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Long-Term Treatment of Metastatic Colorectal Cancer with Panitumumab

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Abstract: Colorectal cancer is one of the leading causes of cancer-related deaths worldwide. More than 30% patients present with metastases at diagnoses and will require systemic chemotherapy. In recent years many anti-EGFR targets have been developed. Among them, panitumumab, a fully human IgG2 monoclonal antibody has shown important benefits in the treatment of this disease.

Keywords: colorectal cancer, metastasis, anti-EGFR, chemotherapy agents

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Background

Colorectal cancer (CCR) is the third-leading cause of cancer-related deaths worldwide, with over 500,000 deaths occurring worldwide each year.¹

More than 35% of CCR patients present with metastases at diagnosis and require systemic chemotherapy. Treatment combinations, including fluorouracil, leucovorin, irinotecan, oxaliplatin and bevacizumab, have increased the survival rates of these patients.²⁻⁴

Despite the results achieved with these agents, most patients will experience a disease relapse. Therefore, there is an urgent need to develop new strategies to aid this challenging patient population.

Recently, a role has been established for the epidermal growth factor receptor (EGFR) signal transduction pathway in the development of a subset of epithelial tumors.⁵ EGFR is involved in multiple cellular proliferation processes, including growth, differentiation, migration, and apoptosis. EGFR overexpression has been shown to predict tumor progression⁶ in colorectal cancer and is overexpressed in 25%–77% of these tumors. EGFR is often associated with a worse prognosis.⁷

In recent years, many EGFR-targeted agents have been developed. The two agents that have demonstrated the best responses are two monoclonal antibodies directed against EGFR: cetuximab and panitumumab (known as anti-EGFR therapy or EGFR inhibitors). These antibodies have presented high response rates when administered with chemotherapy. Cetuximab is a chimeric anti-EGFR monoclonal antibody that has demonstrated antitumor activity in patients with colorectal cancer. However, this antibody's murine component is a potential source of toxicity and immunogenicity. Due to this, there has been a considerable amount of research aimed at eliminating this toxicity. As a result, a new agent was developed: panitumumab, a fully human IgG2 monoclonal antibody that is highly selective for EGFR. The antibody can block EGFR-ligand binding and cause internalization of the receptor, resulting in the inhibition of tumor growth.⁸

Several studies have indicated the benefits of the addition of panitumumab to metastatic colorectal cancer (mCRC) treatment. In this review, we will summarize these studies and update the new indications of panitumumab treatment in this setting.

Pharmacodynamic and Pharmacokinetic Profiles

Panitumumab is a recombinant, fully human IgG2 monoclonal antibody with a high affinity for EGFR.⁹ Panitumumab EGFR binding causes rapid internalization of the EGFR, inducing apoptosis and reducing cell proliferation and the production of proinflammatory cytokines. Panitumumab also reduces EGFR and VEGF (vascular endothelial growth factor) expression.¹⁰

The pharmacokinetics of panitumumab administered at dosages of 1.0, 1.5, 2.0 or 2.5 mg/kg/week have been examined in patients with renal cancer,¹¹ but study data examining dosages of 6 mg/kg every 2 weeks and 9 mg/kg every 3 weeks in solid tumors (including colorectal cancers) are also available.¹² In fact, the standard dosage is 6 mg/kg every 2 weeks, administered as a 60-minute intravenous infusion. The antibody's elimination half-life is 7.5 days, and it has a mean clearance of 4.9 ml/kg/day. The most frequent treatment-emergent adverse events are erythema, dermatitis acneiform, pruritus, hypomagnesemia, skin exfoliation, fatigue, paronychia, abdominal pain, anorexia, nausea, diarrhea, rash and skin fissures.

Several phase I studies have evaluated the safety profile and optimal dosing of panitumumab. In a phase I trial evaluating patients with several types of solid tumors, the optimum weekly dose was determined to be 2.5 mg/kg.¹³ Moreover, two different dosing intervals were studied in the same trial. The results indicated that a dose of 6 mg/kg every 2 weeks or 9 mg/kg every 3 weeks resulted in similar toxicity profiles as the weekly schedule of administration.¹⁴ The most common adverse events reported in phase I trials were fatigue, anorexia and skin toxicity, such as rash and acneiform dermatitis, with an overall incidence of grade 3 or 4 adverse events of 30% and 7%, respectively. Regarding antitumor activity in patients with mCRC, 13% of patients achieved a partial response and 23% of patients had stable disease.¹⁵ No dose-limiting toxicities, reported infusion reactions or deaths occurred. Similarly, no anti-panitumumab antibodies were detected.¹⁶

Therapeutic Efficacy

Several recent studies have shown the efficacy of panitumumab in the treatment of mCRC (Tables 1 and 2). The most important studies will be summarized here.

