Panitumumab

Application for Inclusion of Panitumumab in the WHO Essential Medicines List.

Proposal: treatment of adults with KRAS/NRAS wild-type metastatic colorectal cancer in frontline, second line, and later lines of therapy.

Submitted by Resonance

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1. SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION

Purpose

This application proposes the inclusion of panitumumab on the WHO Essential Medicines List **for the treatment of adults with KRAS/NRAS wild-type metastatic colorectal cancer in frontline, second line, and later lines of therapy.**

Background about treatment of metastatic colorectal cancer

Panitumumab is proposed for inclusion on the WHO EML for the treatment of metastatic colorectal cancer (mCRC), which is a significant and growing burden in low- and middle-income countries (LMICs).[1-17] Colorectal cancer is among the five most common cancers worldwide, with approximately 1.9 million new cases annually. Over 60% of colorectal cancer deaths occur in LMICs, where access to modern targeted therapies is severely limited.

While established colorectal cancer screening programs are present in many high-income countries, few such programs exist in LMICs. Thus, predictably (as for many other cancer types), colorectal cancer in LMICs usually presents at advanced stages.

Panitumumab information

Panitumumab, a fully humanized monoclonal antibody targeting the epidermal growth factor receptor (EGFR) now has a very wide base of use. It has been available since 2006 in the United States and 2007 in the EU, and is reimbursed broadly in high-income countries in first, second, and third-line regimens. It is well-established as a therapeutic option in treatment guidelines, including those from the European Society of Medical Oncology (EMSO) and the American Society of Clinical Oncology (ASCO).

Its inclusion in the WHO EML will provide a critical therapeutic option for mCRC patients in LMICs, improving survival duration and quality of life.

Efficacy, safety, and cost effectiveness of panitumumab

- Compared to traditional chemotherapy alone, panitumumab significantly improves PFS and OS in mCRC patients with wild-type KRAS/NRAS.
- When combined with first-line doublet chemotherapy, panitumumab significantly improves overall survival compared with bevacizumab in left-sided wild-type KRAS or NRAS mCRC.
- Compared to best supportive care in chemorefractory mCRC, panitumumab significantly improves overall survival.
- Compared to conventional chemotherapy, panitumumab does not cause significant myelosuppression, reducing the risk of life-threatening infections, bleeding, and transfusion dependence. Like all medicines, it does have cautions with respect to adverse events, some of which are specifically important to monitor and prevent.
- Panitumumab is reimbursed in multiple lines of therapy and has proven cost-effective in the settings where it is available.
- Addition of panitumumab to the EML would allow national governments to make decisions based on their own affordability criteria, and for some to enter discussions with medicines sponsors for addition to national benefit packages, especially where cancer medicines are funded via universal health coverage schemes.

2. CONSULTATION WITH WHO TECHNICAL DEPARTMENTS

The submitter has engaged with the WHO NCD (Cancer) Section in consideration of preparation of the current submission and sought the advice of the WHO EML Section with respect to content that may be useful in support of the application. No other WHO technical departments were consulted. Letters of support are anticipated to be sent directly to the WHO EML Section.

3. OTHER ORGANIZATIONS CONSULTED AND SUPPORTING THE SUBMISSION

Members of global oncology organizations, professional societies, non-governmental charitable organizations, and academic organizations were consulted with respect to the content and their support for the submission. Letters of support are anticipated to be sent directly to the WHO EML Section.

4. KEY INFORMATION FOR THE PROPOSED MEDICINES

International non-proprietary name (INN) of the proposed medicine

- Panitumumab

Anatomical therapeutic chemical (ATC) code of the proposed medicine

- **L01FE02** (Epidermal Growth Factor Receptor inhibitors), as updated in March, 2021 and found at this Link.

Dosage form(s) and strength(s) of the proposed medicines

- **Dosage forms and strengths**: Panitumumab liquid for injection: 100 mg/5 mL (20 mg/mL) and 400 mg/20 mL (20 mg/mL) in single-dose vials
- **Route of administration**:
    - Panitumumab is administered as a continuous intravenous infusion as an intravenous infusion over 60 minutes (≤ 1000 mg) or 90 minutes (> 1000 mg).
    - If the first infusion is tolerated, administer subsequent infusions over 30 to 60 minutes.

Indications

The ICD-11 code of relevance to metastatic colorectal cancer is **2B90**: Malignant neoplasms of colon. https://icd.who.int/browse/2024-01/mms/en#1265576634

5. LISTING AT AN INDIVIDUAL MEDICINE OR REPRESENTATIVE OF A PHARMACOLOGICAL CLASS/THERAPEUTIC GROUP

The proposal relates to an individual medicine - panitumumab.

Panitumumab is a human IgG2 kappa monoclonal antibody targeting the epidermal growth factor receptor (EGFR). Panitumumab is off patent, but no biosimilars exist yet.

It is beyond the scope of this submission to present clinical safety and efficacy data for other EGFR inhibitors that might be considered like panitumumab, but the Expert Committee may wish to consider whether EGFR inhibitors should be included in the EML as a therapeutic group.

6. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE

Disease burden

Metastatic CRC (mCRC) is an advanced stage of disease in which tumor cells have migrated through either the bloodstream or lymphatic system to other organs such as the liver or lung; 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.[18-20] The 5 year relative survival rate is only 5–15% in patients with widespread metastatic disease, indicating that there is a need to improve treatment outcomes.[21] The goals of therapy in mCRC are to extend survival, potentially cure selected patients, prevent disease progression, reduce tumor-related symptoms and maintain HRQL.[22] The management of mCRC involves numerous lines of systemic therapy (including chemotherapy and targeted biologic agents), salvage surgery, and maintenance therapy, interspersed with treatment-free intervals.[23]

Pre-existing comorbidities complicate the selection of systemic therapy. A retrospective database analysis of patients with mCRC demonstrated that comorbidities are common: the most prevalent are cardiovascular disease (56%), hypertension (41%), other ischemic heart disease (a subcategory of arterial thromboembolic events; 6%), coronary artery disease (14%), dysrhythmias (14%), venous thromboembolic events (5%), and congestive heart failure (7%).[24]

Global epidemiology

Colorectal cancer is a growing public health challenge in LMICs. In 2020, there were about 1,900,000 new cases and 935,000 deaths from colorectal cancer, with a substantial proportion occurring in LMICs, including sub-Saharan Africa, South America, and Southeast Asia.[11-15] As these countries undergo rapid urbanization and lifestyle changes, including increased consumption of processed foods and decreased physical activity, the incidence of colorectal cancer continues to rise.

- **Incidence in LMICs**: Over 60% of colorectal cancer cases occur in LMICs, with limited access to screening, diagnostics, and treatment.
- **Mortality**: Colorectal cancer mortality in LMICs is disproportionately high, often due to late-stage diagnosis and lack of access to effective therapies like panitumumab.

Impact on care in low- and middle-income countries

The primary target population for panitumumab is adult patients with metastatic colorectal cancer (mCRC) that is KRAS/NRAS wild type, which contributes the majority of the mortality in this disease, and which comprises about 50 % of all mCRC patients. Unfortunately, metastatic disease disproportionately affects patients in LMICs due to delayed or intermittent CRC screening programs and other barriers to early diagnosis. The need for KRAS/NRAS testing to identify patients most likely to respond can also pose a barrier in LMICs, where diagnostic capabilities are not available or affordable. However, there is an increasing availability of relevant diagnostic capabilities (locally or via distributed network services), especially in urban centers, academic centers or specialist cancer treatment facilities, which can only be anticipated to increase as further medicines-diagnostic combinations are made available.

Multiple therapeutic options are needed since many patients present with metastatic disease and others develop metastatic disease despite initial therapy for localized disease

The availability of multiple therapeutic options with differing safety profiles and mechanism of action allows treatments to be tailored over multiple lines of therapy according to the characteristics of the individual patient.

7. TREATMENT DETAILS

Indication

The general indications for panitumumab are similar across regions, and summarized as follows:

> Panitumumab is indicated for treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC):
>
> - In first-line in combination with FOLFOX or FOLFIRI.
> - In second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).
> - As monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

Panitumumab was first approved in the United States in 2006, and by the EMA in 2007. Like many medicines, the indications for use have grown over time with the development of the evidence base and with the evolution of other medicines used in the management of the target condition. Specific label indications for the United States and Europe are provided below.

UNITED STATES

Panitumumab is an epidermal growth factor receptor (EGFR) antagonist approved in the United States in 2006. Its current label includes the following (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125147s210lbl.pdf):

Panitumumab is indicated for the treatment of wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC):

- In combination with FOLFOX for first-line treatment.
- As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy.
- Limitation of Use: Panitumumab is not indicated for the treatment of patients with RAS-mutant mCRC or for whom RAS mutation status is unknown.

EUROPE

Panitumumab has been approved by the EMA with a brand name Vectibix. Vectibix is indicated for the treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC):

- In first-line in combination with FOLFOX or FOLFIRI.
- In second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).
- As monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

Administration and toxicity management

- **Dosage forms and strengths**: Panitumumab liquid for injection: 100 mg/5 mL (20 mg/mL) and 400 mg/20 mL (20 mg/mL) in single-dose vials
- **Route of administration**: Panitumumab is administered as a continuous intravenous infusion over 60 minutes (≤ 1000 mg) or 90 minutes (> 1000 mg). If the first infusion is tolerated, administer subsequent infusions over 30 to 60 minutes.
- **Toxicity management:**
  - Infusion Reactions: Reduce infusion rate by 50% for mild reactions; terminate the infusion for severe infusion reactions.
  - Dermatologic Toxicity: Withhold or discontinue for severe or intolerable toxicity; reduce dose for recurrent, grade 3 toxicity.
- **Recommended dosage**: 6 mg/kg every 14 days
- **Duration of therapy**: Until disease progression or unacceptable toxicity occurs.

