was also evaluated in 300 patients with mCRC enrolled in a phase II trial after a disease progression despite treatment with fluoropyrimidine, irinotecan, and oxaliplatin-based chemotherapy. One of the inclusion criteria, was EGFR staining of  $\geq 10\%$  tumor cells on IHC. 8% of patients had PR, 21% achieved SD, and disease progression was seen in 49% of patients.<sup>15</sup>

Controversial data were reported by Malik and Hecht in two separate trials.<sup>24,25</sup>

Malik et al conducted a phase II study enrolling two cohorts of patients with mCRC who failed chemotherapeutic regimens containing fluoropyrimidine plus irinotecan, oxaliplatin, or both.<sup>14</sup> Cohort A consisted of patients with 2+ or 3+ EGFR over-expression in  $\geq 10\%$  of tumor cells and cohort B included patients with the sum of 2+ and 3+ in  $< 10\%$  of tumor cells. PR was observed in 10% of patients (cohort A, 10%; cohort B, 9%). Overall median time to disease progression was 2.5 months (95% CI, 2–4) (cohort A, 3.4 months (95% CI, 2–4); cohort B, 2.1 months (95% CI, 2–4.5). Overall median survival time was 9.4 months (95% CI, 6.6–10.6) (cohort A, 10 months [95% CI, 6.2–11]); cohort B, 9.4 months [95% CI, 6–10.6]). Although no statistical analysis was performed to evaluate the differences between low and high EGFR-expressing tumors the response rates, time to disease progression, and survival time appeared similar irrespective of the level of EGFR expression.

Hecht et al conducted a phase II trial to assess response rates in patients with low (1%–9% of tumor cells) or negative ( $< 1\%$  of tumor cells) EGFR staining on IHC.<sup>25</sup> The study enrolled patients with documented mCRC disease progression during or after 2 to 3 regimens of fluoropyrimidine, irinotecan, and oxaliplatin treatment. 7% of all patients had a PR (low EGFR expression, 8%; negative EGFR expression, 6%). 29% of all patients had SD (low EGFR expression,



29%; negative EGFR expression, 31%), and disease control was observed in 37% (low EGFR expression, 39%; negative EGFR expression, 37%). The median time to response was 9 weeks overall and in patients with low and negative EGFR expression, with a minimum of 7 weeks and a maximum of 12 weeks. Median duration of response was 20 weeks (range, 8–46 weeks) overall. The duration of response was longer in patients with negative EGFR expression: 31 weeks (range, 16–46 weeks) compared with 20 weeks (range, 8–20 weeks) in patients with low EGFR expression. Median PFS was 8 weeks overall (95% CI, 7–11) (low EGFR expression, 8 weeks (95% CI, 7–13); negative EGFR expression, 7 weeks (95% CI, 7–14)).

Objective responses have been observed in patients with low or negative, as well as high, EGFR protein expression, thus suggesting that efficacy of panitumumab may not depend on the level of EGFR expression. Although immunohistochemistry is widely used, its usefulness in predicting the clinical benefit of panitumumab appears limited, probably because of several factors like the absence of a standardized scoring system and the variety on EGFR expression. Therefore, on this basis, the detection of positive EGFR expression actually does not reliably predict clinical outcome and requires further validation before incorporation into clinical practice.

## EGFR findings: affinity, phosphorylation, mutations and polymorphisms

Several studies investigating other potential predictive biomarkers to EGFR inhibitors response are ongoing. Some of these, studied EGFR findings as low or high affinity or presence of phosphorylation to explain the variability of response to EGFR targeted therapy. In this setting, data exist for patients receiving cetuximab while actually we have no elements on panitumumab. Using a specific ligand binding assay, Francoual et al<sup>26</sup> found that many tumors contain both low- and high-affinity EGFRs: 78% of 82 tumor specimens contained only high-affinity binding sites and 22% had both low- and high-affinity sites.