**Table 1.** Phase II trials.

N	EGFR expression	Pmab dose	Treatment	ORR (CR + PR)		PFS (weeks)		OS (months)		Ref.
				WT	MT	WT	MT	WT	MT	
203	≤1%	6 mg/kg/2 weeks	Monotherapy	9%	9%	15	7.1	13.5	7.25	15
52	≥1%	6 mg/kg/2 weeks	Monotherapy	13%	13%	8	8	7.4	7.4	16
116	NA	6 mg/kg/2 weeks	FOLFIRI ± Pmab	23%	16%	23	19	12.5	7.75	38

Abbreviations: Pmab, panitumumab; ORR, overall response rate; CR, complete response; PR, partial response; WT, wild type; MT, mutant type; PFS, progression-free survival; OS, overall survival.

Panitumumab monotherapy

The therapeutic efficacy of intravenous panitumumab monotherapy in patients with chemotherapy-refractory metastatic colorectal cancer has been assessed in a phase III trial conducted by Van Cutsem et al¹⁷ a later extension,¹⁸ and two phase II trials.^{19,20}

Phase II trials

In a multicenter US study, chemotherapy refractory patients with metastatic colorectal cancer treated with panitumumab every 2 weeks (n = 203) were studied. KRAS status was determined in 171 patients. The median progression-free survival (PFS) was 15.0 vs. 7.1 weeks for wild-type (WT) and mutant (MT) KRAS, respectively, and the median overall survival (OS) was 54.0 versus 29.1 weeks, respectively. The second phase II trial was conducted with Japanese patients (n = 52) who had chemotherapy refractory metastatic colorectal cancer. Panitumumab was administered at 6 mg/kg every 2 weeks to achieve an objective response in 13% of patients (partial responses) and in 33% with stable disease.

Comparative phase III trial: Panitumumab versus Best Supportive Care (BSC)

This was a randomized, open-label phase III study of 463 patients with positive EGFR tumor cell staining and radiologically documented disease progression after two (63%) or three (37%) lines of chemotherapy. Patients were randomly assigned to receive panitumumab 6 mg/kg every two weeks plus BSC (n = 231) or BSC alone (n = 232). The primary end point was PFS, and the secondary end-points included best objective response, OS and tolerability. KRAS mutational status was determined in 208 patients from the panitumumab group and in 219 patients from the BSC group, and post hoc analyses were conducted with stratification for WT KRAS and MT KRAS. In this study, panitumumab reduced

the relative progression rate by 46% (HR 0.54, 95% CI 0.44–0.66, $P < 0.0001$). This improvement in PFS was also observed in the non-responder patients (HR 0.63, 95% CI 0.52–0.77, $P < 0.0001$). The improvement in PFS was evident from week 8 and persisted until week 32, with a median PFS time of 8 weeks being observed for patients receiving panitumumab plus BSC compared with 7.3 weeks for patients receiving BSC alone. As expected, this improvement in PFS with panitumumab versus BSC was greater in patients with WT KRAS than in those with MT KRAS ($P < 0.0001$). Moreover, all of the partial responses were achieved by patients with WT KRAS (17%), and no responders were found among patients with MT KRAS. The median response duration was 17 weeks, and stable disease was achieved by 34% of panitumumab recipients. Overall, 176 patients who had been randomly assigned to the BSC group and experienced a progression received panitumumab under the crossover protocol. The differences in OS were not observed in this study (HR = 1) because of the high rate of crossover of the BSC patients, which confounded the survival data. To evaluate this crossover effect, an open-label extension study evaluated the 176 patients who had progressed to BSC and started treatment with panitumumab. In this new study, the median PFS was 9.4 (95% CI 8.0–13.4), and the median OS was 6.3 (95% CI 5.1–6.8 months), similar findings to those previously described in the phase III trial.

