

# Effective Panitumumab Treatment in Patients with Heavily Pre-treated Metastatic Colorectal Cancer: A Case Series

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**Abstract.** In heavily pre-treated patients with metastatic colorectal cancer (mCRC), further chemotherapy has not demonstrated efficacy. Panitumumab is indicated as monotherapy treatment of epidermal growth factor receptor (EGFR)-expressing, Kirsten (K)-RAS wild-type metastatic colorectal cancer after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing regimens. However, panitumumab has not been specifically evaluated in patients following failure of a bevacizumab-containing regimen. One female and two male patients with mCRC presented with tumour recurrence in the para-aortic lymph nodes, the liver and the local presacral lymph nodes, respectively. The patients were confirmed to have K-RAS wild-type-expressing tumours. Following the failure of bevacizumab-containing chemotherapy regimens, all three patients received panitumumab monotherapy. Panitumumab was well-tolerated. All the patients responded to panitumumab monotherapy in this late-stage setting. This patient series suggests that panitumumab can improve patient outcomes and may be an alternative treatment option in patients with mCRC who have received prior treatment with bevacizumab plus chemotherapy.

Colorectal cancer (CRC) represents 12-15% of all new carcinomas diagnosed in Europe, with an age-adjusted annual incidence of 30-43 per 100,000 males and 20-30 per 100,000 females (1). Age-adjusted mortality rates range from 17.1 to 19.7 per 100,000 males and from 11.0 to 14.0 per 100,000 females (1). The prognosis for CRC depends on disease stage. A French study reported a postoperative 5-year

survival rate of 82% for patients with stage I or II disease, compared with only 7.6-9.6% for patients with stage IV disease (2).

Historically, chemotherapy has provided the mainstay of treatment, with patients often receiving multiple lines as their disease progresses. Targeted monoclonal antibody (mAb) therapies such as bevacizumab (Avastin<sup>®</sup>) and cetuximab (Erbitux<sup>®</sup>) are now often used in combination with chemotherapy to improve patient outcomes (3-8). However, this approach may not be appropriate for all patients. Panitumumab (Vectibix<sup>®</sup>) is the first fully human mAb approved for monotherapy treatment of epidermal growth factor receptor (EGFR)-expressing, Kirsten (K)-RAS wild-type, metastatic CRC (mCRC) after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing regimens. Currently available data regarding the use of panitumumab in patients with heavily pre-treated K-RAS wild-type disease show duration of response of 19.7 weeks (range 7.9 to 88.7 weeks) (9). To date, panitumumab has not been specifically evaluated following failure of bevacizumab-containing regimens. Combinations of panitumumab with standard chemotherapies are currently evaluated as first- or second-line strategies in phase III randomized clinical trials.

The cases of three Greek patients who received panitumumab monotherapy for metastatic colorectal cancer (mCRC) are reviewed. All the patients had confirmed K-RAS wild-type tumours and had previously received bevacizumab (Avastin<sup>®</sup>) in combination with standard chemotherapy regimens. Written informed consent was obtained from the patient (case 3) or their next of kin (cases 1 and 2) for the publication of these case reports and accompanying images.

## Case Report 1

A 61-year-old female presented with recurring mCRC in March 2006. The patient had previously undergone surgery for a colon adenocarcinoma (September 2004) and received 2 cycles of adjuvant 5-fluorouracil (5-FU)/leucovorin for an ulcerative tumour 2.5 cm from the surgical margins

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*Key Words:* Panitumumab, metastatic colorectal cancer, bevacizumab, treatment.