EGFR phosphorylation status may reflect the level of receptor utilization by the tumor and this parameter was associated with clinical response in patients treated with cetuximab-based therapy. Patients with an activated or phosphorylated EGFR score, as indicated by an immunohistochemistry-based visual score of 7 or greater, were almost twice as likely to have disease control (objective response or stable disease) than those with a score of less than 7 (100% vs 54%;  $P = 0.05$ ).<sup>27</sup>

EGFR mutations in mCRC account for less than 1% of tumors, therefore this measure is unlikely to be valid as a marker.<sup>28</sup> Moreover, EGFR mutations that are associated with responses to tyrosine-kinase inhibitors in non-small cell lung cancer are not present in mCRC.<sup>29,30</sup>

Moroni et al detected one mutation (3.2%) among 31 patients with mCRC,<sup>31</sup> occurring in a patient who achieved SD for 24 weeks with cetuximab and chemotherapy treatment. This missense heterozygous mutation in exon 21 (Gly857Arg) affected a residue located within the activation loop of the EGFR catalytic domain and was one amino acid away from the Leu858Arg-activating mutation that has been identified in patients with lung cancer who respond to gefitinib or erlotinib.<sup>32</sup> At disease progression, the patient whose tumor had this mutation was treated with gefitinib; this molecular alteration in EGFR was not associated with clinical response because the disease progressed after 4 weeks of treatment.

Notably, a specific polymorphism of EGFR affecting exon 13 at residue 521 Arg/Arg (previously identified as residue 497, rs11543848) has been linked with improved overall survival in women with metastatic colorectal cancer (vs Lys/Lys and/or Lys/Arg variants), although the reverse pattern was observed in men with this disease.<sup>33</sup> This same polymorphism has been linked to cetuximab response in other studies<sup>34–36</sup> while conflicting evidence also exists for a polymorphism affecting the ligand of EGFR, EGF, at position 61 (rs4444903).<sup>35–38</sup> About panitumumab, data in this setting are related to recently analyses. Carcereny et al studied a cohort of 84 mCRC patients receiving cetuximab or panitumumab. A single nucleotide polymorphism (SNP) at codon 497 (497 G/A) was associated with worse RR, PFS and OS, and therefore could be a resistance factor.<sup>39</sup> More recently a retrospectively analyses has not revealed the same conclusion of Carcereny et al. In a total of 117 patients treated with cetuximab or panitumumab, there were no significant differences on response rate (9/59; 15.2 vs 9/52; 17.3%), PFS (13.5 vs 13.2 w) and OS (33 vs 26.8 w) according to EGFR R497K (GG vs GA/AA). Despite, the predictive role of K-RAS mutational status was confirmed.<sup>40</sup> On this basis, actually we have no certain data about these EGFR findings, so further investigations need to better define their exact role in EGFR inhibitors response.

## EGFR amplification

A small proportion of colorectal tumors over-express EGFR via amplification of the gene, which can be detected by fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization.<sup>41</sup> Available data suggest that patients with less

than three EGFR gene copies per nucleus have a relatively low likelihood of responding to EGFR-targeted monoclonal antibody treatment.<sup>42-47</sup>

Despite when EGFR gene copy number was evaluated by polymerase chain reaction, no association was found between this parameter and clinical outcome of panitumumab- or cetuximab-based treatment,<sup>48,49</sup> probably because of tumor DNA dilution by DNA from normal cells during DNA extraction. However, EGFR gene copy number as analyzed by FISH or chromogenic in situ hybridization appears to be a promising biomarker of response to such treatment. In a retrospective analysis of a subgroup of patients participating in the pivotal phase III trial of panitumumab monotherapy,<sup>50</sup> the mean EGFR gene copy number per nucleus and the percentage of tumor cells with chromosome 7 polysomy (three or more EGFR signals per nucleus) were analyzed by FISH and the association between these parameters and clinical outcome was assessed. None of the patients with a mean of <2.47 EGFR gene copies per nucleus or fewer than 43% of tumor cells with chromosome 7 polysomy, respectively, achieved objective response compared with 30% of the patients ( $P = 0.001$ ) and 32% of the patients ( $P = 0.001$ ) who had values above these thresholds.