Results from all these studies indicate that the use of panitumumab results in a clinically significant improvement in PFS in mCRC patients that harbored WT KRAS tumors. Panitumumab has also been shown to improve the clinical benefit in patients with stable disease. Therefore, the use of panitumumab monotherapy should be considered for those mCRC patients who have progressed previously to fluoropyrimidine, oxaliplatin and irinotecan



Table 2. Phase III trials.

N	EGFR expression	Pmab dose	Treatment	ORR (CR + PR)		PFS (Pmab vs. control)	OS (Pmab vs. control)	Ref.
				WT	MT			
463	≥1%	6 mg/kg/2 weeks	BSC ± Pmab	10%	0%	8 weeks 7.3 weeks (HR 0.54)	NR (HR 1)	13
1053	NA	6 mg/kg/2 weeks	Bmab + Ox ± Pmab Bmab + Iri ± Pmab	46%	48%	8.8 m 10.5 m (HR 1.44)	19.4 vs. 24.5 m (HR 1.4)	PACCE
1183	NA	6 mg/kg/2 weeks	FOLFOX ± Pmab	55%	48%	WT: 9.6 m vs. 8 m (HR 0.8) MT: 7.3 m vs. 8.8 m (HR 1.29)	WT: 23.9 m vs. 19.7 m (HR 0.83) MT: 15.5 m vs. 19.3 m (HR 1.24)	PRIME
1186	NA	6 mg/kg/2 weeks	FOLFIRI ± Pmab	35%	13%	WT: 5.9 m vs. 3.9 m (HR 0.73) MT: 5 m vs. 4.9 m (HR 0.85)	WT: 14.5 m vs. 12.5 m (HR 0.85) MT: 11.8 m vs. 11.1 m (HR ND)	28

Abbreviations: NA, not available; Pmab, panitumumab; ORR, overall response rate; CR, complete response; PR, partial response; WT, wild type; MT, mutant type; PFS, progression-free survival; OS, overall survival; ND, not done.

chemotherapy-based regimens and harbor WT KRAS tumors. These promising results with panitumumab monotherapy treatment have led to several trials that studied the benefits of panitumumab in combination with chemotherapy. Despite these good results, we have also seen that panitumumab only benefits a subgroup of patients. Therefore, the question becomes the following: which patients are most likely to benefit from the antibody? We discuss that question in the next chapter.

Predictive factors

The results from the previous studies have shown that panitumumab as a monotherapy agent presents different response rates depending on tumor characteristics. Thus, we need to select the patients that are most likely to benefit from anti-EGFR therapy. A selection prior to treatment could avoid treatment-related toxicities, lack of tumor response and wasted resources.

The identification of valid predictive markers of response should be imperative prior to the election of a therapy. EGFR monoclonal antibodies appear to benefit only certain patients. Therefore, we need to establish validated predictive markers. At this point, the predictive role of EGFR expression, KRAS mutation status and skin toxicity have been widely studied.

EGFR expression

Traditionally, the determination of EGFR expression as determined by immunofluorescence in situ hybridization (FISH) was performed prior to the start of anti-EGFR treatment. In fact, some studies have shown a significant association between the responses to this targeted therapy and an increase in tumor EGFR gene copy number.²¹ Similarly, in another pivotal phase III comparative trial of 58 patients who received panitumumab plus BSC, the presence of an increased EGFR gene copy number, as determined by FISH, was predictive of a response to panitumumab. In this study, patients presenting an EGFR gene copy number ≥ 2.5 /nucleus had significantly longer PFS ($P = 0.0039$) and overall survival ($P = 0.014$).²² Nevertheless, the use of this marker as a predictive factor remains controversial. Results from other studies indicate that the level of membrane EGFR staining is a poor predictor of response. In a multicenter phase II study in which 148 patients received panitumumab



treatment after prior chemotherapy failure, tumor EGFR expression was assessed, and patients with high (>10% EGFR intensely staining cells) or low (<10% EGFR intensely staining cells) expression demonstrated a similar median time to PFS (14 weeks) and median survival time (8.6 months).²³

Thus, the predictive role of EGFR staining remains in doubt and cannot be used as a patient selection tool for anti-EGFR therapy in colorectal cancer patients.