(September-October 2005). Treatment was discontinued due to toxicity. Tumour recurrence was found during total hysterectomy and was confirmed with CT scan which showed stage C (Dukes' classification) disease in the aortoiliac lymph nodes. A biopsy confirmed the lesions on the para-aortic nodes (maximum diameter  $1.8 \times 1.4$  cm). Carcinoembryonic antigen (CEA) levels were 101 ng/ml (institutional normal reference levels <4.7 ng/ml). A minor response was documented in August 2006, following 12 cycles of first-line bevacizumab (5 mg/kg)/irinotecan (180 mg/kg) combination therapy (March-August 2006). Disease progression subsequently occurred during bevacizumab (7.5 mg/kg) maintenance therapy, with new metastatic sites in both lungs (May 2008) and the patient was confirmed to have *K-RAS* wild-type expressing mCRC. Second-line therapy with oxaliplatin was considered unsuitable due to the patient's comorbidities (diabetes mellitus and sensory neuropathy). Panitumumab monotherapy (6 mg/kg every 2 weeks) was initiated in June 2008 and was administered for 14 cycles (until March 2009).

Treatment with panitumumab resulted in a complete response in the lungs and a partial response in the aortoiliac lymph nodes after 4 months, both lasting for 7 months (October 2008-May 2009). The response was also supported by a CT scan showing disappearance of all four nodular metastatic lesions in the lungs and one third regression of the aortoiliac lymph nodes (Figure 1). Concomitantly, CEA levels decreased to 47 ng/ml.

Panitumumab was well-tolerated, with minimal (grade 1) skin rash lasting for two months which did not require treatment. The patient had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 prior to treatment with panitumumab which was maintained throughout the treatment and to the present date (December 2010). The patient gained weight (3 kg) during treatment with panitumumab and showed improvement in everyday activities.

## Case Report 2

A 67-year-old male presented with recurrent metastatic disease of the liver in September 2007, following surgery (without adjuvant therapy) for a rectal adenocarcinoma in September 2004. CT and ultrasound showed multiple lesions in the liver (maximum diameter 2.5 cm) and two micronodular lesions in the right lung. An abdominal perineal incision revealed a  $3.4 \times 3.3$  cm-exophytic tumour 2 cm from the previous surgical margins with pericolic and perineural involvement. Immunohistochemistry showed epidermal growth factor receptor (EGFR) expression >80% and elevated CEA levels of 105 ng/ml. The patient was diagnosed with T4N2M1 metastatic rectal cancer and received 6 cycles of first-line bevacizumab (7.5 mg/kg)/XELIRI (capecitabine 2,000 mg/m<sup>2</sup>, irinotecan 220 mg/m<sup>2</sup>) combination therapy

followed by 6 months of bevacizumab maintenance therapy (October 2007-July 2008). After documented partial response in February 2008, a scheduled CT scan showed disease progression again in the liver in July 2008.

Panitumumab (6 mg/kg every 2 weeks) monotherapy was initiated in July 2008 and was administered for 16 cycles (until March 2009). Treatment with panitumumab resulted in a partial response after 4 months; a scheduled CT scan showed disappearance of the majority of metastatic lesions and regression of the largest lesion by 1 cm (Figure 2). Concomitantly, CEA levels were reduced to 32 ng/ml. This partial response was maintained for 5 months (November 2008-April 2009). Disease progression was documented in April 2009 and no further cycles of panitumumab monotherapy were administered.

During panitumumab monotherapy the patient experienced only two adverse events, namely grade 2 acne-like rash for 6 months and grade 1 diarrhoea for 1 month. The patient gained weight (4 kg) during panitumumab monotherapy and showed improvement in everyday activities. The patient had an ECOG performance status score of 0 prior to treatment, which was maintained until disease progression.

## Case Report 3

A 76-year-old male presented with locally recurring colon cancer in July 2006, following surgery (without adjuvant therapy) for a rectal adenocarcinoma in December 2004. A biopsy confirmed a  $4 \times 4$  cm-intermediate grade adenocarcinoma 0.5 cm from the previous surgical margin. CEA levels were 73 ng/ml. The patient was diagnosed with T2N0Mx mCRC with presacral recurrence.