A mean EGFR gene copy number threshold of less than 2.5 copies per nucleus or fewer than 40% of tumor cells with chromosome 7 polysomy discriminated patients with shorter progression-free ( $P = 0.039$  and  $P = 0.029$ , respectively) and overall survival ( $P = 0.015$  and  $P = 0.014$ , respectively). EGFR gene copy number and chromosome 7 polysomy status did not draw a parallel with progression-free interval in patients receiving only supportive care in this study, suggesting that this parameter is not prognostic in metastatic colorectal cancer. Homogeneous (ie, 100%) chromosome 7 disomy was the most common pattern found in 58 colorectal tumors with non increased gene copy number ( $n = 26$ ; 45%). Chromosome 7 disomy is also easier to detect than an increase in EGFR gene copy number and therefore, might enable a more reproducible FISH assay. For instance, Moroni et al<sup>51</sup> found a 89% response rate in a subgroup of nine patients with colorectal cancer whose tumors had an increased EGFR gene copy number, but these investigators included a relatively high proportion of responders (9 of 29 patients; 31%) in their analysis.

In comparison with patients with normal EGFR gene copy number, patients with an increased EGFR gene copy number exhibit higher response rates to EGFR-targeted monoclonal antibodies, with a longer progression-free interval or time to progression. These results have to be confirmed by further

analyses before the incorporation of this promising parameter into clinical practice.

## EGFR ligands

Several preclinical studies have found that cetuximab decreases levels of epiregulin (ER) and amphiregulin (AR) that are two EGFR ligands even more powerful than EGF for activating EGFR. Therefore the possible predictive roles as biomarkers to selecting patients have been investigated in trials involving cetuximab.<sup>49-52</sup> All data of these studies suggest that cetuximab treated patients with high ER and AR expression levels obtained a better response rate and PFS. Recently the association of a high epiregulin gene expression with a K-RAS status wild-type seems to be more predictive of cetuximab benefit in the treatment of mCRC than these markers analyzed alone. Further studies are needed but the authors suggest that determination of epiregulin gene expression levels should be prospectively evaluated in patient selection for EGFR targeted therapy.<sup>53</sup>

## K-RAS mutations

The K-RAS protein, encoded by K-RAS, is a GTPase that regulates different signaling pathways. This protein may be active (RAS-GTP) or inactive (RAS-GDP). K-RAS mutations yield a defective GTPase activity and then an increased population of active K-RAS protein, activating signaling in two pathways, PI3K/PTEN/AKT and RAF/MEK/ERK which are involved in cell proliferation, survival and angiogenesis. K-RAS is mutated in approximately 30%–50% of colorectal cancer; the most common and clinically relevant K-RAS mutations are nonsense somatic alterations which have been described at codons 12 (about 82% of cases) and 13 (about 13% of cases) in exons 2 of the K-RAS gene; additional mutations can be found at codon 61. All these mutations are associated with cancer progression. Recent studies have revealed that mutation status of K-RAS has emerged as both an important predictor of response to EGFR inhibitors, including panitumumab, and a marker for patient selection.<sup>54</sup>

Benvenuti et al analyzed tumor K-RAS status from 48 patients with mCRC treated with panitumumab or cetuximab.<sup>55</sup> Presence of K-RAS mutations (exon 2) were detected in 33,3% of tumors and it was not significantly linked to objective response to therapy, with a trend toward a negative association with response (1 of 11 mutations versus 15 of 37 mutations for responders versus non-responders;  $P = 0.073$ ); consequently time to progression analysis showed a significantly worse outcome for subjects bearing a mutated K-RAS allele in their tumors compared with those carrying

wild-type K-RAS ( $P = 0.0443$ ). In this study the authors also found that the transfection of mutated K-RAS (G12V) into wild-type cellular models of colorectal cancer confers resistance to the treatment with cetuximab.

A confirm of K-RAS as a predictive marker to therapy with panitumumab was reported by Amado et al<sup>56</sup> in a randomized phase III trial setting. Among the 463 patients enrolled in this study, 427 (92%) were included in the K-RAS analysis. Of these 427, 184 (43%) were found to have tumors harboring mutant K-RAS. Among the 208 patients assigned to panitumumab, 17% of the 124 patients in the wild-type K-RAS subgroup achieved objective response, whereas none of the 84 patients in the mutant K-RAS subgroup responded to this treatment. Median progression-free interval among those treated with panitumumab was 12.3 weeks among those in the wild-type K-RAS subgroup and 7.4 weeks among those in the mutant K-RAS subgroup. The OS time was also longer in patients with wild-type K-RAS tumors, 8.1 months, versus 4.9 months. The hazard ratio (HR) for disease progression or death (panitumumab vs control group) was 0.45 (95% CI = 0.34 to 0.59) for panitumumab in the wild-type K-RAS subgroup, but there was no benefit of panitumumab in the mutant K-RAS subgroup (HR = 0.99, 95% CI = 0.73 to 1.36).