8. REVIEW OF EVIDENCE FOR BENEFITS AND HARMS

Evidence of Efficacy and Safety of epidermal growth factor receptor inhibitors for RAS wild type unresectable metastatic colorectal cancer

- Panitumumab is a fully human monoclonal antibody targeting the epidermal growth factor receptor (EGFR). It is an effective therapy for patients with KRAS/NRAS wild-type mCRC and is approved in more than 70 countries as part of frontline, second line, and third line therapy.[25-29] Pivotal randomized study results are summarized in **Table 1**.

- The *RAS* gene family has three broadly expressed members: *KRAS*, *NRAS*, and *HRAS*.[30-32] These three isoforms share sequence identity in all regions that regulate the activation state and effector functions, and high sequence similarity in most of the remaining gene.[33-38] Each member of the *RAS* gene family functions as an oncogene when mutated, by driving constitutive ligand-independent mitogen-activated protein kinase signaling. The *KRAS* exon 2 mutations in codons 12 and 13 are the most frequent *RAS* mutations in mCRC; however, additional mutations in *KRAS* and *NRAS* also activate *RAS* family oncogenes and may therefore be important in selecting patients for EGFR inhibitor therapy (Vaughn *et al.*, 2011).[39] In this application, *KRAS* (exons 2, 3, and 4) and *NRAS* (exons 2, 3, and 4) are collectively referred to as *RAS*.

- A phase 3 trial evaluating panitumumab plus best supportive care (BSC) vs best supportive care in chemorefractory wild-type KRAS or RAS metastatic colorectal cancer showed that panitumumab significantly increased overall survival.[40] Three hundred seventy-seven patients with chemorefractory wild-type KRAS exon 2 metastatic colorectal cancer (mCRC) were randomized 1:1 in a phase 3 trial to receive panitumumab (6 mg kg 1 Q2W) plus BSC or BSC. On-study crossover was prohibited. RAS mutation status was determined by central laboratory testing. The primary endpoint was OS in wild-type KRAS exon 2 mCRC; OS in wild-type RAS mCRC (KRAS and NRAS exons 2, 3, and 4) was a secondary endpoint. The median OS was 10.0 months with panitumumab plus BSC vs 7.4 months with BSC (HR 0.73; 95% CI 0.57–0.93; P=0.0096). Panitumumab significantly improved OS in wild-type KRAS exon 2 mCRC. The effect was more pronounced in wildtype RAS mCRC, validating previous retrospective analyses.

Table 1. Summary of key efficacy results from pivotal studies of panitumumab in patients with wild type *KRAS* exon 2 mCRC[40]

	Study 20050203 (PRIME) First line		Study 20050181 Second line		Study 20100007 Third line	
	Panitumumab + FOLFOX4 (n = 325)	FOLFOX (n = 331)	Panitumumab + FOLFIRI (n = 303)	FOLFIRI (n = 294)	Panitumumab + BSC (n=189)	BSC (n=188)
KRAS exon 2 ascertainment	93%		91%		92%	
Response rate	55%	48%	35%	10%	17%	0%
Median PFS	9.6 months	8.0 months	5.9 months	3.9 months	3.6 months	1.7 months
PFS benefit	1.6 months		2.0 months		1.9 months	
PFS HR (95% CI)	0.80 (0.66–0.97) *P* = 0.02		0.732 (0.59–0.90) *P* = 0.004		0.51 (0.41–0.64) *P* < 0.0001	
Median OS	23.8 months	19.4 months	14.5 months	12.5 months	10 months vs. 7.4 months	
OS benefit	4.4 months		2.0 months		2.6 months	
OS HR (95% CI)	0.83 (0.70–0.98) *P* = 0.03		0.85 (0.70–1.04) *P* = 0.12		0.73 (0.57-0.93) *P*<0.01	

**76% of control arm received panitumumab after progression*

- The first-line treatment choice of EGFR inhibitors plus doublet chemotherapy vs. bevacizumab plus doublet chemotherapy remains a topic of interest for patients with left-sided RAS WT mCRC. A systematic literature review and meta-analysis of clinical trial data published between 2015 and 2024 evaluated the relative efficacy and safety of first-line EGFRIs plus doublet chemotherapy (FOLFIRI or FOLFOX) vs. bevacizumab plus doublet chemotherapy for patients with RAS WT left-sided mCRC, as well as in all- and right-sided tumors.[41]
    - Eight trials included 2624 patients, and 5 of them reported outcomes by tumor sidedness.
    - In the left-sided population, overall survival (OS) (Hazard Ratio (HR) = 0.80, 95% Confidence Interval (CI): 0.71-0.90) and objective response rate (ORR) (Odds ratio [OR]=1.61, 95% CI: 1.30-1.99) favored EGFR inhibitors plus chemotherapy, while no statistically significant differences were observed for progression-free survival (PFS) (HR=0.93, 95% CI: 0.84-1.04). Similar results were found in the all-sided population.
    - In the right-sided population, PFS favored bevacizumab plus chemotherapy (HR=1.45, 95% CI: 1.19-1.78), while no statistically significant differences were observed for OS (HR=1.17, 95% CI: 0.95-1.44) or ORR (OR=0.99, 95% CI: 0.69-1.41). Early tumor shrinkage in the all-sided population favored EGFRI plus chemotherapy (OR=1.72; 95% CI: 1.36-2.17); limited data precluded evaluation by sidedness.

- Safety information was available in 6 trials for all-sided tumors and 1 trial for left-sided tumors, each demonstrating typical class-specific adverse events. This meta-analysis confirmed the benefits in first-line therapy of EGFR inhibitors plus chemotherapy over bevacizumab plus chemotherapy in patients with left-sided RAS WT mCRC, a finding concordant with 2024 guidelines from NCCN and 2023 guidelines from ESMO (see section 9).

- Multiple randomized clinical trials (RCTs) have demonstrated the efficacy of panitumumab in patients with KRAS/NRAS wild type mCRC. A few are summarized below:
  - In the PRIME trial, panitumumab combined with FOLFOX (a chemotherapy regimen) significantly improved progression-free survival (PFS) and overall survival (OS) compared to chemotherapy alone in patients with wild-type KRAS.
  - A Cochrane Review included 5 randomized studies comparing EGFR inhibitors to standard therapy and documented improved PFS, OS, and response rates, all with GRADE scores of "high" for the quality of the evidence (**Figures 1 and 2**).[42]

Summary of findings for the main comparison. EGFR MAb in *KRAS* exon 2 WT for metastatic colorectal cancer

EGFR MAb in *KRAS* exon 2 WT for metastatic colorectal cancer

Patient or population: people with metastatic colorectal cancer - *KRAS* exon 2 WT
Intervention: EGFR MAb in addition to standard treatment

Comparison: standard treatment

Setting: multicentre international studies

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Standard therapy	EGFR MAb + standard therapy			
Progression-free survival Follow-up: 13 to 38 months	**300 per 1000** (at 1 year)[4]	**221 per 1000** (197 to 254)	**HR 0.70** (0.60 to 0.82)	4402 (12 studies)	⊕⊕⊕⊕ **high** [1]
Overall survival Follow-up: 13 to 38 months	**400 per 1000** (at 2 years)[4]	**352 per 1000** (335 to 392)	**HR 0.88** (0.80 to 0.98)	4249 (12 studies)	⊕⊕⊕⊕ **high**
Tumour response rate Follow-up: 13 to 38 months	**Study population**		**OR 2.41** (1.70 to 3.41)	4147 (12 studies)	⊕⊕⊕⊕ **high** [1]
	331 per 1000	**456 per 1000** (411 to 501)			

Figure 1. Meta-analysis of progression-free survival, overall survival, and tumor response rate with the use of anti-EGFR monoclonal antibodies for patients with KRAS wild type metastatic colorectal cancer.[42]

- Panitumumab is generally well-tolerated, with most side effects being manageable. Common adverse events include skin toxicities (such as rash), diarrhea, and electrolyte imbalances (hypomagnesemia). These toxicities are expected with EGFR inhibitors and can be mitigated with supportive care. Serious adverse effects, such as interstitial lung disease, are rare.
- In the Cochrane Review mentioned above, grade 3 or 4 diarrhea occurred in 16% of patients and grade 3 or 4 rash in 20.5%.

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	331 per 1000	**456 per 1000** (411 to 501)			
Overall grade 3 to 4 toxicity Follow-up: 13 to 38 months	**Study population**		**OR 2.45** (2.07 to 2.89)	2771 (6 studies)	⊕⊕⊕⊖ **moderate** [2] due to risk of bias
	547 per 1000	**747 per 1000** (714 to 777)			
Grade 3 to 4 diarrhoea Follow-up: 13 to 38 months	**Study population**		**OR 1.84** (1.47 to 2.32)	2909 (7 studies)	⊕⊕⊕⊖ **moderate** [2] due to risk of bias
	95 per 1000	**162 per 1000** (134 to 196)			
Grade 3 to 4 rash Follow-up: 13 to 38 months	**Study population**		**OR 23.42** (13.22 to 41.49)	2909 (7 studies)	⊕⊕⊕⊖ **moderate** [2] due to risk of bias
	11 per 1000	**205 per 1000** (127 to 313)			
Grade 3 to 4 neutropenia Follow-up: 13 to 38 months	**Study population**		**OR 1.22** (0.93 to 1.61)	2666 (6 studies)	⊕⊕⊕⊖ **moderate** [3] due to imprecision
	256 per 1000	**296 per 1000** (240 to 357)			
Quality of life	4 of 5 studies showed no difference between the 2 arms or equivocal results; the last study showed significant improvement on quality of life with the addition of EGFR MAb.			2258 (5 studies)	⊕⊕⊕⊖ **moderate** [2] due to risk of bias

Figure 2. Meta-analysis of grade 3 or 4 toxicities with the use of anti-EGFR monoclonal antibodies for patients with KRAS wild type metastatic colorectal cancer.[42]

Comparative Efficacy and Safety

- Compared to traditional chemotherapy alone, panitumumab significantly improves PFS and OS in mCRC patients with wild-type KRAS/NRAS.
- When combined with first-line doublet chemotherapy, panitumumab improves overall survival compared with bevacizumab, an anti-vascular endothelial growth factor (anti-VEGF).[26] The two therapies were compared in a randomized, open-label, phase 3 clinical trial studying the addition of panitumumab vs bevacizumab to standard first-line chemotherapy for treatment of RAS wild-type, left-sided, metastatic colorectal cancer.
    - Treatment included panitumumab (n = 411) or bevacizumab (n = 412) plus modified fluorouracil, l-leucovorin, and oxaliplatin (mFOLFOX6) every 14 days.
    - In the as-treated population (n = 802; median age, 66 years; 282 [35.2%] women), 604 (75.3%) had left-sided tumors. Median follow-up was 61 months. Median overall survival was 37.9 months with panitumumab vs 34.3 months with bevacizumab in participants with left-sided tumors (hazard ratio [HR] for death, 0.82; 95.798% CI, 0.68-0.99; P = .03) and 36.2 vs 31.3 months, respectively, in the overall population (HR, 0.84; 95% CI, 0.72-0.98; P = .03).

