

**REGIONAL DRUG AND THERAPEUTICS CENTRE  
(NEWCASTLE)**

**THE USE OF PANITUMUMAB IN THE  
MANAGEMENT OF METASTATIC  
COLORECTAL CANCER**

**Wolfson Unit  
Claremont Place  
Newcastle upon Tyne  
NE2 4HH**

**June 2009**



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## ABOUT THIS REPORT

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre (Newcastle). The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rest solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

<b>Subject</b>	<b>Date issued</b>
The use of ibritumomab as consolidation therapy after remission induction in previously untreated follicular lymphoma	May 2009
The use of azacitidine for the management of myelodysplastic syndromes	May 2009
The use of aprepitant for the prevention of chemotherapy induced nausea and vomiting	March 2009
Current therapeutic strategies for pulmonary arterial hypertension	March 2009
The use of lapatinib in the management of metastatic breast cancer	November 2008
The use of liposomal doxorubicin in the management of metastatic breast cancer	October 2008
The use of dasatinib in the management of acute lymphoblastic leukaemia in adults	August 2008
The use of bevacizumab in the management of metastatic breast cancer <b>(N)</b>	September 2007
The use of entecavir in the management of chronic hepatitis B infection <b>(N)</b>	March 2007
The use of natalizumab in the management of multiple sclerosis <b>(N)</b>	March 2007
The use of aromatase inhibitors in the treatment of early stage breast cancer <b>(N)</b>	March 2007
Palonosetron for the prevention of nausea and vomiting associated with cancer chemotherapy	March 2007
Alemtuzumab in the management of chronic lymphocytic leukaemia	March 2007
Omalizumab in the management of severe, persistent, allergic asthma <b>(N)</b>	June 2006
Bortezomib second-line in the management of multiple myeloma <b>(N)</b>	March 2006
Adjuvant docetaxel or paclitaxel in the management of early stage breast cancer <b>(N)</b>	March 2006

*Older reports are available via our website or on request*

Agents which have been reviewed by the National Institute for Health and Clinical Excellence (NICE) are indicated by **(N)** after the report name. Please refer to the NICE website to access their guidance for these agents/conditions.

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## SUMMARY

- Colorectal cancer is the third most common cancer in men, and the second in women. The incidence ranges from 20 per 100,000 in the 45 – 49 year age range, to over 200 - 300 per 100,000 in the over 75 year olds. Between 20% and 55% of all new cases present with metastatic disease. The five-year survival rate for metastatic colorectal cancer is 12%.
- Panitumumab is a fully human monoclonal antibody directed against EGFR (epidermal growth factor receptor). It is licensed as monotherapy for the treatment of patients with EGFR-expressing metastatic colorectal cancer with non-mutated *KRAS* (Kirsten rat sarcoma 2 viral oncogene homologue) after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens.
- NICE has proposed a technology appraisal of the first-line use of panitumumab in metastatic colorectal cancer, but no date has been set for publication. The Scottish Medicines Consortium (SMC) does not recommend the use of panitumumab as monotherapy according to its license due to non-submission by the manufacturers.
- A randomised, controlled phase III study in 463 patients comparing panitumumab plus best supportive care (BSC) to BSC alone in chemo-refractory metastatic colorectal cancer has been published. The primary endpoint was progression free survival (PFS).
- At week 8, PFS for the panitumumab arm was 49% compared to 30% in the BSC arm (HR 0.54; 95% CI 0.44 to 0.66;  $p < 0.0001$ ). At disease progression, patients in the BSC arm had the opportunity to receive panitumumab in an open-label extension study; 76% of these patients went on to receive panitumumab. This affects the interpretation of the overall survival results (a secondary endpoint).
- The main toxicities experienced by patients were skin-related (90%), e.g. erythema, dermatitis acneiform and pruritis. No deaths were considered to be related to panitumumab treatment. About 4% of patients discontinued treatment due to adverse effects.
- Sub-analysis of the phase III study found there were differences in clinical responses to panitumumab depending on presence of wild-type or mutant *KRAS*. PFS was significantly greater in wild-type than mutant *KRAS* patients, and the licence reflects this.
- The cost of panitumumab, using a PFS of 13.8 weeks, is estimated at £10,465 per patient. Potential costs are therefore £73,255 per 100,000 population (this includes patients with wild-type *KRAS* only). Additional costs associated with administration will also need to be factored in and this figure does not include the *KRAS* testing costs. The cost for the *KRAS* test is an additional £300 per patient tested.