The patient was unresponsive to 6 cycles of first-line treatment with bevacizumab (7.5 mg/kg)/XELIRI (capecitabine 3,000 mg, 14 days every 21 days; irinotecan 220 mg/m<sup>2</sup>) and discontinued subsequent bevacizumab/capecitabine maintenance therapy after 2 cycles due to diarrhoea and palmar plantar erythrodysesthesia (July-November 2006). Infiltration of the sacrum subsequently occurred in July 2007 during bevacizumab maintenance monotherapy. Second-line bevacizumab (7.0 mg/kg)/oxaliplatin (130 mg/m<sup>2</sup>) combination therapy was discontinued after 3 cycles due to grade 2-3 neurotoxicity (cold intolerance) and 9 cycles of bevacizumab (7.5 mg/kg) maintenance therapy were subsequently administered (November 2007-August 2008). Ascites progression to the peritoneum occurred in August 2008 and CEA levels were further elevated (130 ng/ml). Third-line panitumumab monotherapy (6 mg/kg every 2 weeks) was initiated in August 2008 and was administered for 16 cycles (until April 2009).

Treatment with panitumumab resulted in a significant improvement after 4 months, observed by CT scan showing disappearance of the ascites (Figure 3). This improvement

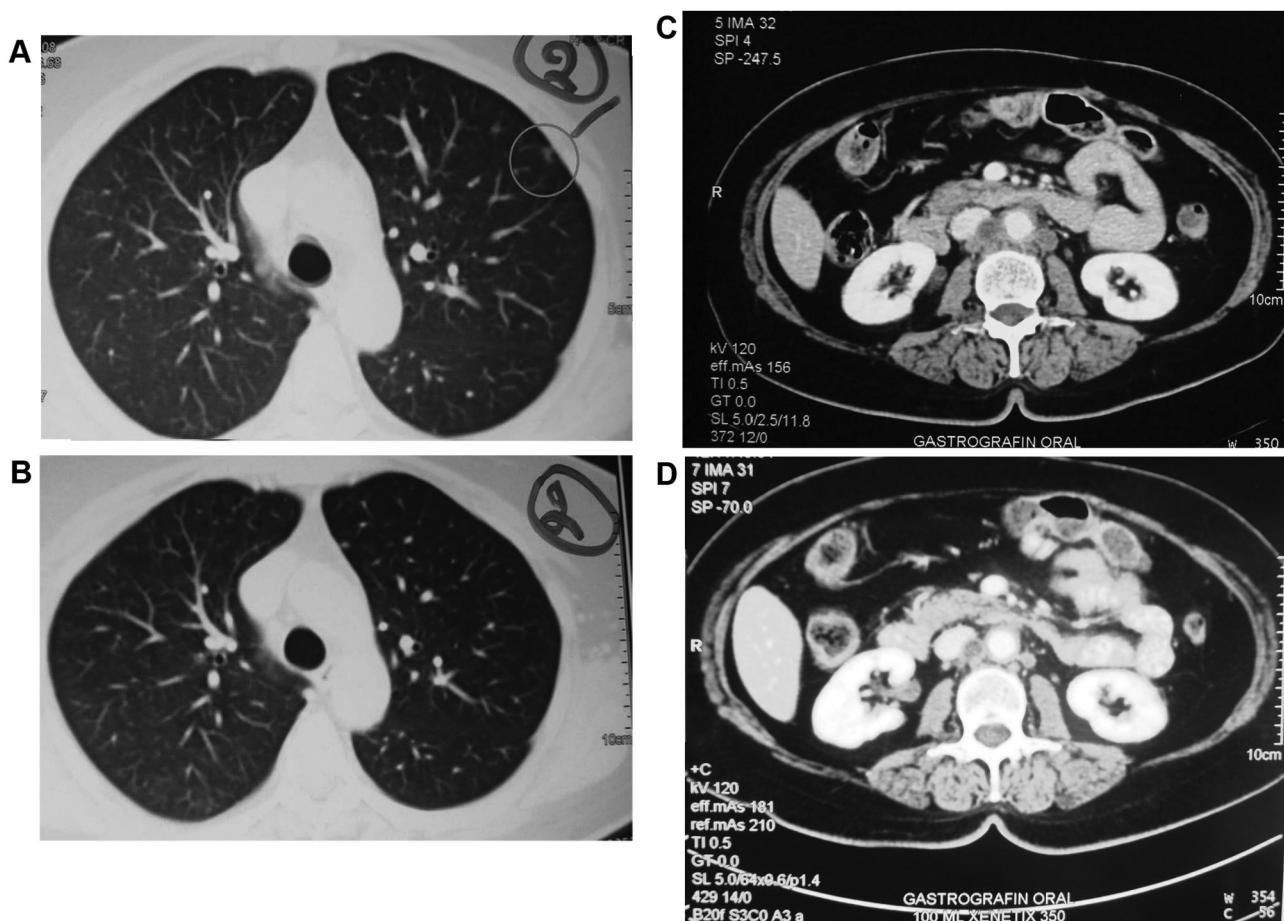


Figure 1. CT scans of metastasis in patient case 1. A) Metastasis in the lungs at initiation of second-line panitumumab treatment (June 2008); B) metastasis in the lungs after 4 months of treatment (October 2008), note the disappearance of all nodular metastatic lesions (circle); C) metastasis in the abdomen/aortoiliac lymph nodes at initiation of second-line panitumumab treatment; D) metastasis in the abdomen/aortoiliac lymph nodes after 4 months of treatment, note one third regression of the aortoiliac lymph nodes.

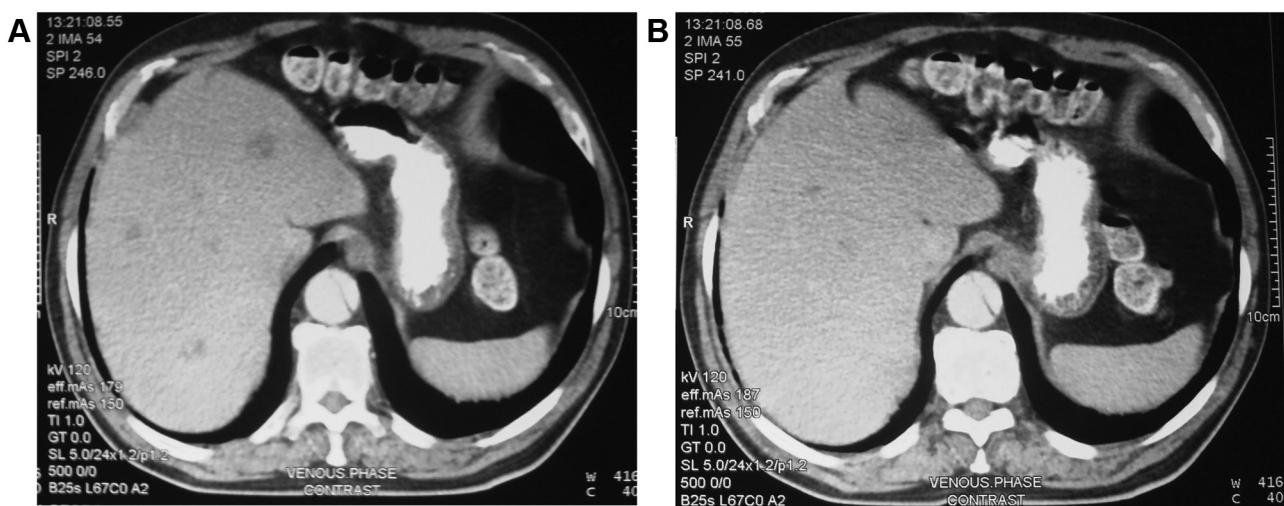


Figure 2. CT scans of metastasis in the liver in patient case 2. A) At initiation of second-line panitumumab monotherapy (July 2008); B) after 4 months of treatment, note the disappearance of the majority of the lesions and regression of the largest lesion by 1 cm.