Similar findings in term of predictive role of K-RAS status to therapy with panitumumab were observed by Hecht et al.<sup>16</sup> In this study, 171 patient samples were available for K-RAS tumor presence. The overall response rate was significantly better in patients with wild-type K-RAS tumors (9% vs 0%). Median PFS was significantly longer in patients with wild-type K-RAS tumors than in patients with mutant K-RAS tumors (15 weeks vs 7.1 weeks, respectively). This study also demonstrated a significant benefit in terms of OS in patients with wild-type K-RAS tumors treated with panitumumab when compared with patients with mutant K-RAS tumors (13.5 months vs 7.3 months, respectively).

Freeman et al retrospectively analyzed 62 patients from three phase II studies with panitumumab in mCRC patients.<sup>57</sup> K-RAS mutation was found in 38.7% of them. In the wild-type K-RAS group, 11% of patients had a PR, 53% had SD, and 37% had progressive disease. In the mutant K-RAS group, 21% of patients had SD and 79% of patients had PD; there were no responses. The absence of a K-RAS mutation was associated with response to panitumumab (PR vs SD vs progressive disease;  $P = 0.0028$ ). The HR for wild-type versus mutant K-RAS was 0.4 (95% CI, 0.2–0.7) for progression-free survival (PFS) and 0.5 (95% CI, 0.3–0.9) for OS. Second-line treatment with panitumumab and FOLFIRI by tumor K-RAS

status in patients with mCRC was also investigated; in interim analyses, numerical significant differences in PFS (26 vs 16 weeks) and median OS (39 vs 31 weeks) in favour of patients with wild-type K-RAS were observed.<sup>58</sup>

More recently the efficacy of panitumumab by tumor K-RAS status was investigated in some phase III trials. Douillard et al enrolled 1183 patients to evaluate the efficacy of FOLFOX-4 with or without panitumumab as first line treatment in patients with mCRC (PRIME trial).<sup>21</sup> Results showed that the addition of panitumumab to chemotherapy improved RR (55% vs 48%) and PFS (9.6 vs 8.0 months; HR = 0.80; 95% CI: 0.66–0.97;  $P = 0.02$ ) in patients with wild-type K-RAS. No benefit in RR and PFS from the addition of panitumumab was noticed in patients with K-RAS mutations. Interim OS showed an improvement only for patients with wild-type K-RAS tumors (HR = 0.83,  $P = 0.16$ ).

Similar results were reported in 1186 patients enrolled in a randomized phase III study which had the aim to evaluate the association of panitumumab with FOLFIRI as second-line treatment in patients with mCRC.<sup>22</sup> In patients with wild-type K-RAS tumors, panitumumab significantly improved response rate (35% vs 10%) and PFS (median 5.9 vs 3.9 mo; HR = 0.73,  $p = 0.004$ ) when added to FOLFIRI. OS was also improved in patients with wild-type K-RAS tumors with panitumumab plus FOLFIRI (median 14.5 vs 12.5 mo; HR = 0.85,  $P = 0.12$ ).

There was no evidence of benefit in patients with mutated K-RAS tumors. In a recently randomised phase III trial which evaluated bevacizumab and chemotherapy with or without panitumumab in mCRC,<sup>20</sup> the predictive role of K-RAS status was confirmed; and progression-free interval was worse among patients with tumors carrying wild-type K-RAS (11.5 months vs 9.8 months in the panitumumab arm).

A recent exploratory analysis investigating the combination of panitumumab with FOLFIRI as first line-treatment in K-RAS wild-type patients, appears to show improvement in PFS and time to disease progression versus the K-RAS mutation population.<sup>59</sup>

As far as cetuximab, across all studies reviewed here, it clearly appears that clinical efficacy of panitumumab therapy is restricted to patients with wild-type K-RAS tumors. Therefore, K-RAS genotyping of tumors should be strongly considered to select patients being treated with panitumumab.