- Median progression-free survival for panitumumab vs bevacizumab was 13.1 vs 11.9 months, respectively, for those with left-sided tumors (HR, 1.00; 95% CI, 0.83-1.20) and 12.2 vs 11.4 months overall (HR, 1.05; 95% CI, 0.90-1.24).
- Response rates with panitumumab vs bevacizumab were 80.2% vs 68.6%, respectively, for left-sided tumors (difference, 11.2%; 95% CI, 4.4%-17.9%) and 74.9% vs 67.3% overall (difference, 7.7%; 95% CI, 1.5%-13.8%).
- Median duration of response with panitumumab vs bevacizumab was 13.1 vs 11.2 months for left-sided tumors (HR, 0.86; 95% CI, 0.70-1.10) and 11.9 vs 10.7 months overall (HR, 0.89; 95% CI, 0.74-1.06).
- Curative resection rates with panitumumab vs bevacizumab were 18.3% vs 11.6% for left-sided tumors; (difference, 6.6%; 95% CI, 1.0%-12.3%) and 16.5% vs 10.9% overall (difference, 5.6%; 95% CI, 1.0%-10.3%).
- Common treatment-emergent adverse events were acneiform rash (panitumumab: 74.8%; bevacizumab: 3.2%), peripheral sensory neuropathy (panitumumab: 70.8%; bevacizumab: 73.7%), and stomatitis (panitumumab: 61.6%; bevacizumab: 40.5%).
- Among patients with RAS wild-type metastatic colorectal cancer, adding panitumumab, compared with bevacizumab, to standard first-line chemotherapy significantly improved overall survival in those with left-sided tumors and in the overall population.

Summary of Comparative Effectiveness

In summary, panitumumab is an effective therapy for patients with KRAS/NRAS wild-type mCRC as part of frontline, second line, and third line therapy, where it improves response rates, progression-free survival, and overall survival.[25-29,42]

Summary of Comparative Safety

The safety profile of panitumumab is favorable compared to conventional chemotherapy, but it does have potential toxicities:

- **Dermatologic toxicity**: Grade 3 or 4 rash complicates the use of panitumumab in 16% of cases, and can require dose reductions, dose omissions, and even treatment cessation in severe or recurrent cases.[43,44] Grade 1 through 4 toxicity is so common that preventive strategies have been used to reduce or mitigate it.[45-48]
- **Diarrhea**: Grade 3 or 4 diarrhea complicates the use of panitumumab in 20% of cases.
- **Reduced hematologic toxicity compared with chemotherapy**: Unlike chemotherapy, panitumumab does not cause significant myelosuppression, reducing the risk of life-threatening infections, bleeding, and transfusion dependence.

In comparison, conventional chemotherapy carries substantial risks of severe myelosuppression, infection, mucositis, organ damage, and secondary malignancies, particularly with prolonged or intensified regimens.

Feasibility of Use in Low- and Middle-Income Countries (LMICs)

Panitumumab is available in some LMICs (see **Table 3 and 4**; some government regulatory agencies may also allow low-volume import for individual patient use without local regulatory approval), but access remains limited due the lack of widespread health system infrastructure for cancer treatment. This includes the general absence of national cancer control plans that are funded via national insurance schemes or Universal Health Coverage (with exceptions), the availability of local diagnostic testing the familiarity of physicians with newer treatment options, high out-of-pocket costs for those under treatment, and other generally known barriers to access in LMICs. Panitumumab can feasibly be administered in any center that can establish IV access and manage dermatologic and other toxicities. The requirement to make a molecular diagnosis of KRAS/NRAS wild type disease may limit use in some settings.

- **Availability**: Panitumumab is approved for use in multiple high-income countries and some LMICs (see Table 3 and 4), and ongoing efforts by global health organizations aim to improve its availability in LMICs. Programs that support expanded access to novel cancer treatments, including partnerships between pharmaceutical companies and global health organizations, could facilitate its wider distribution. Indeed, a central motivation for including panitumumab on the EML is so that it could qualify for expanded access programs for which EML inclusion is pre-requisite.
- **Cost considerations**: In high-income countries (HIC), panitumumab is considered highly effective (grade 1 evidence) and cost-effective (the basis of listing of the many national reimbursement schemes is because panitumumab is cost-effective in the local context – that is, a 'good buy' for the healthcare system). At prices used in HICs, panitumumab may not be considered cost-effective in many LMICs (noting that cost-effectiveness analysis is most effectively deployed in countries with established health care systems and UHC). However, with lower costs, the incremental cost-effectiveness ratio per quality-adjusted year of life gained increases, and the presence of national cancer control plans and UHC funding for cancer medicines in LMICs may further encourage medicines sponsors to engage in fruitful conversations with respect to access.
- **Infrastructure requirements**: Administering panitumumab requires basic infrastructure commonly available in oncology centers, including infusion pumps, trained medical personnel, and venous access. These resources are available in most tertiary care centers in LMICs and are less than the infrastructure typically required for the administration of chemotherapy regimens, which are commonly used for metastatic CRC.

  The successful use of panitumumab in LMICs depends on expanding access to tumor testing for KRAS/NRAS status and improving the infrastructure for administering intravenous biologic therapies. Various countries in LMICs have NGS capabilities (reported in India, Brazil, South Africa, Mexico, Ghana, Kenya, Nigeria, and others), and its implementation could widely be expected to expand in the medium-term in other countries in Southeast Asia, Latin America, and Africa. Single gene PCR testing is acceptable for RAS testing, which is available in many LMICs, although access varies widely depending on each country's infrastructure, funding, and availability of trained personnel. Existing capacity-building programs in LMICs, supported by global

organizations like C/Can and others, have demonstrated that improving cancer care infrastructure and capacity is feasible and impactful.

- **Required Health System Strengthening**

  Panitumumab's inclusion in the EML would likely require capacity building in molecular diagnostics (KRAS/NRAS testing), improvements in cancer care infrastructure, and health workforce training in oncology treatment protocols. However, with increased international support and commitment, such changes can lead to sustainable improvements in cancer care in LMICs.

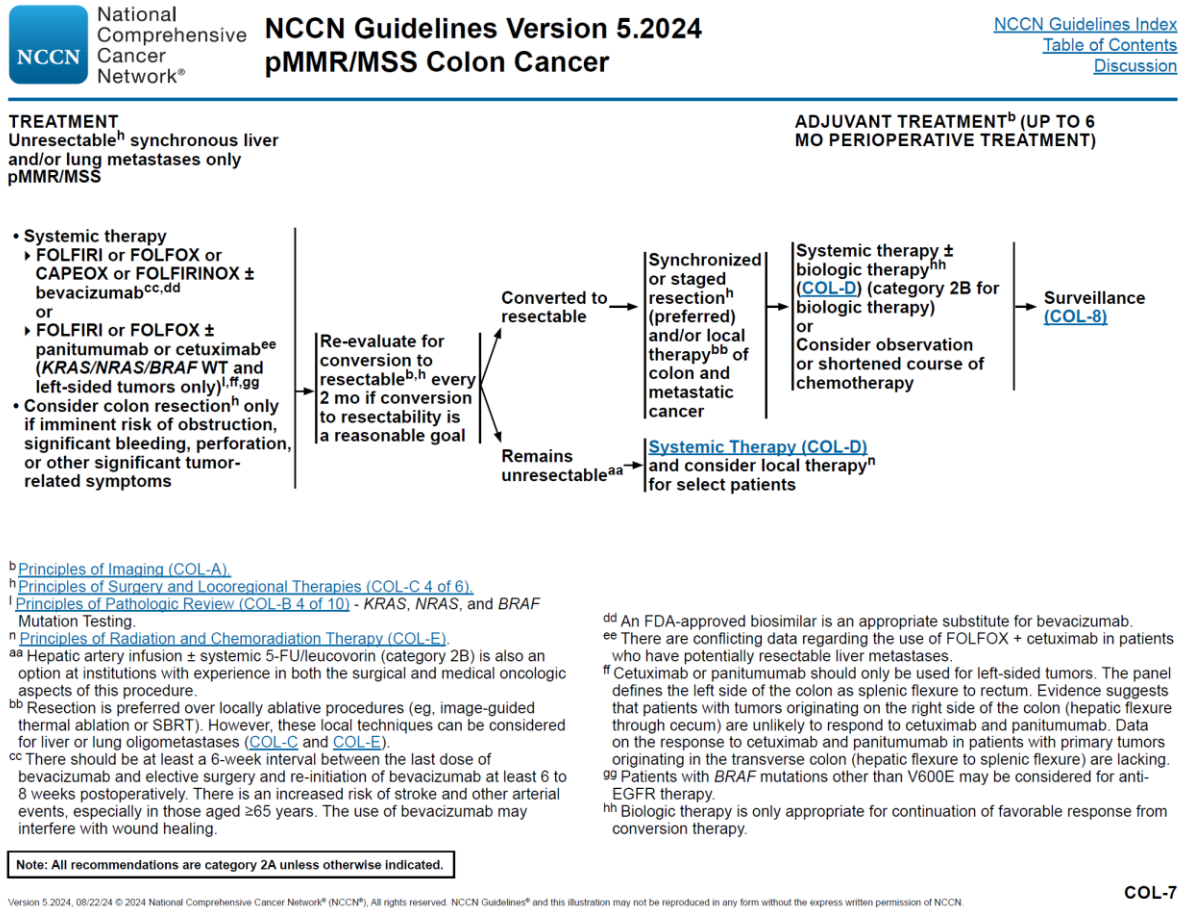
9. SUMMARY OF RECOMMENDATIONS IN CURRENT CLINICAL GUIDELINES

All major international guidelines support the use of panitumumab for KRAS/NRAS wild type metastatic CRC.

