Panitumumab

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.2. Targeted therapies

ATC codes: L01FE02

Indication	Other specified malignant neoplasms of large intestine ICD11 code: 2B9Y
INN	Panitumumab
Medicine type	Biological agent
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 20 mg per mL in 5 mL vial concentrate for solution for infusion ; 20 mg per mL in 20 mL vial
EML status history	Application rejected in 2025 (TRS 1064)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Panitumumab
DrugBank	Panitumumab

Expert Committee recommendation

The Expert Committee recognized the substantial and increasing burden of metastatic colorectal cancer, particularly in low- and middle-income countries. The Committee noted that survival outcomes are worse in these settings as patients typically present in more advanced disease stages, in part due to limited screening programmes and limited access to effective diagnostic infrastructure. After diagnosis, access to surgery, chemotherapy, and radiotherapy is constrained by resource limitations and workforce shortages. In consideration of the evidence for benefits and harms, the Committee noted that overall survival benefit of panitumumab plus chemotherapy over chemotherapy alone in the second-line setting, and of panitumumab over best supportive care in the third-line setting was limited and below the established EML threshold of at least 4–6 months overall survival gain. The Committee considered the benefit of panitumumab plus chemotherapy over chemotherapy alone in the first-line setting was modest. Furthermore, the benefit appeared inconsistent in different patient subpopulations. Factors such as tumour location and additional RAS/BRAF mutations have been proposed as predictor of panitumumab efficacy. The Committee noted that the role of primary tumour location (right- versus left-sided) was a less definitive predictor: left-sided tumours respond better to anti-EGFR therapy than right-sided tumours. However, the effect is not absolute and is also influenced by RAS/BRAF mutation status. The Committee noted that in patients with metastatic colorectal cancer with RAS mutations, the addition of panitumumab to

chemotherapy was associated with a decrease in overall survival. Thus, the Committee emphasized the need to identify RAS mutation status and exclude patients with RAS mutations from receiving panitumumab. The Committee considered that limited access to the required diagnostic testing in resourced-constrained settings was likely to be an important barrier to appropriate and safe use of panitumumab. The Committee also noted that panitumumab was associated substantial risk of harms and showed no meaningful improvement in quality of life in most studies. Based on these considerations, the Expert Committee did not recommend the inclusion of panitumumab on the EML for the treatment of KRAS wild-type metastatic colorectal cancer.

Background

Panitumumab has not previously been considered for inclusion on the EML for treatment of KRAS/NRAS wild-type metastatic colorectal cancer or any other indication. The EML currently includes calcium folinate, capecitabine, fluorouracil, irinotecan and oxaliplatin for use in the treatment of metastatic colorectal cancer, as part of the fluorouracil, leucovorin and oxaliplatin (FOLFOX), fluorouracil, leucovorin and irinotecan (FOLFIRI), or capecitabine and oxaliplatin (CapeOx) treatment regimens. Panitumumab is indicated for treatment of adult patients with KRAS/NRAS wild-type metastatic colorectal cancer: in the first-line setting in combination with FOLFOX or FOLFIRI; in the second-line setting in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan); and as monotherapy after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens.

Public health relevance

Metastatic colorectal cancer is an advanced stage of disease in which tumour cells have migrated through either the bloodstream or lymphatic system to other organs such as the liver or lung. Around 20–25% of patients have metastatic disease at diagnosis and metastases eventually develop in up to 50% of all patients, most of whom die as a result (1–3). The 5-year relative survival rate is 5–15% in patients with widespread metastatic disease (4). The goals of therapy in metastatic colorectal cancer are to extend survival, potentially cure selected patients, prevent disease progression, reduce tumour-related symptoms and maintain health-related quality of life (5). The management of metastatic colorectal cancer involves numerous lines of systemic therapy (including chemotherapy and targeted biological agents), salvage surgery and maintenance therapy, interspersed with treatment-free intervals (6). Globally in 2022, there were about 1.9 million new cases and more than 900 000 deaths from colorectal cancer. About 60% of incident cases and 70% of deaths occurred in low- and middle-income countries (7). The primary target population for panitumumab is adult patients with KRAS/NRAS wild type metastatic colorectal cancer, which is responsible for most of the mortality in this disease, and which comprises about 50% of all metastatic colorectal cancer patients. Metastatic disease disproportionately affects patients in low- and middle-income countries due to delayed or intermittent screening programmes for colorectal cancer and other barriers to early diagnosis. The need for KRAS/NRAS testing to identify patients most likely to respond to treatment with panitumumab can also pose a barrier in low- and middle-income countries, where diagnostic capabilities are not available or affordable. However, the application reported that relevant diagnostic capabilities were increasingly available, especially in urban centres, academic centres or specialist cancer treatment facilities, which is anticipated to increase as further medicines-diagnostic combinations are made available.