Further evaluations need to assess the relationship between K-RAS mutations and response to panitumumab combined with chemotherapy in earlier lines of therapy.

## B-RAF

The B-Raf proto-oncogene serine/threonine-protein kinase (B-RAF) is involved in transducing mitogenic signals via the MAP kinase/ERK (MAPK) signaling pathway. Mutations in B-RAF are involved in mCRC. A thymine to adenine transversion mutation results in the substitution of valine with glutamate (V600E) and converts B-RAF into a dominant transforming protein that causes the constitutive activation of the MAPK pathway independently of RAS. The V600E B-RAF mutation appears in 4%–15% of CRC.<sup>60–62</sup>

The possible relationship between of B-RAF mutational status and response to treatment with panitumumab in 48 patients with mCRC was investigated by Benvenuti et al.<sup>55</sup> B-RAF mutations were detected in 12.5% tumors and they were mutually exclusive with K-RAS alterations. The only B-RAF mutation found was the V600E substitution. The most important thing was that patients who received panitumumab or cetuximab but had B-RAF alteration, presented no objective response to therapy; consequently TTP was worse for subjects bearing a mutated B-RAF although not statistically significant probably due to the limited number of tumors carrying these mutations.

More recently Di Nicolantonio et al analysed response rate, PFS, OS and the mutational status of K-RAS and B-RAF in 113 tumors from cetuximab- or panitumumab-treated mCRC patients.<sup>63</sup> K-RAS was mutated in 30% of cases and B-RAF was mutated in 14% of the K-RAS-wt cases. None of the B-RAF mutated patients responded to treatment, and none of the responders carried any B-RAF mutations. B-RAF mutated patients had a significantly shorter PFS and OS than the wild-type cases. Di Nicolantonio et al also demonstrated that introduction of the B-RAF V600E allele could confer resistance to either cetuximab or panitumumab in wild-type B-RAF colorectal cancer cells.

Thus, the low incidence of B-RAF mutations in patients with mCRC probably do not permit to select patients who have been treated with panitumumab. In clinical practice, a B-RAF alteration could explain the resistance to anti-EGFR inhibitors in a 10% subpopulation who have K-RAS wild-type; however, 41% of patients had no mutations in either K-RAS or B-RAF and did not respond to therapy, therefore other biomarkers are required.

## Alternative K-RAS pathways: PI3K, PTEN/AKT

The PIK3CA gene encodes for a lipid kinase that regulates, alongside with K-RAS, signaling pathways downstream of the EGFR. The PIK3CA gene is mutated in 10%–18%

of mCRC cases.<sup>64,65</sup> PI3K-initiated signaling is normally inhibited by phosphatase and tensin homolog deleted on chromosome ten (PTEN). Thus, PTEN functions as a tumor suppressor gene through the action of its phosphatase protein product. The encoded protein negatively regulates intracellular levels of phosphatidylinositol-3,4,5-trisphosphate (PIP-3) in cells and functions as a tumor suppressor by negatively regulating the PI3K/AKT signaling pathway. PTEN loss increases levels of PIP-3 and PKB/AKT, thus increasing cell survival signalling.<sup>66,67</sup>

Several studies have evaluated the possible role of PI3K and PTEN as predictive biomarkers of anti-EGFR drug activity, especially in patients receiving cetuximab, but data seem more controversial.<sup>68–71</sup> In mCRC, it has been reported that loss of PTEN expression, which occurs in 30% of sporadic cases, may be associated with lack of response to cetuximab.

Our present knowledge of the active pathways for panitumumab is based on a single study conducted by Sartore-Bianchi.<sup>72</sup> In this analysis, mutational profiling of 110 CRC tumors from patients receiving cetuximab or panitumumab led to the identification of 13.6% PIK3CA and 29.0% K-RAS mutations. The study showed that mutations in PIK3CA, K-RAS, and PTEN loss were associated with lack of objective response to panitumumab or cetuximab. PIK3CA mutations were significantly associated with lack of response to panitumumab or cetuximab, with none of the mutated patients achieving objective tumor response ( $P = 0.038$ ).