1. National Comprehensive Cancer Network (NCCN) updated its colon cancer guidelines in August of 2024 (https://www.nccn.org/professionals/physician_gls/pdf/all.pdf)[6,49,50]
   - The NCCN guidelines for colorectal cancer recommend the use of panitumumab as part of first-line, second-line, or subsequent treatment for KRAS/NRAS wild-type mCRC.
   - In first-line therapy, these agents are recommended in combination with chemotherapy, while in later lines of treatment, they can be used as monotherapy or in combination with chemotherapy.

2. European Society for Medical Oncology (ESMO) Guidelines[51-54]
   - The ESMO guidelines support the use of EGFR inhibitors for patients with KRAS/NRAS wild-type mCRC as part of first- or second-line therapy, particularly in combination with FOLFIRI or FOLFOX chemotherapy.
   - ESMO guidelines highlight that targeted therapies such as panitumumab should be considered essential for achieving optimal outcomes in mCRC patients.
3. American Society of Clinical Oncology (ASCO) Guidelines[55,56]
   - ASCO recommends panitumumab for mCRC in patients with wild-type RAS tumors, highlighting their significant role in improving survival outcomes.
   - EGFR inhibitors (e.g., panitumumab) are recommended in combination with chemotherapy or as monotherapy in patients who have failed chemotherapy-based regimens.

The NCCN and ESMO guidelines are summarized in the following **Figures**.



[b] Principles of Imaging (COL-A).
[h] Principles of Surgery and Locoregional Therapies (COL-C 4 of 6).
[l] Principles of Pathologic Review (COL-B 4 of 10) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing.
[n] Principles of Radiation and Chemoradiation Therapy (COL-E).
[aa] Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
[bb] Resection is preferred over locally ablative procedures (eg, image-guided thermal ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (COL-C and COL-E).
[cc] There should be at least a 6-week interval between the last dose of bevacizumab and elective surgery and re-initiation of bevacizumab at least 6 to 8 weeks postoperatively. There is an increased risk of stroke and other arterial events, especially in those aged ≥65 years. The use of bevacizumab may interfere with wound healing.
[dd] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[ee] There are conflicting data regarding the use of FOLFOX + cetuximab in patients who have potentially resectable liver metastases.
[ff] Cetuximab or panitumumab should only be used for left-sided tumors. The panel defines the left side of the colon as splenic flexure to rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through cecum) are unlikely to respond to cetuximab and panitumumab. Data on the response to cetuximab and panitumumab in patients with primary tumors originating in the transverse colon (hepatic flexure to splenic flexure) are lacking.
[gg] Patients with *BRAF* mutations other than V600E may be considered for anti-EGFR therapy.
[hh] Biologic therapy is only appropriate for continuation of favorable response from conversion therapy.

Note: All recommendations are category 2A unless otherwise indicated.

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Figure 3. NCCN Guidelines for frontline treatment of unresectable synchronous liver or lung-only metastatic colon cancer.[50]
(https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf)

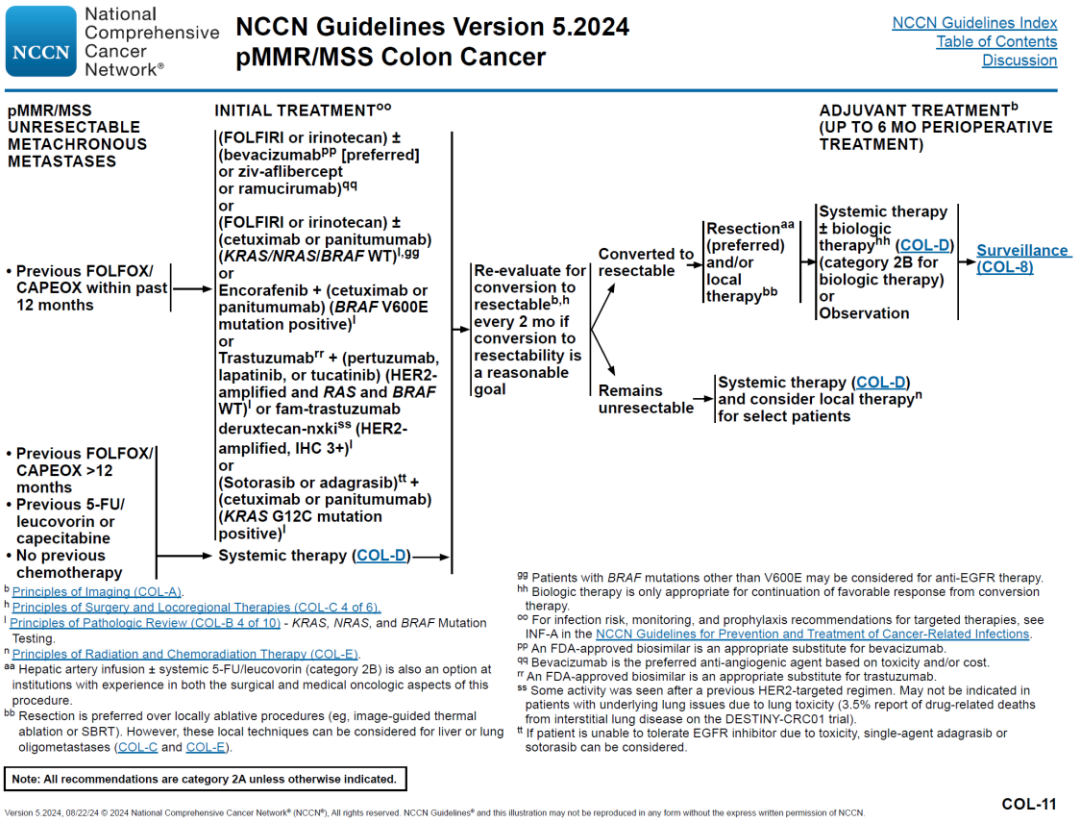


Figure 4. NCCN Guidelines for frontline treatment of unresectable metachronous metastatic colon cancer.[50]