Benefits

Comparison of panitumumab and chemotherapy or best supportive care A 2017 Cochrane systematic review and meta-analysis of 33 randomized controlled trials (15 025 participants) evaluated the efficacy and safety of epidermal growth factor receptor (EGFR) inhibitors for metastatic colorectal cancer (8). Comparisons evaluated included: (i) EGFR monoclonal antibodies (cetuximab and panitumumab) plus standard therapy (chemotherapy or best supportive care) versus standard therapy alone; (ii) EGFR tyrosine kinase inhibitors plus standard therapy versus standard therapy alone; (iii) EGFR inhibitor plus standard therapy versus another EGFR inhibitor; and (iv) EGFR inhibitor, anti-angiogenic therapy plus standard therapy versus anti-angiogenic therapy plus standard therapy alone. For the comparison of EGFR monoclonal antibody added to standard therapy in patients with KRAS exon 2 wild-type metastatic colorectal cancer, pooled analysis of trials in first-, second- and third-line treatment

settings showed high quality evidence that EGFR monoclonal antibody therapy added to standard therapy improved progression-free survival (hazard ration (HR) 0.70, 95% confidence interval (CI) 0.60 to 0.82; 12 studies, 4402 participants, unclear risk of bias), overall survival (HR 0.88, 95% CI 0.80 to 0.98; 12 studies, 4249 participants, low risk of bias) and tumour response rate (odds ratio (OR) 2.41, 95% CI 1.70 to 3.41; 12 studies, 4147 participants, unclear risk of bias). Of the 12 studies included in the comparison, 10 (eight with cetuximab, two with panitumumab) compared EGFR monoclonal antibodies and chemotherapy with the same chemotherapy alone, and two (one each with cetuximab and panitumumab) compared with best supportive care. The PRIME study was an open-label, randomized, multicentre phase III trial which evaluated the efficacy and safety of panitumumab with FOLFOX versus FOLFOX alone as first-line treatment of patients with metastatic colorectal cancer and Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 (9). A total of 1183 patients were randomized 1:1 to receive panitumumab 6 mg/kg every 2 weeks plus FOLFOX, or FOLFOX alone until disease progression or unacceptable toxicity. KRAS status was available for 1096 (93%) patients: 656/1096 (60%) had wild-type KRAS tumours and 440/1096 (40%) had mutant KRAS tumours. Outcome measures of progression-free and overall survival were analysed by KRAS status. In the KRAS wild-type subpopulation, addition of panitumumab to chemotherapy showed a significant improvement in progression-free survival (median progression-free survival 9.6 months versus 8.0 months; HR 0.80, 95% CI 0.66 to 0.97; P = 0.02). For overall survival, no significant difference was seen between treatment arms (median overall survival 23.9 months versus 19.7 months; HR 0.83, 95% CI 0.67 to 1.02; P = 0.07). In patients with mutant KRAS tumours, significant reductions were seen in both progression-free survival and overall survival in the panitumumab arm. In a subsequent prospective–retrospective analysis of data from the PRIME study, the efficacy and safety of panitumumab plus FOLFOX versus FOLFOX alone, based on the RAS (KRAS or NRAS) or BRAF mutation status, were evaluated (10). Among 512 patients without RAS mutations, the addition of panitumumab was associated with significant improvements in progression-free survival (10.1 months versus 7.9 months; HR 0.72, 95% CI 0.58 to 0.90; P = 0.04) and overall survival (26.0 months versus 20.2 months; HR 0.78, 95% CI 0.62 to 0.99; P = 0.04). In patients without KRAS mutations, the addition of panitumumab was associated with a significant improvement in overall survival (median overall survival 23.8 months versus 19.4 months; HR 0.83, 95% CI 0.70 to 0.98; P = 0.03). Based on this study, panitumumab received a score of 4 on the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) (11). Study 20050181 was a randomized phase III study