KRAS mutation status

RAS proteins belong to a superfamily of GTP-binding proteins that play an important role in the transduction of EGFR signals,²⁴ as the stimulation of EGFR causes activation of RAS proteins. Unfortunately, mutations in KRAS genes occur frequently in human cancers (>30% in colorectal cancers). When these mutations occur, they alter downstream signaling, even if the EGFR receptor is silenced by anti-EGFR monoclonal antibodies.²⁵ In the literature, we found several retrospective studies that have reported the lack of benefit of the anti-EGFR cetuximab in MT KRAS tumors.²⁶ Similar results have been reported for panitumumab. Amado et al assessed the predictive role of KRAS in panitumumab treatment in a phase III randomized trial.²⁷ In this study, 462 patients were randomized to panitumumab plus BSC versus BSC alone, and KRAS status was determined in almost all patients (92%). The PFS achieved with panitumumab in patients harboring WT KRAS tumors was significantly longer (HR 0.45, $P < 0.0001$) than in patients with MT KRAS tumors in which panitumumab treatment did not demonstrate any benefit at all (response rates to panitumumab were 17% for WT patients and 0% for MT patients, respectively). Based on the results from this study, panitumumab is only approved for KRAS WT tumors, and RAS testing is mandatory prior to the initiation of this treatment. Moreover, the results from the PRIME study,²⁷ which are discussed below, confirmed the importance of KRAS as a predictive biomarker of efficacy for anti-EGFR monoclonal antibody therapy. In this study, and in keeping with the trials that were just discussed, the addition of panitumumab in the mutated KRAS group resulted in a lower PFS. The phase III trial, which demonstrated the benefits of panitumumab addition to FOLFIRI in second-line therapy, also confirmed the usefulness of KRAS mutational status as a predictive biomarker in

this setting.³² Interestingly, in contrast to its important role as a predictive marker for anti-EGFR therapy, KRAS has not been shown to be a prognostic biomarker in this setting.

Despite these achievements, in daily practice, certain patients with WT tumors do not respond to panitumumab therapy. In fact, only 30%–40% patients who do not respond to anti-EGFR therapy harbor MT KRAS tumors. Therefore, there has been an effort to identify other genetic determinants of primary resistance to anti-EGFR therapy. Results from recent studies indicate that mutations in other molecules that belong to the EGFR signaling pathways can contribute to this lack of sensitivity to anti-EGFR therapy.²⁸ One of these molecules is BRAF, which acts in the downstream pathway of EGFR, similar to KRAS. This activity has been demonstrated in a retrospective study by Di Nicolantonio et al. These researchers assessed KRAS and BRAF mutational status in 113 patients who had received treatment with cetuximab or panitumumab. None of the BRAF-mutated patients responded to treatment with anti-EGFR antibodies, whereas none of the responders carried a BRAF mutation ($P = 0.029$). Moreover, BRAF-mutated patients had significantly shorter progression-free survival ($P = 0.011$) and overall survival ($P < 0.0001$) than WT patients.²⁹

Therefore, it appears that patients harboring MT BRAF tumors are also refractory to panitumumab treatment, but further prospective studies are required to confirm this observation.

Skin toxicity

Skin-related toxicities are the most common adverse events reported for the majority of EGFR inhibitors,³⁰ and the efficacy of panitumumab treatment has been associated with skin rash severity, as well. Van Cutsem et al demonstrated that the incidence of skin toxicity in panitumumab-treated patients is dose-related. In their study, it was shown that a greater PFS duration (HR 0.62, 95% CI 0.44–0.88) and a greater overall survival (HR 0.59, 95% CI 0.42–0.85) was correlated with a more severe rash (grades 2–4 versus 1).¹⁷ In addition, 86% of responders had grade 2–3 rashes versus 14% of responders with grade 1 rashes. Even though skin rash appears to be a marker of the drug activity and associated with clinical benefit, skin rash may also develop in patients who do not benefit from treatment at all;



therefore, it cannot be used for selection of therapy discontinuation. A more thorough investigation of this topic is being developed. In the PRIME study (see below), an association between skin toxicity and efficacy was also observed, and additional analyses are currently underway to determine the importance of this type of toxicity as a predictive factor.

Apart from skin toxicity (including erythema, acneiform dermatitis, pruritus, skin exfoliation, rash, skin fissures, dry skin and acne), there are other important adverse events associated with panitumumab treatment. The most frequently reported adverse events are hypomagnesemia (39%), paronychia (25%), fatigue (26%), abdominal pain (25%), nausea (23%) and diarrhea (21%). The most serious adverse events observed were pulmonary fibrosis, infection and septic death secondary to severe dermatologic toxicity, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting and constipation (Vectibix®).