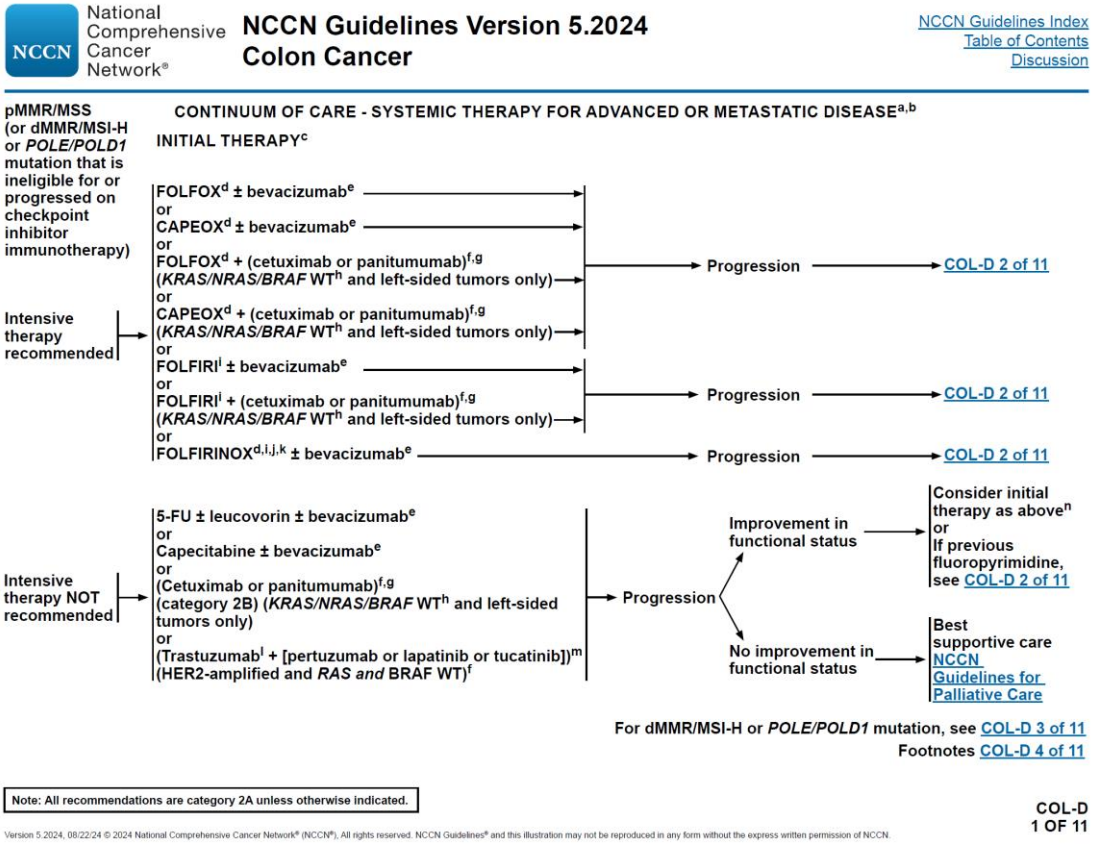
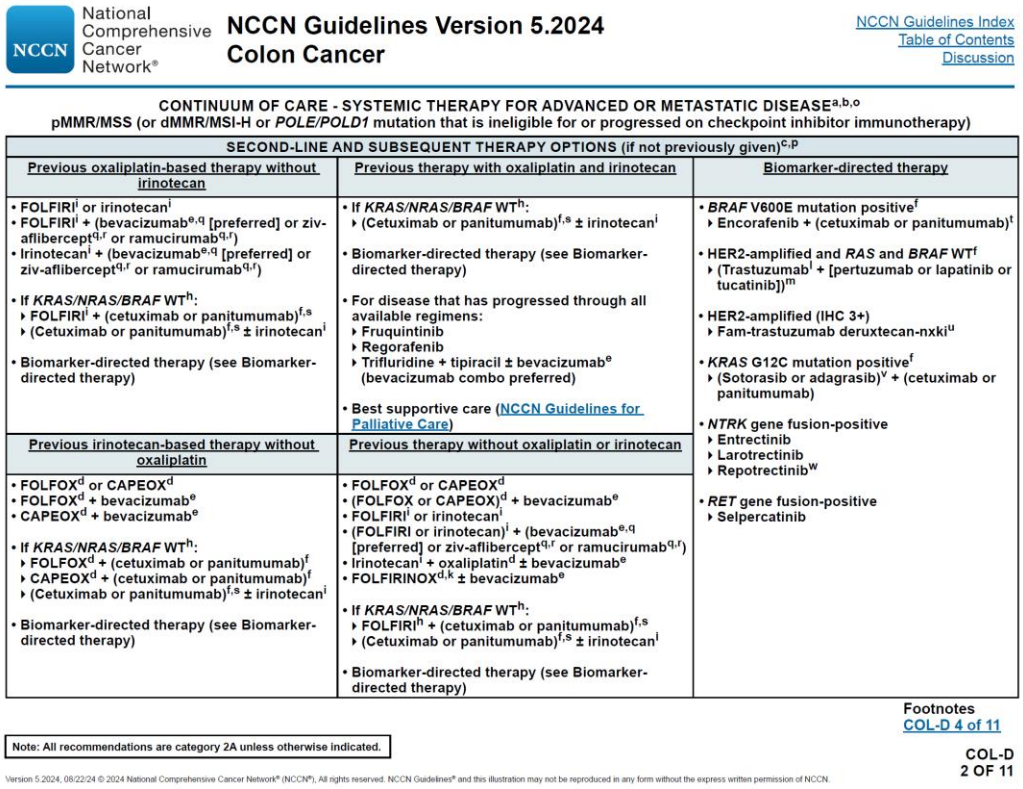


Figure 5. NCCN Guidelines for second line treatment of metastatic colon cancer that is ineligible for or has progressed on checkpoint inhibitor immunotherapy.[50]



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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,o]
pMMR/MSS (or dMMR/MSI-H or *POLE/POLD1* mutation that is ineligible for or progressed on checkpoint inhibitor immunotherapy)

SECOND-LINE AND SUBSEQUENT THERAPY OPTIONS (if not previously given)[c,p]

Previous oxaliplatin-based therapy without irinotecan	Previous therapy with oxaliplatin and irinotecan	Biomarker-directed therapy
• FOLFIRI[l] or irinotecan[i] • FOLFIRI[l] + (bevacizumab[e,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r]) • Irinotecan[i] + (bevacizumab[e,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r]) • If *KRAS/NRAS/BRAF* WT[h]: ‣ FOLFIRI[l] + (cetuximab or panitumumab)[f,s] ‣ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy)	• If *KRAS/NRAS/BRAF* WT[h]: ‣ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy) • For disease that has progressed through all available regimens: ‣ Fruquintinib ‣ Regorafenib ‣ Trifluridine + tipiracil ± bevacizumab[e] (bevacizumab combo preferred) • Best supportive care (NCCN Guidelines for Palliative Care)	• *BRAF* V600E mutation positive[f] ‣ Encorafenib + (cetuximab or panitumumab)[t] • HER2-amplified and *RAS* and *BRAF* WT[f] ‣ (Trastuzumab[l] + [pertuzumab or lapatinib or tucatinib])[m] • HER2-amplified (IHC 3+) ‣ Fam-trastuzumab deruxtecan-nxki[u] • *KRAS* G12C mutation positive[f] ‣ (Sotorasib or adagrasib)[v] + (cetuximab or panitumumab) • *NTRK* gene fusion-positive ‣ Entrectinib ‣ Larotrectinib ‣ Repotrectinib[w] • *RET* gene fusion-positive ‣ Selpercatinib
Previous irinotecan-based therapy without oxaliplatin	**Previous therapy without oxaliplatin or irinotecan**	
• FOLFOX[d] or CAPEOX[d] • FOLFOX[d] + bevacizumab[e] • CAPEOX[d] + bevacizumab[e] • If *KRAS/NRAS/BRAF* WT[h]: ‣ FOLFOX[d] + (cetuximab or panitumumab)[f] ‣ CAPEOX[d] + (cetuximab or panitumumab)[f] ‣ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy)	• FOLFOX[d] or CAPEOX[d] • (FOLFOX or CAPEOX)[d] + bevacizumab[e] • FOLFIRI[l] or irinotecan[i] • (FOLFIRI or irinotecan)[i] + (bevacizumab[e,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r]) • Irinotecan[i] + oxaliplatin[d] ± bevacizumab[e] • FOLFIRINOX[d,k] ± bevacizumab[e] • If *KRAS/NRAS/BRAF* WT[h]: ‣ FOLFIRI[h] + (cetuximab or panitumumab)[f,s] ‣ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy)	

Footnotes
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Note: All recommendations are category 2A unless otherwise indicated.

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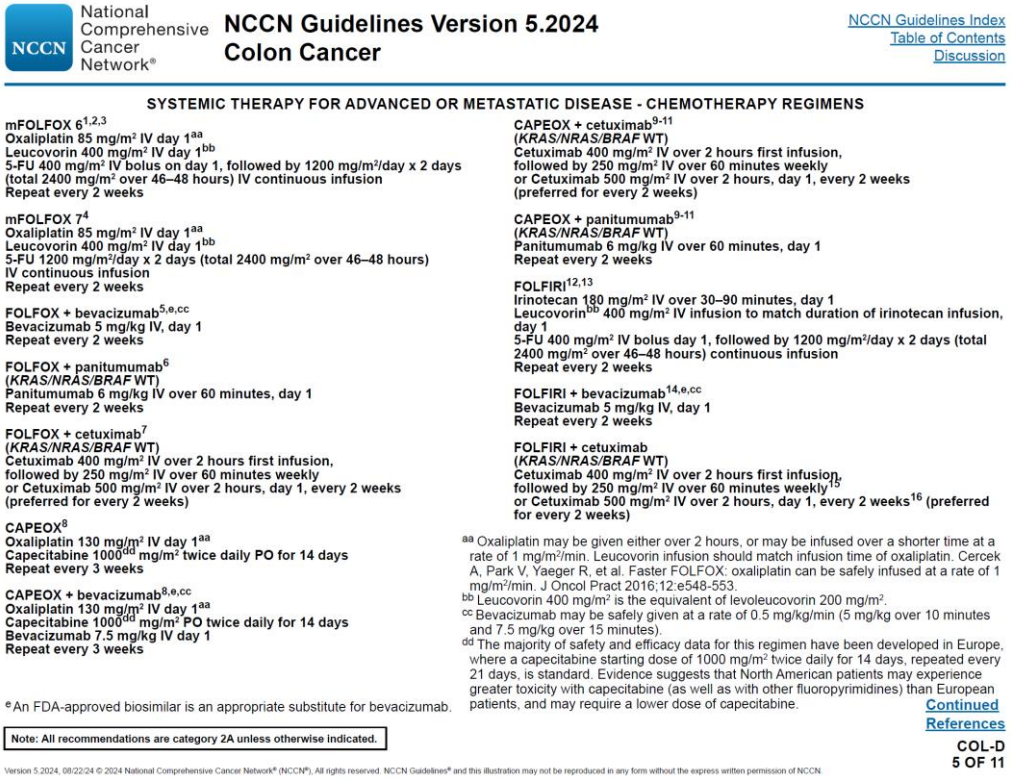
Figure 6. NCCN Guidelines for second-line and subsequent therapy for metastatic colon cancer that has progressed after previous oxaliplatin-based therapies.[50]



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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS

mFOLFOX 6[1,2,3]
Oxaliplatin 85 mg/m² IV day 1[aa]
Leucovorin 400 mg/m² IV day 1[bb]
5-FU 400 mg/m² IV bolus on day 1, followed by 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion
Repeat every 2 weeks

mFOLFOX 7[4]
Oxaliplatin 85 mg/m² IV day 1[aa]
Leucovorin 400 mg/m² IV day 1[bb]
5-FU 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion
Repeat every 2 weeks

FOLFOX + bevacizumab[5,e,cc]
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

FOLFOX + panitumumab[6]
(*KRAS/NRAS/BRAF* WT)
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFOX + cetuximab[7]
(*KRAS/NRAS/BRAF* WT)
Cetuximab 400 mg/m² IV over 2 hours first infusion, followed by 250 mg/m² IV over 60 minutes weekly
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks
(preferred for every 2 weeks)

CAPEOX[8]
Oxaliplatin 130 mg/m² IV day 1[aa]
Capecitabine 1000[dd] mg/m² twice daily PO for 14 days
Repeat every 3 weeks

CAPEOX + bevacizumab[8,e,cc]
Oxaliplatin 130 mg/m² IV day 1[aa]
Capecitabine 1000[dd] mg/m² PO twice daily for 14 days
Bevacizumab 7.5 mg/kg IV day 1
Repeat every 3 weeks

CAPEOX + cetuximab[9-11]
(*KRAS/NRAS/BRAF* WT)
Cetuximab 400 mg/m² IV over 2 hours first infusion, followed by 250 mg/m² IV over 60 minutes weekly
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks
(preferred for every 2 weeks)

CAPEOX + panitumumab[9-11]
(*KRAS/NRAS/BRAF* WT)
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI[12,13]
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin[bb] 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, followed by 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion
Repeat every 2 weeks

FOLFIRI + bevacizumab[14,e,cc]
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

FOLFIRI + cetuximab
(*KRAS/NRAS/BRAF* WT)
Cetuximab 400 mg/m² IV over 2 hours first infusion, followed by 250 mg/m² IV over 60 minutes weekly[15]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[16] (preferred for every 2 weeks)

[aa] Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract 2016;12:e548-553.
[bb] Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
[cc] Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).
[dd] The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.