## BACKGROUND

Colorectal cancer (also known as bowel, or large bowel cancer) develops from the lining of the colon and the rectum (the large intestine).<sup>1</sup> In England, it is the third most common cancer in men, with 16,475 new registrations in 2006 (13.6% of all malignancies) and is the second most common cancer in women, with 13,571 new registrations in 2006 (11.3% of all malignancies).<sup>2</sup> Colorectal cancer incidence increases with age, ranging from 20/100,000 population in people between the ages of 45 and 49 years to over 300/100,000 population in males and 200/100,000 in females over the age of 75 years. The median age at diagnosis is over 70 years.<sup>1</sup> The five-year relative survival rates for men and women diagnosed with colon cancer are 49.7% and 51.1% respectively, based on 2001-2007 data.<sup>3</sup>

Metastatic colorectal cancer is defined as being at stage IV of the American Joint Committee on Cancer (AJCC) tumour node metastases (TNM) system.<sup>1</sup> Patients presenting with metastatic disease range from 20% to 55% of all new cases.<sup>1</sup> This is possibly due to the often non-specific presenting features of the condition.<sup>4</sup> Of those who undergo surgery, approximately half will usually re-present within two years demonstrating advanced disease and distant metastases. The five-year survival rate for metastatic colorectal cancer is 12%.<sup>1</sup>

The main form of treatment is surgery (80% of patients).<sup>4</sup> The main causes of or risk factors for colorectal cancer are thought to include high intake of red and processed meat, excessive weight or obesity, inactivity, high alcohol intake and having a first-degree relative with bowel cancer.<sup>5</sup>

The main aims of treatment of metastatic colorectal cancer are to improve the duration and quality of life; management is usually palliative.<sup>1</sup> Patients with metastatic disease who are relatively fit are treated with chemotherapy as first- or second-line therapy. Chemotherapy options include 5-fluorouracil + folinic acid or leucovorin (5-FU/FA or 5-FU/LV), oxaliplatin plus infusional 5-FU/FA (FOLFOX), and irinotecan plus infusional 5-FU/FA (FOLFIRI). Capecitabine as single agent or in combination with oxaliplatin and occasionally tegafur with uracil are also used.<sup>1,6</sup>

Survival estimates for metastatic colorectal cancer managed with best supportive care (BSC) only, are roughly six months. This increases to 10-12 months with infusional 5-FU/FA and up to 20-21 months with FOLFIRI followed by FOLFOX or FOLFOX followed by irinotecan.<sup>1,6</sup>

Panitumumab (Vectibix ®, Amgen Ltd)<sup>7</sup> is a human IgG2 monoclonal antibody, directed against epidermal growth factor receptor (EGFR) administered by IV infusion. This receptor promotes cell growth so blockade results in inhibited tumour growth.<sup>8</sup> Panitumumab is licensed as monotherapy for the treatment of patients with EGFR-expressing metastatic colorectal carcinoma with non-mutated (wild-type) *KRAS* (Kirsten rat sarcoma 2 viral oncogene homologue) genotype after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens.<sup>7</sup>

Panitumumab was launched in the United Kingdom in January 2008.<sup>9</sup> The Committee for Medicinal Products for Human Use (CHMP) originally adopted a negative opinion in May 2007 and did not recommend granting of the marketing authorisation because when various factors were taken into account from the pivotal trial, including treatment cross-over issues, the small progression-free survival effect, absence of a favourable overall survival effect and adverse effect data; the overall risk:benefit ratio was considered to be unfavourable.<sup>8</sup>

This decision was re-examined and the company provided further information, including *KRAS* biomarker analysis. After further discussions, the CHMP felt that the adverse effects were manageable (~75% of patients who decreased or interrupted their panitumumab due to skin-related adverse effects restarted their initial dose).<sup>8</sup> The benefit:risk profile was considered 'marginally positive'.<sup>8</sup> A conditional marketing authorisation was granted in December 2007<sup>9</sup> in the specific, licensed patient group outlined above. The conditional aspect to the marketing authorisation means there is more evidence to come, particularly with regard to its safety and efficacy in patients whose tumours contain non-mutated *KRAS*.<sup>8</sup>