that evaluated the efficacy and safety of panitumumab in combination with FOLFIRI versus FOLFIRI alone as second-line treatment of patients with metastatic colorectal cancer and ECOG performance of ≤ 2 (12). A total of 1186 patients were randomized 1:1 to receive panitumumab 6 mg/kg every 2 weeks plus FOLFIRI or FOLFIRI alone. KRAS status was available for 1083 (91%) patients: 597/1083 (55%) had wild-type KRAS tumours, and 486/1083 (45%) had mutant KRAS tumours. Outcome measures of progression-free and overall survival were analysed by KRAS status. In the KRAS wild-type subpopulation, addition of panitumumab to chemotherapy showed a significant improvement in progression-free survival (median progression-free survival 5.9 months versus 3.9 months; HR 0.73, 95% CI 0.59 to 0.90; P = 0.004). For overall survival, no significant difference was seen between treatment arms (median overall survival 14.5 months versus 12.5 months; HR 0.85, 95% CI 0.70 to 1.04; P = 0.12). In patients with mutant KRAS tumours, no differences in efficacy were observed. Based on this study, panitumumab received a score of 3 on the ESMO-MCBS (11). Study 20020007, an open-label, randomized, multicentre phase III study, evaluated the effect on overall survival of panitumumab plus best supportive care versus best supportive care alone in patients with chemorefractory KRAS or RAS wild-type metastatic colorectal cancer and ECOG performance status of ≤ 2 (13). Best supportive care was defined as investigator-judged best available palliative care. A total of 377 patients with wild-type KRAS exon 2 metastatic colorectal cancer were randomized 1:1 to receive panitumumab 6 mg/kg every 2 weeks plus best supportive care or best supportive care alone. RAS status was available for 324 (86%) patients: 270/324 (83%) had wild-type RAS tumours and 54 (17%) had mutant KRAS tumours. The primary endpoint was overall survival in wild-type KRAS exon 2 metastatic colorectal cancer. A secondary endpoint was overall survival in wild-type RAS metastatic colorectal cancer. Patients were followed for survival for the later of either 24 months or until ~250 deaths were observed. For patients with wild-type KRAS exon 2 tumours, a significant improvement was seen in overall survival for patients receiving panitumumab (median overall survival 10.0 months versus 7.4 months; HR 0.73, 95% CI 0.57 to 0.93; P < 0.01). Similarly, treatment with panitumumab also significantly improved overall

survival in patients with wild-type RAS tumours (median overall survival 10.0 months versus 6.9 months; HR 0.70, 95% CI 0.53 to 0.93; P = 0.01). Progression-free survival was also significantly improved among patients receiving panitumumab (median progression-free survival 3.6 months versus 1.7 months; HR 0.51, 95% CI 0.41 to 0.64; P < 0.0001). No overall survival benefit from panitumumab was observed in patients with RAS mutations. Comparison of panitumumab and bevacizumab A 2024 systematic review and meta-analysis of eight trials (2624 participants) evaluated the efficacy and safety of first-line cetuximab or panitumumab plus FOLFOX or FOLFIRI versus bevacizumab plus doublet chemotherapy in patients with RAS wild-type left-sided, right-sided and all-sided metastatic colorectal cancer (14). Five of the trials reported outcomes by tumour sidedness. In the left-sided population, no significant difference was seen between treatment arms for progression-free survival (HR 0.93, 95% CI 0.84 to 1.04). For overall survival, a significant difference was found favouring EGFR inhibitors plus chemotherapy (HR 0.80, 95% CI 0.71 to 0.90). Similar results were seen in the all-sided population. In the right-sided population, significant improvement was seen in progression-free survival favouring bevacizumab plus chemotherapy (HR 1.45, 95% CI 1.19 to 1.78), while no significant difference between treatment arms was observed for overall survival (HR 1.17, 95% CI 0.95 to 1.44).