Based on the promising results achieved by panitumumab monotherapy in the first-line treatment of metastatic colorectal cancer (mCRC), various combination regimes with chemotherapy agents have been developed and studied. Two of these studies were published last year and indicated a relevant clinical benefit when panitumumab was combined with chemotherapy: the PRIME study of first-line treatment³¹ and a second-line therapy randomized study.³² In contrast, panitumumab in combination with the anti-VEGF bevacizumab has been shown to result in increased toxicity and shortened PFS.³³

Panitumumab combination regimens

Combination with bevacizumab and oxaliplatin-irinotecan chemotherapy: the PACCE (Panitumumab Advanced Colorectal Cancer Evaluation) study³³

This study was a randomized, open-label multicenter, phase IIIB trial designed to evaluate the contribution of panitumumab to bevacizumab and chemotherapy for first-line treatment of mCRC. PFS was the primary end point. The secondary end points included objective response rate (RR), OS and safety. Overall, 1053 patients were enrolled into one of two cohorts: bevacizumab plus fluorouracil, leucovorin and oxaliplatin-based chemotherapy or bevacizumab plus a fluorouracil, leucovorin and irinotecan-based chemotherapy. The patients were randomly assigned

to receive concomitant panitumumab or no additional treatment.

PFS was significantly worse in the panitumumab arm (HR 1.44, 95% CI, 1.13–1.85, $P = 0.004$). The median PFS was 8.8 months (95% CI, 8.3–9.5 months) for the panitumumab arm versus 10.5 months (95% CI, 9.4–12.0 months) for the control arm. Due to these results, an unplanned interim analysis of survival was performed. The median OS was 19.4 months for the panitumumab group and 24.5 months for control group in the oxaliplatin chemotherapy arm. In the irinotecan chemotherapy cohort, the median OS was 20.7 months for the panitumumab arm and 20.5 for the control arm. Interestingly, RR was similar between the panitumumab and control arms in both chemotherapy cohorts (46% and 48%, respectively). The safety analyses indicated that in both cohorts, more patients experienced grade 3 or higher adverse events (AEs) in the panitumumab arm than in the control arm (90% versus 77% in the oxaliplatin cohort and 90% versus 63% in the irinotecan cohort). As expected, skin toxicities were the most common grade 3 events, but other AEs occurring more frequently in the panitumumab arms included diarrhea, dehydration, hypomagnesemia, infections and pulmonary embolism. The exact explanation for this toxicity is unknown, but it is thought that it was exacerbated by dual-pathway inhibition of the EGFR and by pharmacokinetic interactions between the chemotherapy and antibodies.

In conclusion, the combination of panitumumab with bevacizumab and chemotherapy resulted in a decrease in PFS and is related to an increase in serious toxicity. Therefore, the combination is not recommended in daily clinical practice.

Combination with oxaliplatin-based chemotherapy: the PRIME study

First-line therapy. The PRIME (Panitumumab Randomized Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy) was an open-label, multicenter, phase III trial. This study compared the efficacy of panitumumab-FOLFOX4 (oxaliplatin 85 mgr/m², folinic acid 200 mgr/m², 5-fluorouracil 400 mgr/m² bolus + 600 mgr/m²/22 hours on day 1 plus the same doses of 5-fluorouracil on day 2) with FOLFOX4 alone in patients with previously untreated mCRC according to tumor KRAS status.³¹ Overall, 1183 patients



were randomized. Panitumumab was administered intravenously over 1 hour at 6 mgr/kg every 2 weeks before chemotherapy. KRAS testing was performed in all patients. PFS was the primary end point, and OS was the secondary end point.