The National Institute for Health and Clinical Excellence (NICE) has proposed a technology appraisal of panitumumab in metastatic colorectal cancer, but no date has been set for publication.<sup>10</sup> NICE issued guidance in January 2007 on bevacizumab and cetuximab in metastatic colorectal cancer in a similar patient group.<sup>1</sup> Bevacizumab was not recommended for first-line treatment in combination with 5-FU plus folinic acid, with or without irinotecan and cetuximab in combination with irinotecan was not recommended for second-line or subsequent treatment after failure of an irinotecan containing regimen. A technology appraisal on cetuximab first-line in colorectal cancer is underway and due to be issued in July 2009.<sup>11</sup>

The Scottish Medicines Consortium (SMC) issued the following recommendation in May 2008:

"Panitumumab (Vectibix®▼) is not recommended as monotherapy for the treatment of patients with EGFR-expressing metastatic colorectal carcinoma with non-mutated (wild-type) *KRAS* after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens.

The holder of the marketing authorisation has not made a submission to the SMC regarding this product in this indication. As a result, we cannot recommend its use within NHS Scotland."<sup>12</sup>

The SMC therefore, rejected the use of panitumumab in Scotland due to the lack of a manufacturer's submission. Neither clinical nor cost effectiveness were considered.

## EFFICACY

### PHASE III STUDY

An open-label, multicentre, randomised controlled phase III trial (RCT) comparing panitumumab 6 mg/kg once every two weeks, plus best supportive care (BSC) with BSC alone in patients with chemo-refractory metastatic colorectal cancer was published in May 2007. BSC was defined in the trial as the best palliative care, not including antineoplastic agents. The primary endpoint was progression free survival (PFS) – calculated from the day of random assignment until radiologic progression or death. Secondary endpoints included objective response, overall survival (OS), time to and duration of response, and safety (adverse effect incidence, infusion reactions and anti-panitumumab antibody formation).<sup>13</sup>

The study was not blinded due to the skin toxicity that was an expected adverse effect of panitumumab. A total of 463 patients were randomly assigned (out of an original 1,040 screened) to panitumumab (n = 231) or BSC (n = 232).

A large number of patients screened failed to be included in the trial: 38% were not eligible for inclusion because they failed to meet laboratory inclusion criteria, and 27% did not meet the EGFR-staining criteria. All except one had received at least two prior chemotherapy regimens, and 37% had received three. The median follow up was 35 weeks (range: 15 – 76).<sup>13</sup>

At disease progression, patients in the BSC arm had the opportunity to receive panitumumab in an open-label extension study. This was an important confounder in the trial; 76% (n = 176) received panitumumab under this cross-over protocol. This cross-over also occurred early in the study, at a median progression time of seven weeks. This cross-over affected the long-term results of the study and made interpretation of OS very difficult.<sup>13</sup>

**TABLE 1: RESULTS OF THE VAN CUTSEM TRIAL**

Endpoint	Panitumumab + BSC (n = 231)	BSC (n = 232)
PFS (at week 8)*	49%	30%
	HR (Hazard Ratio) 0.54; 95% CI (Confidence Interval), 0.44 to 0.66; p < 0.0001	
Median PFS time	8 weeks (95% CI, 7.9 to 8.4)	7.3 weeks (95% CI, 7.1 to 7.7)
Mean PFS time	13.8 weeks	8.5 weeks
Objective response (after 12 months minimum)	n = 22 (10%)	0
Overall Survival	n = 45 (19%)	n = 38 (16%)
(Minimum follow up time was 52 weeks with a median follow up of 72 weeks (range, 52 to 113 weeks))	HR 1.00; 95%CI, 0.82 to 1.22; p = 0.81)	

\*It is important to note that for the primary endpoint, the only actual figures quoted for PFS were at eight weeks, the first assessment of progression. The results were presented graphically, and as such, the exact figures beyond eight weeks can not be determined from the published trial. A large proportion of patients had already progressed at this stage, which probably reflects the stage of illness of patients included in the trial. There was no significant difference between the OS rates of the two groups, but these results were confounded by the 76% of patients who crossed over from the BSC group.