[e] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

Continued
References

Note: All recommendations are category 2A unless otherwise indicated.

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Figure 7. NCCN Guidelines for metastatic colon cancer treatment combinations with dose and schedule included.[50]

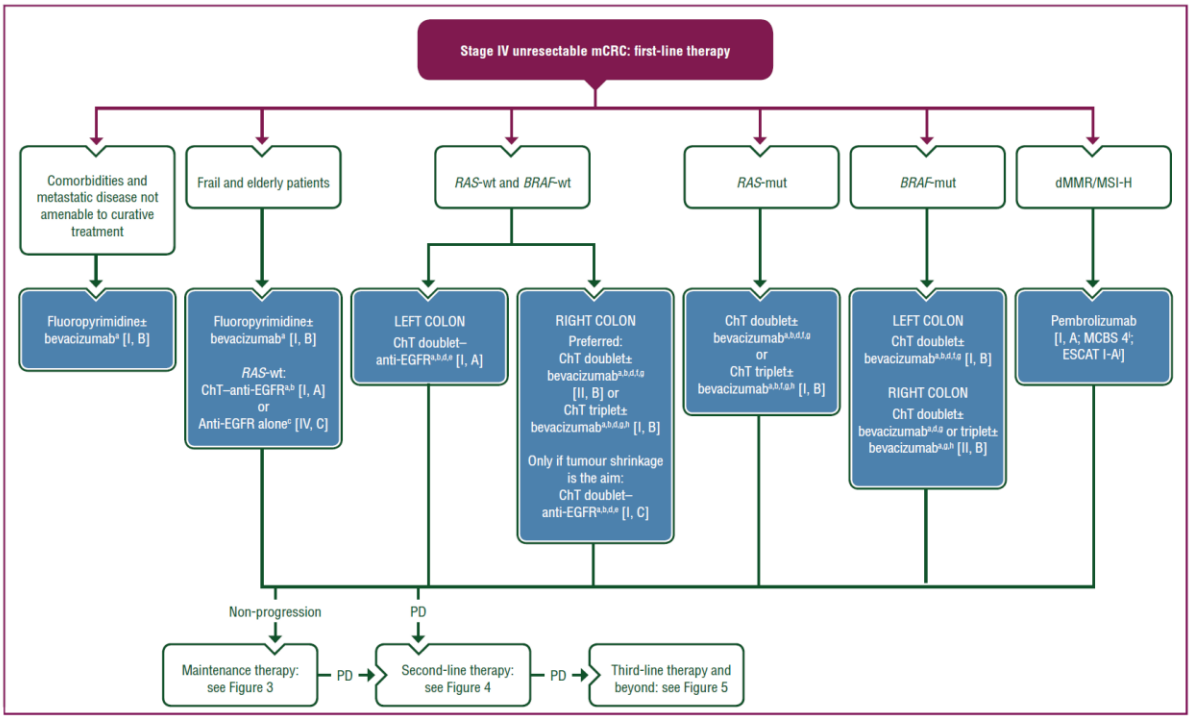


Figure 2. Management of stage IV unresectable mCRC in first-line therapy. Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

5-FU, 5-fluorouracil; ChT, chemotherapy; dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; FOLFIRI, leucovorin—5-fluorouracil—irinotecan; FOLFOX, leucovorin—5-fluorouracil—oxaliplatin; FOLFOXIRI, leucovorin—5-fluorouracil—oxaliplatin—irinotecan; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; mut, mutant; PD, progressive disease; PS, performance status; S-1, tegafur—gimeracil—oteracil; wt, wild-type.

[a]In patients presenting with cardiotoxicity and/or hand-foot syndrome on 5-FU or capecitabine-based ChT, S-1 may be used as an alternative [III, B].

[b]Additional details on treatments and drug combinations can be found under the section 'Management of advanced and metastatic disease without potential conversion' (subsections 'First-line treatment' and 'Second-line treatment').

[c]In frail or elderly patients unable to tolerate ChT whose tumours are left-sided and RAS-wt.

[d]FOLFIRI—cetuximab ESMO-MCBS v1.1 score: 4; FOLFOX4—panitumumab ESMO-MCBS v1.1 score: 4; mFOLFOX6—panitumumab ESMO-MCBS v1.1 score: 3.[i]

[e]FOLFOX4—panitumumab ESMO-MCBS v1.1 score: 4; modified FOLFOX6—panitumumab ESMO-MCBS v1.1 score: 3; for FOLFIRI—cetuximab ESMO-MCBS v1.1 score: 4.[i]

[f]In a very selected population.

[g]CAPOX— or FOLFOX4—bevacizumab ESMO-MCBS v1.1 score: 1.[i]

[h]A triplet with FOLFOXIRI plus bevacizumab is an option for selected patients with good PS and without comorbidities [I, B; ESMO-MCBS v1.1 score: 2].[i]

[i]ESMO-MCBS v1.1[165] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[j]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[164] See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.003, for more information on ESCAT scores.

Figure 8. ESMO guidelines for frontline therapy of unresectable metastatic colorectal cancer includes the option for anti-EGFR therapy (e.g., panitumumab) in patients with RAS wild type disease.[54]

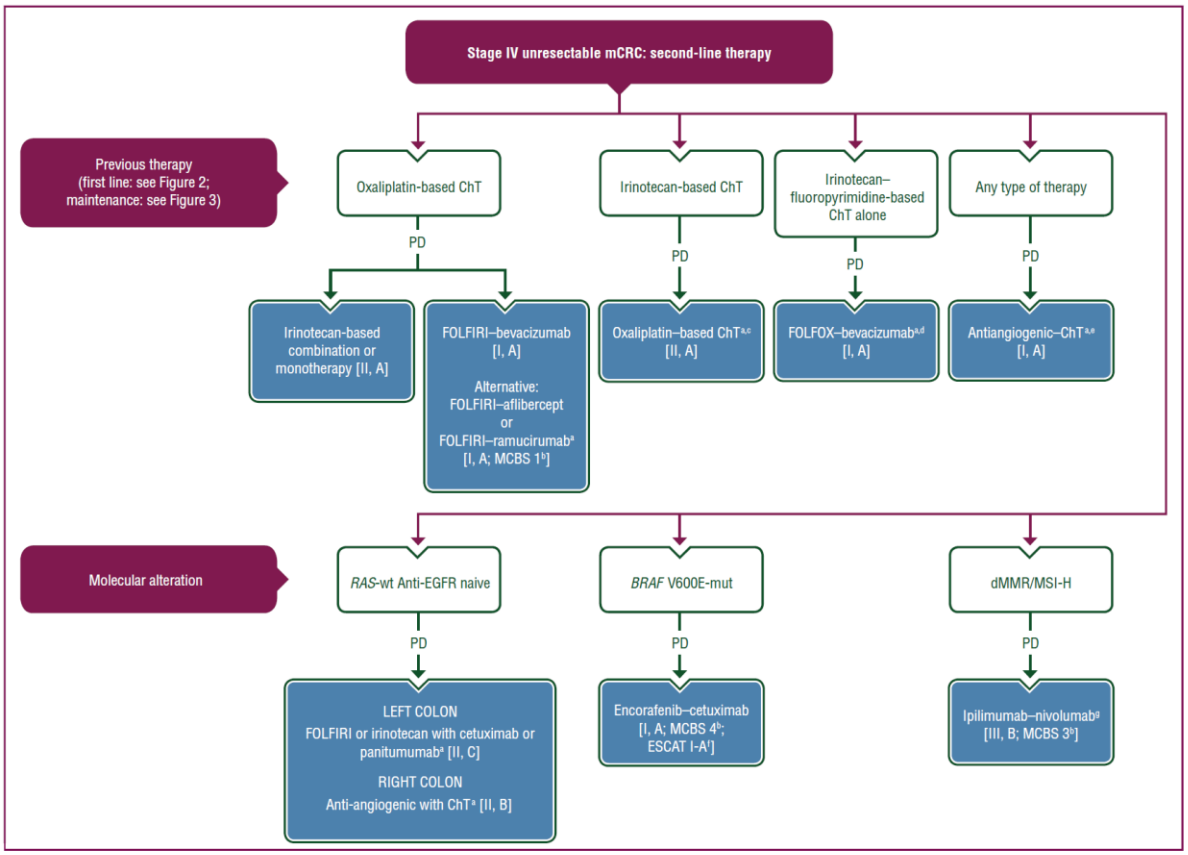


Figure 4. Management of stage IV unresectable mCRC in the second line. Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

5-FU, fluorouracil; CAPOX, capecitabine—oxaliplatin; ChT, chemotherapy; dMMR, deficient mismatch repair; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; FOLFIRI, leucovorin—5-fluorouracil—irinotecan; FOLFOX, leucovorin—5-fluorouracil—oxaliplatin; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; mut, mutant; PD, progressive disease; PTL, primary tumour location; S-1, tegafur—gimeracil—oteracil; wt, wild-type.