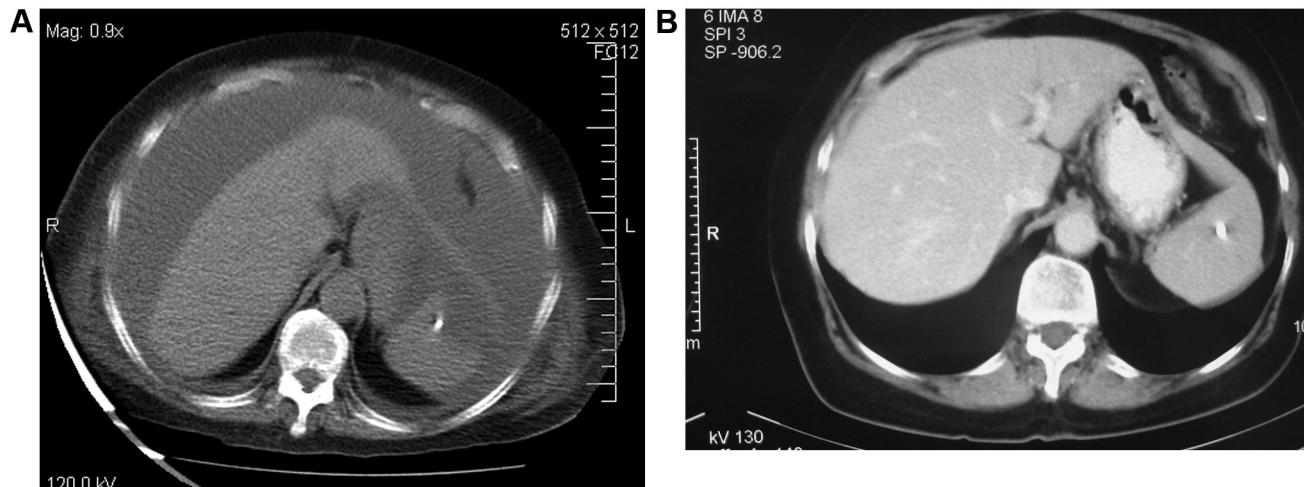


Figure 3. CT scans of ascites progression to the peritoneum in patient case 3. A) At initiation of third-line panitumumab monotherapy (August 2008); B) after 4 months of treatment, note the disappearance of the ascites.

lasted for 5 months (December 2008-May 2009). CEA levels also decreased to 34 ng/ml. Panitumumab was well-tolerated with a mild (grade 1) rash lasting 5 months, which did not require treatment. The patient showed improvement in everyday activities, supported by an ECOG performance status score of 0 following treatment with panitumumab compared to a score of 1 prior to treatment. In addition, the patient gained weight during treatment. The patient died in June 2009 due to renal disease, which was considered unrelated to mCRC.

## Discussion

This series of three patients demonstrated that panitumumab monotherapy may lead to partial/long-lasting response in patients with heavily pre-treated mCRC. Panitumumab may be an effective and safe treatment option in patients with advanced disease who are unable to tolerate or are refractory to chemotherapy. All three patients were judged to have achieved disease response after 4 months of panitumumab monotherapy. Moreover the responses observed were maintained for between 4 and 7 months. All the patients gained weight and experienced an improvement in everyday activities. Such responses have not previously been reported in this late treatment setting. All three patients had received bevacizumab in combination with chemotherapy for mCRC; hence the efficacy of panitumumab did not appear to be affected by prior exposure to bevacizumab in the cases described. Very few adverse events attributed to panitumumab were seen. Of note, skin toxicity commonly associated with anti-EGFR therapy was minimal and was easily managed in these patients.

## Conclusion

Panitumumab monotherapy may comprise an alternative therapeutic option in patients with mCRC following failure of bevacizumab-containing regimens. Verification of these preliminary results in larger studies is required before a definite conclusion can be drawn.

## Competing Interests

The Authors declare that they have no competing interests. Amgen (Europe) GmbH funded the article processing charge for this article.

## Acknowledgements

The Authors would like to thank Claire Desborough who provided medical writing assistance on behalf of Amgen (Europe) GmbH. The Authors are fully responsible for content and editorial decisions for this manuscript.

AT and AA followed-up the patients, provided clinical data, wrote and reviewed the paper. AK and CM followed-up the patients, provided clinical data and reviewed the paper. GB followed-up the patients and reviewed the paper.

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Received December 12, 2010

Revised February 28, 2011

Accepted February 28, 2011