A multicentre, open-label, single-arm extension study<sup>14</sup> assessing the efficacy and safety of panitumumab in metastatic colorectal cancer patients who had disease progression while receiving BSC in the original phase III trial was published.

Panitumumab was administered once every two weeks until disease progression, unacceptable toxicity or until discontinuation because of investigator/patient request. The primary endpoint was safety.<sup>14</sup>

No secondary endpoints were pre-specified, but efficacy was 'explored'. This included PFS, objective response rate, time to and duration of response, duration of stable disease and OS.<sup>14</sup> The safety data are reported in the 'Adverse Effects' section.

### **KRAS STATUS**

*KRAS* mutational status may be a marker of clinical outcome in colorectal cancer. *KRAS* is the human homolog of the Kirsten rat sarcoma-2 virus oncogene.<sup>15</sup> It can have mutations that are found in between 30 and 50% of colorectal cancer tumours.<sup>15</sup> It is postulated that patients with a *KRAS* mutation are unlikely to benefit from panitumumab and those with the wild-type, non-mutated form are more likely to show a response. Following the above phase III trial and extension study, further *KRAS* analysis was undertaken. The main objective of this analysis was to determine whether there was any difference in PFS between patients taking panitumumab whose tumours had wild-type or mutant *KRAS*.<sup>15</sup> The original trial data<sup>13</sup> were reanalysed<sup>15</sup> to assess the predictive role of *KRAS*; 427 of the original 463 patients were included in this *KRAS* analysis. The *KRAS* status could not be determined in the remaining 36 patients due to unavailable samples or samples with insufficient or poor quality DNA.<sup>15</sup> The primary endpoint was the difference between the relative effects of panitumumab compared with BSC on PFS in patients with tumours expressing mutant vs. wild-type *KRAS*. The results are shown in table 2 below;<sup>15</sup>

**TABLE 2: RESULTS OF THE KRAS ANALYSIS OF THE VAN CUTSEM TRIAL**

	<b>Panitumumab + BSC Wild-type <i>KRAS</i></b>	<b>BSC alone Wild-type <i>KRAS</i></b>	<b>Panitumumab + BSC Mutant <i>KRAS</i></b>	<b>BSC alone Mutant <i>KRAS</i></b>
PFS	12.3 weeks (93%)	7.3 weeks (96%)	7.4 weeks (90%)	7.3 weeks (95%)
	HR = 0.45, 95% CI; 0.34 to 0.59		HR = 0.99, 95% CI; 0.73 to 1.36	

As seen in table 2, PFS in patients with wild-type *KRAS* was significantly greater than PFS in patients with mutant *KRAS*, the p value was quoted as  $p < 0.0001$ . This analysis suggests that patients with tumours with wild-type rather than mutant *KRAS* should be selected. Similar results of a study with the EGFR inhibitor, cetuximab, support this.<sup>16</sup>

### **PACCE STUDY**

The 'Panitumumab Advanced Colorectal Cancer Evaluation' study was a phase III trial designed to assess whether panitumumab given with oxaliplatin and bevacizumab, or irinotecan and bevacizumab, improved PFS compared to oxaliplatin and bevacizumab or irinotecan and bevacizumab alone as first-line treatment in metastatic colorectal cancer.<sup>17-19</sup>

This trial was terminated early after an interim analysis suggested there was excess toxicity in the panitumumab / oxaliplatin / bevacizumab arms with inferior efficacy (PFS).<sup>8,18,20</sup> Whether this could be due to the triple combination or the panitumumab element is not fully understood. It is important to note that this trial studied panitumumab at an earlier stage i.e. first-line, than the licensed population considered in this document (patients who have failed fluoropyrimidine-, oxaliplatin- and irinotecan- containing regimens).

### **ADVERSE EFFECTS**

In the main trial discussed above,<sup>13</sup> the main toxicity experienced by patients was skin-related (90%).<sup>12</sup> The top five adverse events (AEs) experienced by patients in the panitumumab group are listed in Table 3 below:<sup>12,13</sup>

**TABLE 3: ADVERSE EVENTS**

<b>Adverse event</b>	<b>Panitumumab + BSC (n = 229)*</b>	<b>BSC (n = 234)</b>
Erythema	n = 146 (64%)	n = 2 (1%)
Dermatitis acneiform	n = 142 (62%)	n = 2 (1%)
Pruritis	n = 130 (57%)	n = 5 (2%)
Skin exfoliation	n = 56 (24%)	n = 0
Fatigue	n = 55 (24%)	n = 34 (15%)

\*Two patients in the panitumumab group did not receive it and were included in the BSC group for the safety analyses.