Harms

The application stated that panitumumab is generally well tolerated, with most side-effects being manageable. Common adverse events include skin toxicities (such as rash), diarrhoea and electrolyte imbalances (hypomagnesaemia), in order of frequency. These toxicities are expected with EGFR inhibitors and can be mitigated with supportive care. Serious adverse effects, such as interstitial lung disease, are rare. Panitumumab does not cause significant myelosuppression. In the 2017 Cochrane systematic review and meta-analysis, for the comparison of EGFR monoclonal antibodies added to standard therapy in patients with KRAS exon 2 wild-type metastatic colorectal cancer, pooled analysis of trials in first-, second- and third-line treatment settings found moderate-certainty evidence of an increased risk associated with the addition of EGFR monoclonal antibodies of: overall grade 3 to 4 toxicity (OR 2.45, 95% CI 2.07 to 2.89; six studies, 2771 participants); grade 3 to 4 diarrhoea (OR 1.84, 95% CI 1.47 to 2.32; seven studies, 2909 participants); grade 3 to 4 rash (OR 23.42, 95% CI 13.22 to 41.49; seven studies, 2909 participants); and grade 3 to 4 neutropenia (OR 1.22, 95% CI 0.93 to 1.61; six studies, 2666 participants) (8). In the pivotal studies for panitumumab, adverse events of any grade were reported more frequently in patients receiving panitumumab than patients in the comparator arms. In the PRIME study, grade 3 to 4 adverse events occurring more frequently in the panitumumab arm and with > 5% difference compared with the FOLFOX arm included skin toxicity, diarrhoea, fatigue, mucositis and hypomagnesaemia (9). In study 20050181, reported grade 3 to 4 adverse events were similar to those reported in the PRIME study (12). In study 20020007, adverse events of any grade with a ≥ 5% difference between treatment arms included rash, dermatitis acneiform and hypomangnesaemia (13).

Additional evidence

A 2023 systematic review and meta-analysis of two randomized controlled trials and two cohort studies (1436 participants) evaluated the benefits and safety of panitumumab (alone or in combination with chemotherapy) and cetuximab (alone or in combination with chemotherapy) for the treatment of KRAS wild-type metastatic colorectal cancer (15). Meta-analysis of pooled data found no significant differences between treatments for progression-free survival (HR 0.92, 95% CI 0.83 to 1.02), overall survival (HR 0.91, 95% CI 0.81 to 1.03) or response rate (HR 1.22 95% CI 0.96 to 1.61). In terms of safety, no significant differences were seen between groups in the incidence of acneiform rash, severe acneiform rash, diarrhoea or severe diarrhoea. In the panitumumab arm, a significantly lower incidence of paronychia was seen, while in the cetuximab arm, significantly lower incidences of hypomagnesaemia and severe hypomagnesaemia were observed. The ASPECCT study was a randomized, multicentre, open-label phase III non-inferiority trial comparing panitumumab and cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer and EGOC performance of ≤ 2 (16). A total of 999 patients were randomized in a 1:1 ratio to receive panitumumab 6 mg/kg every 2 weeks or cetuximab 400 mg/m2 initially, followed by 250 mg/m2 every week until disease progression, intolerability, or withdrawal of consent. In the primary analysis of overall survival, panitumumab was reported to be non-inferior to cetuximab.

Median overall survival in the panitumumab and cetuximab arms were 10.4 months and 10.0 months, respectively (HR 0.97, 95% CI 0.84 to 1.11). Panitumumab retained 105.7% of the effect of cetuximab of overall survival seen in this study, meeting the predefined non-inferiority criteria. The incidence of adverse events between treatment arms was similar, including any grade and grade 3 or4. Grade 3 or4 skin toxicity occurred in 13% and 10% of patients treated with panitumumab and cetuximab, respectively. In patients receiving panitumumab, there was a lower occurrence of grade 3 or 4 infusion reactions, but a higher occurrence of grade 3 or 4 hypomagnesaemia.