The same negative association was confirmed for K-RAS mutations (9.1% of mutations among responders versus 34.5% among non responders;  $P = 0.019$ ) and was confirmed when at least a mutation of either K-RAS or PIK3CA was considered ( $P = 0.001$ ). Consequently patients with tumors harboring PIK3CA mutations had a worse clinical outcome in terms of PFS, compared with wild-type tumors ( $P = 0.0035$ ). Patients with K-RAS mutations had a trend toward a decreased PFS ( $P = 0.0815$ ). Shorter PFS was also detected in patients harboring at least a mutation of either K-RAS or PIK3CA ( $P = 0.0032$ ).

Despite the results of this study, further investigation is needed to establish the effective roles of PI3K and PTEN/AKT as predictive biomarkers to selecting patients who could have been treated with EGFR inhibitors, including panitumumab.

## Other potential biomarkers

Increased gene copy number of HER2 (the preferred heterodimer of EGFR) was linked to a statistically significantly

shorter overall survival ( $P = 0.03$ ), with a trend toward a shorter time to progression ( $P = 0.09$ ), in 85 patients receiving cetuximab with or without chemotherapy.<sup>73</sup>

The interaction between IGF-1 expression and K-RAS mutational analysis was also tested in order to verify the ability of IGF-1 to identify a sub-group of patients more likely to benefit from EGFR-targeted antibodies treatment.<sup>74</sup> Among K-RAS wild type patients, median time to progression in IGF-1 negative tumors was 11 months and 3.2 months in IGF-1 positive CRC ( $P = 0.03$ ). IGF-1 proved to be a reliable predictive factor for resistance to anti-EGFR monoclonal antibodies in K-RAS wild type CRC. Thus combined IGF-1 and K-RAS analysis may represent an effective strategy for a better selection of responding CRCs in this setting. Other potential mechanisms of acquired resistance to EGFR inhibitors, such as those involving activation HER3, mesenchymal-epithelial transition factor (C-MET), MAPK, AKT, VEGF, IL8, COX-2 and Cyclin D are under investigation in patients with mCRC receiving EGFR inhibitors but data on their use in selecting patients are not available.<sup>75-77</sup>

## Skin toxicity

Skin toxicity is most frequently seen as acneiform rash generally confined to the seborrhoeic areas; this particularly toxicity is a characteristic finding seen with most EGFR inhibitors, including panitumumab. It appears to be dose-related and may indicate EGFR saturation, given the high expression of this receptor in keratinocytes skin fibroblasts and hair follicles. Skin rash observed in most patients who have been treated with EGFR inhibitors has been studied as a potential marker of efficacy. Skin toxicity has been significantly linked with higher response rate and longer survival in several trials with patients with mCRC and treated with cetuximab.

Longer PFS and OS were significantly observed in patients with worst skin toxicity of grade 2–4 compared with those with at worst grade 1.<sup>78,79</sup> The association between skin toxicity and PFS was only seen for panitumumab patients with wild-type K-RAS. No association between skin toxicity and PFS was seen in the mutant K-RAS group. Of note, a higher incidence of grade 3 skin toxicity was observed in patients with wild-type K-RAS tumors as compared with mutant K-RAS, consistent with longer time on treatment. The association of OS with skin toxicity severity was more pronounced for the wild-type K-RAS than the mutant K-RAS group.

Berlin et al conducted a pooled analysis of five clinical trials which involved a total of 612 patients with mCRC treated with panitumumab.<sup>80</sup> They showed better overall response rate, PFS, and OS in patients who developed a grade 2–4 skin toxicity than in patients with grade 0–1 skin toxicity.

Although there is some evidence that skin toxicity represents a marker of clinical benefit in patients treated with panitumumab, its utility in the clinical setting is limited, as it cannot be used a priori to select patients who may derive greater benefit from anti-EGFR treatment, or conversely, exclude those who may not. Potentially, however, this marker could be used clinically to titrate treatment doses to achieve a skin toxicity grade consistent with maximum treatment benefit.

## Economic evidence

Because of substantial increase in costs, physicians need to consider the cost-effectiveness of new therapies as well as the clinical issues. Consideration of a treatment's cost effectiveness can help to avoid therapies that produce too little benefit at too high a cost.