BSC patients who had disease progression in the original trial<sup>13</sup> were allowed to receive panitumumab in a cross over study.<sup>14</sup> The primary endpoint of this extension study was safety. Of the original 232 BSC patients, 177 were enrolled in the extension study, and 176 received at least one dose of panitumumab. Median follow-up was 61 weeks, and patients received a median of five (1 – 29) infusions.<sup>14</sup>

No deaths were considered to be related to AEs due to panitumumab treatment.<sup>14</sup> A total of 94 (53%) patients had at least one serious AE, 11 (6%) had a serious AE that was possibly linked to panitumumab and 29 (16%) and three (2%) experienced grade 3 and 4 respectively, treatment-related AEs. As before, the most frequently experienced AE were skin-related (including erythema, pruritis, acne, rash and paronychia), with similar incidences to those above. Hypomagnesaemia was exhibited by 51 (29%) patients, with grades 3 and 4 seen in five (3%) and two (1%) respectively.

Hypocalcaemia was exhibited in 25 (14%) patients with one (1%) having a grade 4 AE. Nineteen (11%) discontinued treatment with seven (4%) discontinuing because of skin and subcutaneous tissue disorders possibly related to panitumumab.

In summary, the AEs that patients are most likely to experience with panitumumab are skin-related – erythema, dermatitis and pruritis - and approximately 4% may need to discontinue treatment due to these AEs. Based on phase III trial data, patients are unlikely to experience a fatal AE.

## DOSAGE, ADMINISTRATION AND COST

Panitumumab is supplied as a concentration for solution for infusion. The recommended dose is 6 mg/kg once every two weeks. It is administered as an intravenous (IV) infusion over approximately 60 minutes; higher doses may take 90 minutes to administer.<sup>7</sup> The main trial continued treatment until patients' disease progressed or unacceptable toxicity occurred.<sup>13</sup> The mean PFS was 13.8 weeks for panitumumab, and this figure has been used to estimate expected costs.

The cost of panitumumab is £1,437 every two weeks (assuming an average weight of 70 kg) per patient.<sup>21</sup> Using the above mean PFS of 13.8 weeks, gives an approximate cost of £10,059 per patient for seven doses. This figure is the acquisition costs of panitumumab only, and does not take into consideration additional hospital costs.

Based on 2005 data, there are about 30,000 new cases of colorectal cancer per year in England,<sup>2</sup> 20-55% of which are metastatic,<sup>1</sup> i.e. an average of 37.5% (11,250) of new cases will have metastatic disease. There was little accurate data to work out what proportion of patients would be likely to benefit from treatment with panitumumab, so a number of consultants and network cancer pharmacists across the North of England were consulted to obtain estimates for the numbers of likely patients. Replies were received back from six of those contacted<sup>6,22-26</sup>, and numbers per 100,000 population ranged from 1 to 15. Taking an average of these figures gives us a potential number of patients of 7 per 100,000 population. At a cost of £10,059 per patient, this gives a potential cost of £70,413 per 100,000 population (this includes patients with wild-type *KRAS* only). Additional costs associated with administration will also need to be factored in.

A commercially available test for *KRAS* is available from a company external to the manufacturers (Lab 21). The cost for each test per patient is £300.<sup>27</sup> This would add a further £2,100 per 100,000 population to the above figures, although this does not include the cost of testing patients who then test negative to wild-type *KRAS*. About 57% of the population are estimated to have wild-type *KRAS* according to our experts contacted<sup>25,26</sup> so total *KRAS* testing may be around £3,900 per 100,000 population.

## PLACE IN TREATMENT

Panitumumab may offer patients with an otherwise poor prognosis the possibility of a small extended progression free survival. The European Medicines Agency (EMA) has issued conditional approval, which means that the company still has certain obligations to fulfil. Once these are fulfilled, the status will change to normal approval.