In the WT subgroup, median PFS was 9.6 months (95% CI, 9.2–11.1 months) for panitumumab-FOLFOX4 and 8.0 months (95% CI, 7.5–9.3 months) for FOLFOX4 alone. In the MT KRAS subgroup, median PFS was 7.3 months (95% CI, 6.3–8.0 months) for panitumumab-FOLFOX4 and 8.8 months (95% CI, 7.7–9.4 months) for FOLFOX4. In the WT KRAS subgroup, the median OS was 23.9 months (95% CI, 20.3–28.3 months) for panitumumab-FOLFOX4 and 19.7 months (95% CI, 17.6–22.6 months) for FOLFOX4. The HR was 0.83 (95% CI, 0.67–1.02, $P = 0.072$), favoring the panitumumab-FOLFOX4 arm. In the mutated KRAS subgroup, the median OS was 15.5 months (95% CI, 13.1–17.6 months) for panitumumab-FOLFOX4 and 19.3 months (95% CI, 16.5–21.8) for FOLFOX4 (HR = 1.24, 95% CI 0.98–1.57, $P = 0.068$).

The PRIME is the first study that evaluated the benefits of adding panitumumab treatment to first-line FOLFOX chemotherapy regimen, and in addition, prospectively evaluated KRAS status. The study indicated that the addition of panitumumab to oxaliplatin-based chemotherapy results in an increased PFS for patients with WT KRAS tumors. Interestingly, the difference in median OS, although not statistically significant, also favored patients with WT KRAS. Even responses were more frequent in the panitumumab-chemotherapy group, although resection rates were similar.

The results observed in WT patients in the PRIME study are consistent with those seen in two other first-line studies examining cetuximab chemotherapy, although in the other studies, KRAS status was analyzed retrospectively.^{34,35} To date, the only anti-EGFR approved for mCRC in combination with chemotherapy is cetuximab, but similar clinical benefit is achieved with panitumumab in the treatment of this disease. The 4.2 month benefit in median OS observed in the PRIME study in the WT KRAS population, although not statistically significant, is similar to the 3.5 month benefit in median OS reported in the phase III CRYSTAL (Cetuximab Combined with Irinotecan in First Line Therapy for Metastatic Colorectal Cancer) trial in which cetuximab was added to first-line

irinotecan-based chemotherapy.³⁶ In contrast, the addition of cetuximab to first-line oxaliplatin-based chemotherapy does not improve OS or PFS, as has been highlighted in the recently reported Medical Research Council COIN (Continuous Chemotherapy versus Intermittent Chemotherapy) trial.³⁷ As a result, panitumumab instead of cetuximab should be considered in first-line WT patients.

The efficacy in the WT KRAS population in the PRIME study is similar to that reported in studies that included bevacizumab in first-line treatment.³⁸ In fact, to elucidate which is the best treatment option for first-line WT patients (bevacizumab vs. anti-EGFR), there is a currently ongoing study aimed at estimating the treatment effect on PFS of panitumumab compared to bevacizumab in combination with FOLFOX6 chemotherapy as first-line therapy for mCRC (the PEAK study).³⁹ The primary outcome is PFS, and the estimated study completion date is March 2015.

Combination with irinotecan-based chemotherapy Second line

An open-label, randomized, multicenter, phase III trial compared the efficacy of panitumumab plus chemotherapy versus chemotherapy alone in patients with previously treated mCRC.³² This trial included 1186 patients who had progressed to a first-line fluoropyrimidine-based chemotherapy. These patients were randomized to receive FOLFIRI (180 mgr/m² irinotecan + 400 mgr/m² leucovorin + 400 mgr/m² folinic acid in bolus plus 2400 mgr/m² of 5-fluorouracil in continuous infusion) alone versus panitumumab 6.0 mgr/kg plus FOLFIRI. KRAS mutational status was assessed after the recruitment. The objective of this study was to evaluate improvements of PFS and OS with the addition of panitumumab to FOLFIRI as second-line therapy for mCRC. The secondary end points were objective response rate, duration of response, safety (including the incidence of AEs) and patient-reported outcomes.

For the primary analysis of PFS in the WT KRAS population, the addition of panitumumab to chemotherapy resulted in a statistically significant improvement in PFS (HR = 0.73, 95% CI 0.59–0.90, $P = 0.004$). Median PFS was 5.9 months (95% CI, 5.5–6.7 months) for panitumumab-FOLFIRI and 3.9 months (95% CI, 3.7–5.3 months) for FOLFIRI alone. In the MT KRAS patients, there was no



statistically significant difference in PFS (HR = 0.85, 95% CI 0.68–1.06, $P = 0.14$). The median PFS was 5.0 months for the panitumumab-FOLFIRI group and 4.9 months (95% CI, 3.6–5.6 months for the FOLFIRI alone group).