Cost / cost effectiveness

The application presented a summary of available list price information for panitumumab. Among high-income countries, list prices for the 100 mg (400 mg) vials ranged from 277 United States dollars (US$) (US$ 1109) in Taiwan, China to US$ 750 (US$ 3000) in Kuwait. In upper middle-income countries, list prices for the 100 mg (400 mg) vials ranged from US$ 228 (US$ 912) in South Africa to US$ 11 354 (US$ 45 416) in Argentina. In lower middle-income countries, list prices for the 100 mg (400 mg) vials ranged from US$ 120 (US$ 480) in Egypt to US$ 447 (US$ 1788) in Morocco. A 2014 study evaluated the cost–effectiveness of panitumumab plus modified FOLFOX6 versus bevacizumab plus modified FOLFOX6 as first-line treatment of patients with RAS wild-type metastatic colorectal cancer from a French health-care system perspective (20). Based on efficacy outcomes from the PEAK study which showed better efficacy outcomes for people treated with panitumumab plus FOLFOX6 versus those treated with bevacizumab plus FOLFOX6, the incremental costs per life year gained and per quality-adjusted life year (QALY) were 26 918 euros (€) and €36 577, respectively. The authors concluded that compared with bevacizumab treatment, panitumumab treatment represented good value for money and could be considered cost-effective in France at a willingness-to-pay threshold of between €40 000 and €60 000. A similar study evaluated the cost–effectiveness of panitumumab plus modified FOLFOX6 versus bevacizumab plus modified FOLFOX6 as first-line treatment of patients with RAS wild-type metastatic colorectal cancer from a Greek health-care system perspective (21). The incremental cost–effectiveness ratio of panitumumab treatment was €34 664 per QALY. Probabilistic sensitivity analysis found that the probability of panitumumab treatment being cost-effective over bevacizumab treatment was 81.5% at the predetermined threshold of €51 000 per QALY gained. A 2013 study from the United Kingdom of Great Britain and Northern Ireland evaluated the clinical effectiveness and cost–effectiveness of panitumumab monotherapy and cetuximab (mono- or combination chemotherapy) for treatment of KRAS wild-type metastatic colorectal cancer, and bevacizumab in combination with non-oxaliplatin chemotherapy for treatment of metastatic colorectal cancer after first-line chemotherapy (22). The economic evaluation included five studies. The base-case incremental cost–effectiveness ratio was: 98 000 pounds sterling (£) per QALY for cetuximab in KRAS wild-type patients compared with best supportive care; £150 000 per QALY for panitumumab compared with best supportive care; and £88 000 per QALY or cetuximab plus irinotecan compared with best supportive care. The authors concluded that although cetuximab and panitumumab appear to be clinically beneficial for patients with KRAS wild-type metastatic colorectal cancer compared with best supportive care, they are likely to represent poor value for money when judged by cost–effectiveness criteria currently used in the United Kingdom.

WHO guidelines

WHO guidelines for the treatment of metastatic colorectal cancer are not currently available. Guidelines for metastatic colorectal cancer from the National Comprehensive Cancer Network (NCCN) (17), the European Society for Medical Oncology (18), and the American Society of Clinical Oncology (19) include recommendations for the use of panitumumab or cetuximab as part of first-, second- or later-line treatment of KRAS/NRAS wild-type metastatic colorectal cancer. In first-line therapy, these medicines are recommended in combination with chemotherapy, while in later lines, they may be used as monotherapy or in combination with chemotherapy.

Availability

Panitumumab has regulatory approval for use in the treatment of metastatic colorectal cancer in more than 50 countries globally.

Other considerations

The EML cancer experts group reviewed the application and provided its advice for the Expert Committee. The group did not support the inclusion of panitumumab on the EML for treatment of adults with KRAS/NRAS wild-type metastatic colorectal cancer. The group judged that the magnitude of the overall survival gains were moderate in the first-line setting, and below the recommended threshold of 4–6 months in the second- and third-line settings. The group also highlighted the need for RAS mutation testing to identify patients with RAS mutations, given that the addition of panitumumab to chemotherapy in this population is associated with decreased overall survival compared with chemotherapy alone. The cancer team within the Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed the application and advised that it did not support the inclusion of panitumumab on the EML because the therapeutic benefit was insufficient based on the available evidence.

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