Panitumumab has a limited evidence base, and cross-over trial design means there are no useful overall survival data.

It would appear that limiting its use to the specific licensed population i.e. patients with wild-type *KRAS*, improves the likelihood of patients benefiting from it but the magnitude of benefit is still small.

## ARRANGEMENTS FOR PRESCRIBING

The summary of product characteristics for panitumumab states that treatment should be supervised by a physician experienced in the use of anti-cancer therapy.<sup>7</sup> Treatment should be prescribed and response supervised by an oncologist experienced in the use of anti-cancer therapies. It is not envisaged that shared care is appropriate or necessary for this drug.

## FUTURE DEVELOPMENTS

Panitumumab is also in phase II trials comparing:

- FOLFIRI plus panitumumab or FOLFIRI plus bevacizumab for second-line use for metastatic colorectal cancer;<sup>28</sup>
- Panitumumab compared to and in combination with irinotecan as third-line treatment in patients without *KRAS* mutations;<sup>29</sup>
- Panitumumab in combination with irinotecan as second-line therapy;<sup>30</sup>
- Evaluating panitumumab with FOLFIRI as first-line treatment for metastatic colorectal cancer.<sup>31</sup>

The following phase III trials are underway:

- Panitumumab in combination with and compared to FOLFOX as first-line therapy.<sup>32</sup>
- A comparison of panitumumab in combination with FOLFIRI with FOLFIRI alone as second-line treatment.<sup>33</sup>

Further information is also expected from studies looking at the safety, efficacy and quality of life in patients with and without the mutated form of *KRAS* who are taking panitumumab. The PICCOLO study is ongoing throughout the UK and is a randomised clinical trial of treatment for fluorouracil-resistant advanced colorectal cancer comparing standard single-agent irinotecan versus irinotecan plus panitumumab and versus irinotecan plus ciclosporin.<sup>34</sup>

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## REFERENCES

1. National Institute for Clinical Excellence. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. 2007;Technology Appraisal Guidance No 118. <http://www.nice.org.uk/nicemedia/pdf/TA118Guidance.pdf>.
2. Office for National Statistics. Cancer statistics registrations - Registrations of cancer diagnosed in 2006, England. Series MB1 No.37 [http://www.statistics.gov.uk/downloads/theme\\_health/MB1-37/MB1\\_37\\_2006.pdf](http://www.statistics.gov.uk/downloads/theme_health/MB1-37/MB1_37_2006.pdf) (accessed 11.06.2009).
3. Office for National Statistics. News Release. Cancer Survival. Survival rates in England, patients diagnosed 2001 - 2006 followed up to 2007. [http://www.statistics.gov.uk/downloads/theme\\_health/cancer-survival-Eng-2001-2006.pdf](http://www.statistics.gov.uk/downloads/theme_health/cancer-survival-Eng-2001-2006.pdf) (accessed 11.06.2009).
4. Cancer Research UK. Bowel Cancer Symptoms and Treatment. <http://info.cancerresearchuk.org/cancerstats/types/bowel/symptomsandtreatment/> (accessed 11.06.2009).
5. Cancer Research UK. CancerStats Key Facts - Large Bowel Cancer (Colorectal Cancer). [http://publications.cancerresearchuk.org/WebRoot/crukstoredb/CRUK\\_PDFs/CSBOWELKEYFACT08.pdf](http://publications.cancerresearchuk.org/WebRoot/crukstoredb/CRUK_PDFs/CSBOWELKEYFACT08.pdf). October 2008 (accessed 11.06.2009).
6. Dr Nicholas Wadd, Consultant Oncologist. Expert Comment. James Cook University Hospital. 23.02.09.
7. Electronic Medicines Compendium. Amgen Ltd - Vectibix Summary of Product Characteristics. <http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=20528> (accessed 11.06.2009).