There was no statistically significant difference in OS in the WT KRAS subpopulation (HR=0.85, 95% CI 0.70–1.04, $P = 0.12$). The median OS was 14.5 months (95% CI, 13.0–16.0 months) for the panitumumab-FOLFIRI group and 12.5 months (95% CI, 11.2–14.2 months) for the FOLFIRI alone group. In the MT KRAS group, the median OS was 11.8 months (95% CI, 10.4–13.3 months) for the panitumumab-FOLFIRI subgroup and 11.1 months (95% CI, 10.3–12.4 months) for the FOLFIRI alone subgroup. In patients with WT KRAS, the objective response rate was 35% (95% CI, 30%–41%) in the panitumumab-FOLFIRI arm versus 10% (95% CI, 7%–14%) in the FOLFIRI arm. In patients with MT KRAS, there were no differences in RR (13% for panitumumab-FOLFIRI versus 14% for FOLFIRI alone). Skin toxicity was the most frequent AE reported.

This study has special relevance, as it was the first trial to analyze the treatment effect of an anti-EGFR therapy according to tumor KRAS mutational status. In this trial, the addition of panitumumab to FOLFIRI reduced the risk of progression or death in 27% of the WT KRAS population ($P = 0.004$). This result is important in the treatment of mCRC, as these results are similar to the previous second-line study that evaluated the benefits of cetuximab addition to irinotecan (350 mg/m²) in second-line therapy.⁴⁰

Even though the effect on OS was not statistically significant in the WT KRAS population, the RR of 35% is the highest reported in a randomized phase III second-line study (RR for irinotecan-based regimens are generally between 4% and 16%, independent of KRAS status).⁴¹ Considering the high response rate seen with panitumumab-FOLFIRI, this regimen may be of particular value in those patients who experience disease progression during first-line therapy. This regimen might be of particular interest if patients present with potentially resectable metastases or symptomatic disease, due to its good results in controlling the response rate. Although no benefit was shown in patients with MT KRAS tumors, the addition of panitumumab to FOLFIRI did not result in a decrease of OS in contrast to what was observed in other studies

with panitumumab in combination with oxaliplatin therapy.³¹ The panitumumab and FOLFIRI combination has an acceptable safety profile, with skin toxicity and hypomagnesemia being more frequent with the use of panitumumab and diarrhea secondary to both EGFR inhibitor and irinotecan. The incidence of panitumumab-related infusion reactions is <1%.

Another phase II, open-label, single arm study was performed to evaluate the benefits of adding panitumumab to FOLFIRI in patients who had progressed to oxaliplatin and bevacizumab first-line treatment.⁴² The efficacy endpoints were objective RR, PFS and OS, and the safety endpoints were the incidence of AEs. All of the endpoints were evaluated by KRAS tumor status. The median PFS was 23 weeks (95% CI 19–33 weeks) in patients with WT KRAS tumors and 19 weeks (95% CI 12–25 weeks) in patients with MT KRAS tumors patients. The median OS was 50 weeks (95% CI 39–76 weeks) and 31 weeks (95% CI 23–47 weeks) respectively. Overall panitumumab improved RR, PFS and OS in KRAS WT patients.

Therefore, the results of these phase II and phase III trials have demonstrated the efficacy of panitumumab when added to FOLFIRI in previously treated mCRC patients. In addition, this regimen has a convenient administration schedule and a manageable toxicity profile, thereby representing an important new treatment option in second-line treatment of WT KRAS patients.

First-line therapy

An ongoing first—line, single-arm, phase II study is evaluating the benefits of adding panitumumab to first-line FOLFIRI treatment.⁴³ KRAS is being prospectively evaluated, and the primary endpoint is objective RR. This combination seems also well-tolerated in this first-line setting, although the study is still ongoing.

Other settings

Panitumumab is also being studied in the peri-operative setting prior to liver metastases resection,⁴⁴ but the results from randomized trials are still not available. There is a single-arm, multicenter, phase II study of panitumumab in combination with capecitabine/oxaliplatin in first-line WT KRAS cancer patients⁴⁵ whose primary endpoint is the objective response rate with the combination. The study is currently recruiting patients.