[a]In patients presenting with cardiotoxicity and/or hand-foot syndrome on 5-FU or capecitabine-based ChT, S-1 may be used as an alternative [III, B].

[b]ESMO-MCBS v1.1[165] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[c]FOLFOX or CAPOX, if no contraindications.

[d]Bevacizumab can be combined with ChT doublet (a fluoropyrimidine with oxaliplatin or irinotecan, depending on the first-line ChT backbone delivered) [I, A; ESMO-MCBS v1.1 score: 1].

[e]With or without previous first-line treatment with bevacizumab and independently of *RAS* mutational status and the PTL.

[f]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[164] See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.003, for more information on ESCAT scores.

[g]Indicated for immunotherapy-naive patients.

Figure 9. ESMO guidelines for second-line therapy of unresectable metastatic colorectal cancer includes the option for anti-EGFR therapy (e.g., panitumumab) in patients with RAS wild type disease who have not previously received anti-EGFR therapy.[54]

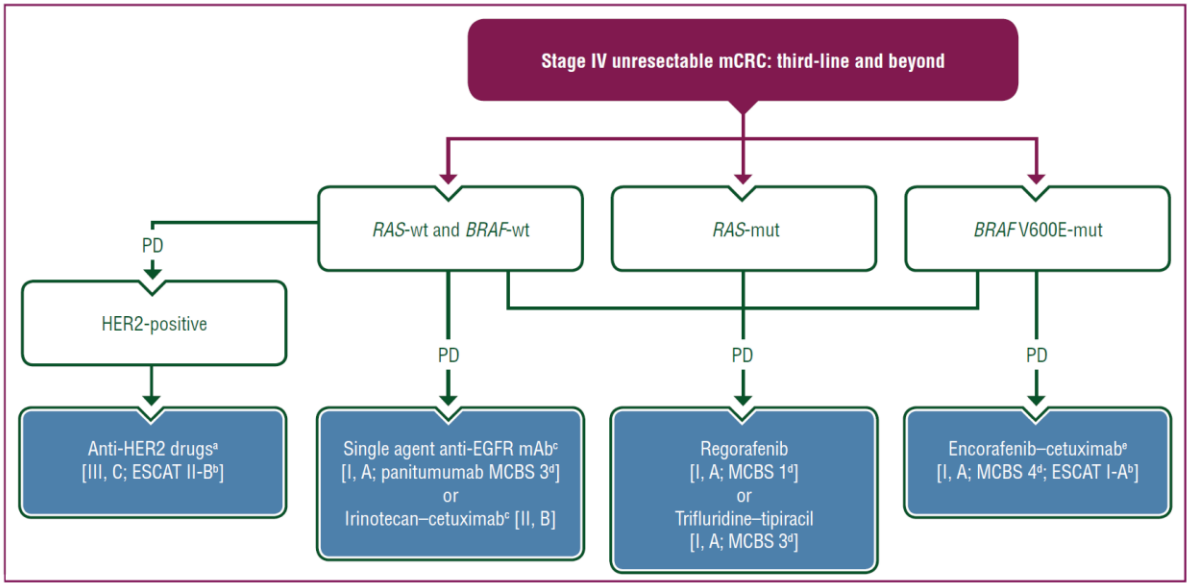
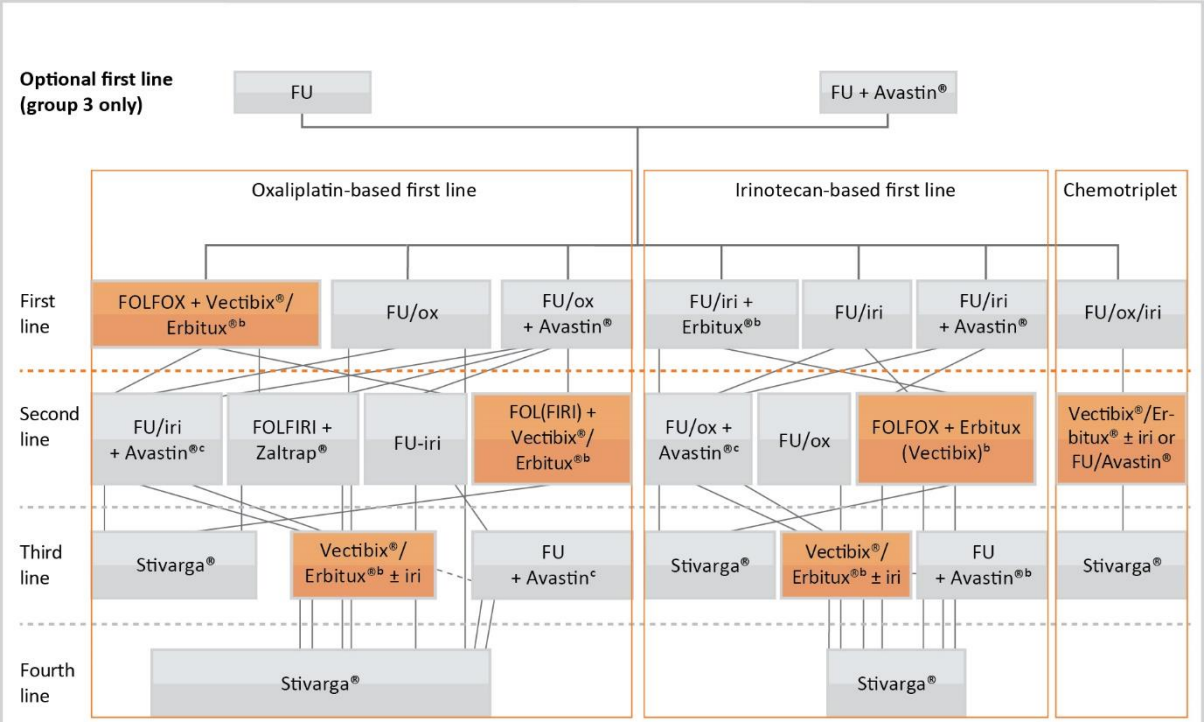


Figure 5. Management of stage IV unresectable mCRC in third-line therapy and beyond. Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.
EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; mut, mutant; PD, progressive disease; wt, wild-type.
[a]For a summary of recommended anti-HER2 regimens for mCRC see Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2022.10.003.
[b]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[164] See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.003, for more information on ESCAT scores.
[c]In *RAS*-wt patients not previously treated with anti-EGFR monoclonal antibodies.
[d]ESMO-MCBS v1.1[165] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[e]Treatment for *BRAF*-mut patients if not used in the second line.

Figure 10. ESMO guidelines for third-line and subsequent therapy of unresectable metastatic colorectal cancer includes the option for anti-EGFR monotherapy or combined with irinotecan in patients with RAS wild type disease.[54]

The ESMO treatment algorithm for mCRC adapted below (**Figure 11**) shows the complexity of the therapeutic strategy for mCRC. It is imperative that each patient receives the right regimen at each line of treatment, so that they are not exposed to agents that have a limited chance of success, to avoid therapies that are contraindicated because of pre-existing comorbidities, to reduce overall toxicity, and to optimize HRQL[57-59]



Note that these guidelines were published before the RAS data.
[a]Patients with multiple metastases/sites, with no option for resection and/or no major symptoms or risk of rapid deterioration, and/or severe comorbidity that would exclude them from later surgery and/or intensive systemic treatment; [b]wild-type KRAS only; [c]Avastin® should not be continued beyond second line if it is used in first line.
FOLFIRI, 5-fluorouracil + leucovorin (folinic acid) + irinotecan; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; FU, fluoropyrimidines; iri, irinotecan; ox, oxaliplatin

Figure 11. ESMO guidelines for the treatment of patients with metastatic colorectal cancer. Orange boxes indicate where panitumumab (Vectibix®) is recommended.[19]

Various medical bodies have also adapted their guidelines for pan-Asian populations (ESMO – representing HIC and LMIC countries in the region) and resource-constrained settings (ESMO, ASCO).[51,52,60] ESMO has also adapted its guidelines for use in LMICs.[51,52] ASCO has done the same, including specifically for late-stage colorectal cancer.[60] These guidelines and the meta-analysis by Yoshino et al.[41] support the of anti-EGFR mAbs in frontline therapy for metastatic colorectal cancer. However, the best decision makers for National Medicines Lists would of course be those who are formally charged with and accountable for, decision making and price negotiation to achieve locally acceptable cost-effective therapies for which they are willing to pay, since both health and healthcare financing is a member state responsibility.

ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) assessment

The European Society for Medical Oncology (ESMO)-Magnitude of Clinical Benefit Scale (MCBS) was developed from 2013 to provide a methodology to consistently categorize the magnitude of clinical benefit from new therapeutic approaches.[61-63] The rationale was developed to distinguish therapies delivering a high level of benefit to patients from those in which benefits were small or marginal. This was considered increasingly important as the pace of new oncology medicine approvals were increasing rapidly in the 2010s. Since its introduction the ESMO MCBS has been

accepted as a robust tool to evaluate the magnitude of clinical benefit reported in trials for oncological therapies. The methodology of the ESMO MCBS with respect to solid tumor assessment has been thoroughly evaluated and validated.[61-66] ESMO also maintains a comprehensive website with scorecards (https://www.esmo.org/guidelines/esmo-mcbs), which has provided a useful framework for previous WHO EML reviews. Indeed, since 2019 the WHO Expert Committee on Selection and Use of Medicines acknowledge the role of the ESMO-MCBS as a screening tool to identify cancer treatments that have potential therapeutic value that warrants full evaluation for the Essential Medicines List (EML) listing. Potential new EML cancer medicines, in general, should have a score on the ESMO-MCBS of A or B in the curative setting and of 4 or 5 in the non-curative setting (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-in-action).