8. European Medicines Agency. European Public Assessment Report 2007. Panitumumab - Scientific Discussion.  
<http://www.emea.europa.eu/humandocs/PDFs/EPAR/vectibix/H-741-en6.pdf>  
(accessed 02.12.2008).
9. New Drugs Online. Report for Panitumumab.  
[http://www.ukmi.nhs.uk/applications/ndo/record\\_view.asp?newDrugID=4165](http://www.ukmi.nhs.uk/applications/ndo/record_view.asp?newDrugID=4165)  
(accessed 18.11.2008).
10. National Institute for Clinical Excellence. Proposed Technology Appraisals. Colorectal cancer (metastatic)- panitumumab. <http://guidance.nice.org.uk/TA/Wave20/63>.
11. National Institute for Clinical Excellence. Colorectal cancer (first line) - cetuximab. 2008.  
<http://guidance.nice.org.uk/TA/Wave15/82> (accessed 11.06.2009).
12. Scottish Medicines Consortium. Statement of advice (No. 486/08). Panitumumab 20mg/ml concentrate for solution for infusion (Vectibix). Amgen Ltd. 2008.  
[http://www.scottishmedicines.org.uk/smc/files/panitumumab\\_Vectibix\\_Non\\_Submission\\_FINAL\\_May\\_2008\\_for\\_website\\_.pdf](http://www.scottishmedicines.org.uk/smc/files/panitumumab_Vectibix_Non_Submission_FINAL_May_2008_for_website_.pdf) (accessed 11.06.2009).
13. Van Cutsem E et al. Open label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol* 2007;25:1658-64.
14. Van Cutsem E et al. An open-label, single-arm study assessing safety and efficacy of panitumumab in patients with metastatic colorectal cancer refractory to standard chemotherapy. *Annals of Oncology* 2007;19:92-98.
15. Amado RG et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;26:1626-34.
16. Karapetis C et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008;359:1757-65.
17. ClinicalTrials.gov. PACCE: Panitumumab Advanced Colorectal Cancer Evaluation Study.  
<http://www.clinicaltrials.gov/ct/show/NCT00115765>  
(accessed 12.06.2009).
18. Hecht JR et al. An updated analysis of safety and efficacy of oxaliplatin (Ox)/bevacizumab (bev) +/- panitumumab (pmab) for first-line treatment (tx) of metastatic colorectal cancer (mCRC) from a randomized, controlled trial (PACCE). Abstract No 273. American Society of Clinical Oncology.  
[http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst\\_detail\\_view&confID=53&abstractID=10384\\_2008](http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=53&abstractID=10384_2008).
19. Hecht JR et al. Interim results from PACCE: Irinotecan (Iri)/bevacizumab (bev) ± panitumumab (pmab) as first-line treatment (tx) for metastatic colorectal cancer (mCRC). Abstract No 279. American Society of Clinical Oncology.  
[http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst\\_detail\\_view&confID=53&abstractID=10392\\_2008](http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=53&abstractID=10392_2008).
20. Hecht et al. OncologyEducation at ASCO GI 2008. Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) Update. April 3 2008  
[http://www.oncologyeducation.ca/Content/File/Latest\\_GI\\_updates/Apr\\_2008/ASCO\\_GI\\_2008\\_Update\\_-\\_PACCE\\_Irinotecan\\_Update.ppt](http://www.oncologyeducation.ca/Content/File/Latest_GI_updates/Apr_2008/ASCO_GI_2008_Update_-_PACCE_Irinotecan_Update.ppt) (accessed 18.12.08).
21. eMIMS. Vectibix. <http://www.mims.co.uk/drugs/index.cfm?fuseaction=MM2.Drugs.Detail&sSectionURL=cancer&sSubSectionURL=antineoplastics&sDrugURL=vectibix> (accessed 11.06.2009).
22. Dr Gregory Wilson, Consultant Medical Oncologist. Expert Opinion. The Christie Hospital, Manchester. 25.01.09.
23. Calum Polwart, Network Pharmacist. Expert Comment. North of England Cancer Network.12.05.09.