As seen in this review and in contrast to cetuximab therapy, the addition of panitumumab to first-line FOLFOX4 treatment in untreated WT KRAS mCRC patients significantly improves PFS. The results of a recent summary of clinical safety results of panitumumab in combination with chemotherapy from 5 clinical trials in 823 patients indicates the combination is generally well-tolerated.⁴⁶ This treatment represents a new therapeutic option for the treatment of patients with WT KRAS mCRC.

Ongoing trials

Numerous studies are currently evaluating the role of panitumumab in different settings. The VOLFI phase II study is recruiting patients to test the combination of FOLFOXIRI and panitumumab vs. panitumumab monotherapy in untreated patients with mCRC.⁴⁷ Another phase II trial is assigning patients to receive mFOLFOX6 in combination with panitumumab or bevacizumab⁴⁸ every two weeks, and antibodies are also being assessed in combination with oxaliplatin and capecitabine every three weeks.³⁹ For patients with chemorefractory tumors, panitumumab is being tested in several phase III trials administered as a single agent vs. BSC⁴⁹ vs. cetuximab⁵⁰ and in combination with irinotecan-based chemotherapy.⁵¹

Long-term Treatment with Panitumumab

Considering the favorable results achieved in the previously noted randomized controlled trials, treatment with anti-EGFR inhibitors is recommended until progression.⁵² Nevertheless, we do not have any data to support the post-progression use of anti-EGFR. Certain physicians support this approach, while others treat their patients until the best response is achieved and stop treatment until progression occurs. If the patient presents with severe toxicity, this “stop and go” intermittent therapy is especially preferred.⁵³

Nevertheless, some case reports indicate that long-term responses are possible during panitumumab therapy. With a low toxicity,⁵⁴ this agent may be an option for long-term treatment of selected patients. In this setting, grade 3 cutaneous toxicity is the most frequently observed adverse event, and the incidence increases with the duration of the therapy. Nevertheless, cutaneous toxicity can be managed

with doxycycline in addition to topical steroids, oily cream and levocetirizine hydrochloride in cases of intolerable itching. We still do not know the optimal management strategy for patients with mCRC. When a patient progresses to a first-line treatment and responds to panitumumab therapy, the prognosis might be improved by the addition of a panitumumab maintenance treatment, secondary to achieving better control of the disease. One of the reasons physicians tend to discontinue panitumumab treatment is the appearance of dermatological toxicities. However, the toxicities seen with these agents are usually mild. Skin-related toxicities are well-managed by physicians, and diarrhea is also easily controlled. Moreover, infusion reactions are extremely rare during the treatment, due to the fully human nature of the antibody.

Therefore, although clinical daily practice supports the use of panitumumab during long-term therapy, there are no clinical trials to confirm its superiority when it is used with the “stop and go” treatment strategy. Efforts should be made to identify the factors associated with response to anti-EGFR therapy. The identification of these potential biomarkers could be of great help in selecting those patients who are likely to benefit most from treatment with anti-EGFR antibodies.

Summary

- Panitumumab is a fully human IgG2 monoclonal antibody that is highly selective for the EGFR. Skin rash and diarrhea are the most frequent AEs reported. Infusion reactions are extremely rare.
- Panitumumab has only demonstrated activity in the treatment of EGFR-expressing mCRC with WT KRAS.
- Panitumumab has shown an important clinical benefit in mCRC patients who have progressed to oxaliplatin and irinotecan-based chemotherapy.
- According to the EMA, panitumumab is indicated as monotherapy after the failure of irinotecan- and oxaliplatin fluoropyrimidine-containing treatment regimens for mCRC.
- Two recent phase III trials have shown that panitumumab is associated with a clinical benefit in combination with oxaliplatin-based chemotherapy in first-line treatment and with irinotecan-based chemotherapy in second-line therapy.



- On June 2011, the Committee for Human Medicinal Products for Human Use (CHMP) adopted two new indications for panitumumab:
 - In first-line therapy in combination with FOLFOX
 - In second-line therapy in combination with FOLFIRI for patients who had received first-line fluoropyrimidine-based therapy (excluding irinotecan).
- The PEAK study will attempt to clarify whether panitumumab or bevacizumab is the best option for first-line WT KRAS mCRC patients.
- Panitumumab combinations with capecitabine are currently being researched.

Author Contributions

MLG, MM, EC were responsible for data collection/entry/analysis and assistance with manuscript preparation. MLG was responsible for the study design and preparation of the manuscript. All authors read and approved the final manuscript.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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