More progress has been made in increasing the duration of survival in patients with mCRC in the past 5 years than in most other cancers. Although the introduction of better systemic therapy and novel therapeutic agents has considerably improved the prognosis in this setting, these potential clinical benefits caused escalating drug costs. The near-doubling of the median survival time achieved over the past decade has been accompanied by a 340-fold increase in drug costs for the initial 8 weeks of therapy alone.<sup>81</sup> Many countries are experiencing increased pressure on their budgets to finance these therapies.

Conversely, Paramore et al showed that the economic impact of mCRC is substantial and increasing over time, and that monthly cost almost tripled from 1998 to 2004.<sup>82</sup> Large-scale economic analyses reported that employing cetuximab in patients with metastatic colorectal cancer is clinically effective but associated with high costs per life year.

Regarding panitumumab, the average wholesale price for panitumumab (20 mg/mL 20 mL vial) is US \$4000. Therefore, the cost of therapy for a 60 kg patient is about \$8000/month.

A recent Italian treatment costs analysis to evaluate the safety of panitumumab comparing with cetuximab in third line mCRC, identified savings per patient of 111 euro per month.<sup>83</sup> The safety savings were 50 euro per month and the administration savings were 690 euro per month, giving a combined saving of 851 euro. Treatment cost savings associated with panitumumab were related to a low rate of severe infusion reaction versus cetuximab, reduced hospital costs associated with a less frequent dosing regimen and patients' weight savings across a normally distributed patient population. Based on the calculated prevalence and the assumption of a 4 month treatment period, panitumumab is modeled to provide savings of 7.67 million euro/year to the Italian healthcare system compared

with cetuximab. Reduced drug costs and further improvements in clinical effectiveness may alter this finding.<sup>84,85</sup>

Moreover, K-RAS mutational status has emerged as an important biomarker for mCRC and should be assessed before patients begin therapy.<sup>86</sup> Because K-RAS status can aid in therapy selection, oncologists can avoid unnecessary toxicities and expenses related to patients unlikely to respond. A recent study by Mancl et al reviewed the clinical use of cetuximab and panitumumab and the role of K-RAS testing in clinical practice.<sup>87</sup> A simple breakeven analysis using a group of 100 hypothetical patients with metastatic colorectal cancer revealed that Preemptive K-RAS screening had tremendous cost-saving potential.

Screening could cost several thousand dollars per patient and still result in a lower overall cost of care, based on very conservative estimates of the cost reduction associated with treatment avoidance in patients with K-RAS mutations. Moreover, because EGFR inhibitors are indicated as third-line therapy for metastatic colorectal cancer, few options exist for patients who do not respond to treatment or have mutant K-RAS. Such patients will most likely receive best supportive care or choose to enroll in a clinical trial.<sup>87</sup>

Implementing routine K-RAS screening and limiting the use of EGFR inhibitors to patients with wild-type (not mutated) K-RAS may have the potential for cost savings.

## Conclusions

The evidence to hand and the implications of these are summarized from the above discussion into clinical impact summary.

Intravenous panitumumab has been approved as monotherapy for the treatment of adult patients with chemotherapy-refractory, EGFR-expressing, mCRC with non mutated K-RAS.

The improvement in PFS and RR produced by panitumumab monotherapy was significantly greater in patients with non mutated (wild-type) K-RAS than in those with mutant K-RAS in whom no benefit from panitumumab was observed.

The predictive value of mutant K-RAS for a lack of clinical benefit with panitumumab monotherapy was supported and also confirmed by results recently from some phase II–III studies. Therefore K-RAS status evaluation is the only sure predictive biomarker of response that have to be investigated before starting a therapy with EGFR-inhibitors in patients with mCRC. Thus implementing routine K-RAS screening and limiting the use of EGFR inhibitors to patients with wild-type K-RAS appears the better strategy for selecting only patients who could benefit from the therapy with panitumumab and also may have the

potential for significant cost savings while improving positive outcomes for patients.

Uncertain data are about new biomarkers, such as B-RAF or PTEN, which may play a role in predictive response, that will further narrow the selection of mCRC patients.

## Disclosure

The authors report no conflicts of interest in this work.

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