24. David Thomson, Lead Pharmacist. Expert Comment. Yorkshire Cancer Network. 13.05.09.
25. Dr Hans van der Voet, Clinical Oncologist. Expert Comment. The James Cook University Hospital, Middlesbrough. 14.05.09.
26. Amgen Medical Information. Expert Comment. Senior Medical Information Executive, Amgen UK Ltd. 18.05.09.
27. Personal Communication. Lab 21 - Conversation with Becky McCormack, Customer Services Manager regarding the KRAS test. 18.12.2008 + re-checked 12.06.2009.
28. ClinicalTrials.gov. SPIRITT: Second-Line Panitumumab Irinotecan Treatment Trial. Q2W FOLFIRI Regimen plus Panitumumab or a Q2W FOLFIRI Regimen plus Bevacizumab for 2nd-Line mCRC. <http://www.clinicaltrials.gov/ct2/show/NCT00418938?term=Panitumumab&rank=41> (accessed 12.06.2009).
29. ClinicalTrials.gov. Irinotecan and Panitumumab as 3rd line treatment for mCRC without KRAS mutations. <http://www.clinicaltrials.gov/ct2/show/NCT00792363?term=panitumumab&rank=46> (accessed 12.06.2009).
30. ClinicalTrials.gov. Panitumumab in Combination With Irinotecan Chemotherapy as 2nd-Line Therapy in Subjects With mCRC. <http://www.clinicaltrials.gov/ct2/show/NCT00475293?term=panitumumab&rank=31> (accessed 12.06.2009).
31. ClinicalTrials.gov. Panitumumab Plus FOLFIRI in First-Line Treatment of Metastatic Colorectal Cancer. <http://www.clinicaltrials.gov/ct2/show/NCT00508404?term=panitumumab&rank=22> (accessed 12.06.2009).
32. ClinicalTrials.gov. PRIME: Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy. <http://www.clinicaltrials.gov/ct2/show/NCT00364013?term=panitumumab&rank=23> (accessed 12.06.2009).
33. ClinicalTrials.gov. Comparison of Treatment Effect of Chemotherapy With Panitumumab to Chemotherapy Alone. <http://www.clinicaltrials.gov/ct2/show/NCT00339183?term=panitumumab&rank=20> (accessed 12.06.2009).
34. UK Clinical Research Network. Piccolo Study. <http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=1468> (accessed 14.04.2009).

**SUMMARY TABLE OF KEY STUDY**

Abbreviations: AE – adverse event, BSC – best supportive care, ECOG – Eastern Cooperative Oncology Group, EGFR - epidermal growth factor receptor, PFS – progression free survival, OS – overall survival

Trial	Design	Endpoints	Inclusion criteria	Exclusion criteria	Results	Adverse effects
Van Cutsem E et al. <sup>13</sup>	Phase III, multicentre, open-label, randomised controlled trial. Patients were randomly assigned 1:1 to panitumumab 6mg/kg every 2 weeks plus BSC, or BSC alone.	Primary endpoint was PFS (from the day of random assignment until radiologic progression or death). Secondary endpoints were best objective response by blinded central review, OS time, time to and duration of response and safety endpoints (incidences of AEs, infusion reactions and anti-panitumumab antibody formation).	Pathologic diagnosis of metastatic colorectal adenocarcinoma and radiologic disease progression during or within 6 months following the last dose of fluoropyrimidine, irinotecan and oxaliplatin. Patients also needed to be 18 years or older, ECOG score of 0-2, two or three prior chemo regimens for metastatic colorectal cancer, ≥1% EGFR positive membrane staining in evaluated tumour cells.	Symptomatic brain metastases, interstitial pneumonitis or pulmonary fibrosis, systemic chemotherapy or radiotherapy within 30 days before random assignment and prior EGFR agents.	For the panitumumab group (n = 231) compared to the control arm (n = 232), the primary endpoint of PFS was significantly improved at 8 weeks (49%) vs (30%), HR 0.54; 95% CI 0.44 to 0.66; p < 0.0001. Median PFS was 8 weeks (95% CI 7.9 to 8.4) vs 7.3 weeks (95% CI 7.1 to 7.7) respectively. There was no significant difference in OS with a minimum follow up time of 52 weeks, and a median follow up of 72 weeks. Results were 19% (n = 45) for the panitumumab arm and 16% (n = 38) for the control arm (HR 1.00; 95% CI 0.82 to 1.22; p = 0.81).	The main toxicity was skin related (90% in the panitumumab group vs 9% in the control group). The most common AE's in patients in the panitumumab arm compared to the control arm were erythema; 64%, (n = 146) vs 1% (n = 2), dermatitis acneiform; 62% (n = 142) vs 1% (n = 2) and pruritis; 57% (n = 130) vs 2% (n = 5). No deaths were considered to be related to AE's due to panitumumab treatment.