Panitumumab has been assessed in combination with FOLFOX4 and was assigned ESMO-MCBS scores of 4 and 3, respectively, indicating substantial benefit (**Table 2**)

Table 2. FOLFOX4 panitumumab has a score of 4 on the ESMO Magnitude of Clinical Benefit Scale version 1.1

	Tested Agent(s)	Combined Agent(s)	Control Arm	Therapeutic Indication	Tumour Sub-type	Ref.	Score	Scorecard
☐	Panitumumab	FOLFOX4 (5-fluorouracil, leucovorin, and oxaliplatin)	FOLFOX4 (5-fluorouracil, leucovorin, and oxaliplatin)	First-line treatment of patients with wild-type RAS mCRC PRIME	Colorectal Cancer		4	PRELIMINARY SCORE NON-CURATIVE OS; ADJUSTMENTS; FINAL SCORE NON-CURATIVE F2a 4
☐	Panitumumab	FOLFIRI (folinic acid, 5-fluorouracil, irinotecan)	FOLFIRI (folinic acid, 5-fluorouracil, irinotecan)	Second-line treatment of patients with wild-type RAS mCRC who have received first-line fluoropyrimidine-based ChT (excluding irinotecan) 20050181 study	Colorectal Cancer		3	PRELIMINARY SCORE NON-CURATIVE PFS; ADJUSTMENTS; FINAL SCORE NON-CURATIVE F2b 3
☐	Panitumumab	-	Best supportive care	Treatment of patients with wild-type RAS mCRC after failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing ChT regimens Study 20020408	Colorectal Cancer		2	PRELIMINARY SCORE NON-CURATIVE PFS; ADJUSTMENTS; FINAL SCORE NON-CURATIVE F2b 2

In summary, NCCN, ESMO, and ASCO support the use of panitumumab combined with chemotherapy in first-line and second-line therapy and with chemotherapy or as monotherapy in third-line therapy for patients with RAS wild type disease.

10. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST-EFFECTIVENESS (NEW MEDICINES)

Search strategy

PubMed was searched combining the terms colon cancer and colorectal cancer with combinations of panitumumab, epidermal growth factor inhibitors, and chemotherapy regimens (FOLFOX, FOLFIRI, and others). A repository of 6106 articles was developed, from which the relevant references for this application were selected.

Affordability and Cost-Effectiveness

Many treatment strategies that include targeted therapies for metastatic CRC are cost-effective in HIC.[67-77] Panitumumab is no exception.[78-82] Panitumumab cost-effectiveness has been assessed in first-line, second-line, and later lines of therapy relative to chemotherapy and bevacizumab.

Cost-effectiveness of panitumumab in first-line therapy

The cost-effectiveness of panitumumab in first-line therapy has been extensively studied.[79,80,83-89] For example, using a French healthcare system perspective, a lifetime Markov model was constructed, with health states related to first-line therapy (progression-free), disease progression with/without subsequent active treatment, resection of metastases, disease-free after successful resection, and death.[83] Transitions to disease progression and death were estimated using parametric survival analyses of patient-level progression-free (PFS) and overall (OS) survival from the only head-to-head clinical trial of panitumumab versus bevacizumab in mCRC (PEAK).

Additional data from PEAK informed the amount of each drug consumed, duration of therapy, subsequent therapy use, and toxicities related to mCRC treatment. Literature and French public data sources were used to estimate unit costs associated with treatment, duration of subsequent active therapies, and survival post-resection. Patient-level data from panitumumab trials in the first-, second-, and third-line settings were used to determine utility weights. One-way and probabilistic sensitivity analyses were performed. Scenario analyses examined modelling of PFS and OS using observational survival data and PEAK hazard ratios.

Based on the better efficacy outcomes for patients with wild type *RAS* mCRC who received panitumumab plus mFOLFOX6 versus bevacizumab plus mFOLFOX6 in PEAK, the incremental cost per life-year gained was estimated to be €26,918, and the incremental cost per quality-adjusted life year (QALY) gained was estimated to be €36,577. Sensitivity and scenario analyses indicate the model is robust to alternative parameters and assumptions.

Therefore, panitumumab plus mFOLFOX6 can be considered cost-effective in first-line treatment of patients with wild-type *RAS* mCRC in France.[83]

In Greece, the cost-effectiveness of panitumumab plus mFOLFOX6 versus bevacizumab plus mFOLFOX6 as first-line treatment of mCRC was assessed in patients with wild-type RAS.[85] An existing Markov model consisting of seven health states was adapted from the public third-party-payer perspective. Both efficacy and safety data considered in the model were extracted from the PEAK trial and other published studies. Utility values were also extracted from the literature. Direct medical costs consisting of drug-acquisition costs for frontline therapy, administration

costs, subsequent therapy costs and other medical costs were incorporated into the model and reflect (2014 Euros). Primary outcomes were patient survival (life-years), quality-adjusted life years (QALYs) and the incremental cost-effectiveness ratio (ICER) per QALY gained. Probabilistic sensitivity analysis (PSA) was conducted to account for uncertainty and variation in the parameters of the model.

The analysis showed that panitumumab plus mFOLFOX6 produced greater discounted survival and quality adjusted survival by 0.87 LYs and 0.65 QALY benefit in relation to bevacizumab plus mFOLFOX6. The total lifetime cost was €75,200 and €52,736 for panitumumab and bevacizumab plus mFOLFOX6, respectively. This difference was mainly attributed to the higher acquisition cost of panitumumab compared to bevacizumab during the pre-progression health state (€32,223 and €14,730 respectively). Incremental analysis showed that panitumumab plus mFOLFOX6 was more effective and more costly than bevacizumab plus mFOLFOX6 resulting in an ICER equal to €34,644 per QALY gained. PSA revealed that the probability of panitumumab plus mFOLFOX6 being cost-effective over bevacizumab plus mFOLFOX6 was 81.5% at the pre-determined threshold of €51,000 per QALY gained (3 times the GDP per capita of Greece).

These results suggest that panitumumab plus mFOLFOX6 may be a cost-effective alternative relative to bevacizumab plus mFOLFOX6 as first-line therapy for mCRC patients with wild-type RAS in Greece.

Cost-effectiveness of panitumumab in second-line or subsequent lines of therapy

Randomized controlled trials (RCTs) or systematic reviews of RCTs of cetuximab, bevacizumab or panitumumab in participants with EGFR-expressing metastatic colorectal cancer with KRAS wild type status that progressed after first-line chemotherapy were analyzed. An economic model was developed focusing on third-line and subsequent lines of treatment. Costs and benefits were discounted at 3.5% per annum. Probabilistic and univariate deterministic sensitivity analyses were performed.

The searches identified 7745 titles and abstracts. Two clinical trials (reported in 12 papers) were included. No data were available for bevacizumab in combination with non-oxaliplatin-based chemotherapy in previously treated patients. Neither of the studies included had KRAS status performed prospectively, but the studies did report retrospective analyses of the results for the KRAS wild type subgroups. Third-line treatment with cetuximab plus best supportive care or panitumumab plus best supportive care appears to have statistically significant advantages over treatment with best supportive care alone in patients with KRAS WT status. For the economic evaluation, five studies met the inclusion criteria. The base-case incremental cost-effectiveness ratio (ICER) for KRAS WT patients for cetuximab compared with best supportive care was 98,000 British pounds per quality-adjusted life-year (QALY), for panitumumab compared with best supportive care is pound150,000 per QALY and for cetuximab plus irinotecan compared with best supportive care is pound88,000 per QALY. All ICERs are sensitive to treatment duration. Although cetuximab and panitumumab appear to be clinically beneficial for KRAS WT patients compared with best supportive care, they are likely to represent poor value for money when judged by cost-effectiveness criteria currently used in the UK.

List price information by country (where reimbursed and public)

Table 3 provides the available list price information by country (and categorization by country income criteria using WB Atlas method, where public prices are available.

The table also provides classification according to the World Bank Atlas method. For operational and analytical purposes, the World Bank divides economies among income groups according to 2023 gross national income (GNI) per capita in US dollars. For the 2025 fiscal year, the thresholds are defined as follows:

- low income ($1,145 or less)
- lower middle income ($1,146 to $4,515)
- upper middle income ($4,516 to $14,005)
- high income (more than $14,005)

Further details on the World Bank Atlas method can be found at
https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups
Technical details are provided in the accompanying Excel sheet
https://datacatalogapi.worldbank.org/ddhxext/ResourceDownload?resource_unique_id=DR0090755

Most countries in which panitumumab has public list price information are high-income countries. This is expected, given the nature of high-income countries and their health systems, which include the generalized adoption of contemporary clinical practice, as well as usually having reimbursement agencies (or health insurance systems) that use health technology appraisal methodology to assess the value of medicines to their health systems (that is, economic analysis that assess the relative safety and efficacy and the cost effectiveness of new medicines). Furthermore, high-income countries have sufficient resources to invest in their healthcare systems and accept a willingness-to-pay value for each life year or QALY that is significantly higher than those feasible in LMICs. However, there are several lower-middle income and upper-middle income countries where panitumumab is available.

Table 3: List price information by country of registration

Countries	WB Atlas*	List price USD/mg	100 mg	400 mg
Australia	HIC	$ 2.84	$ 284.47	$ 1,137.88
Austria	HIC	$ 4.48	$ 447.81	$ 1,791.22
Bahrain	HIC	$ 5.12	$ 512.02	$ 2,048.08
Belgium	HIC	$ 3.47	$ 346.60	$ 1,386.41
Bulgaria	HIC	$ 2.90	$ 289.83	$ 1,159.31
Canada	HIC	$ 4.64	$ 464.06	$ 1,856.26
Croatia	HIC	$ 3.86	$ 386.46	$ 1,545.85
Czech Republic	HIC	$ 3.47	$ 347.45	$ 1,389.79
Denmark	HIC	$ 3.58	$ 357.80	$ 1,431.18
Estonia	HIC	$ 4.64	$ 463.61	$ 1,854.44
Finland	HIC	$ 4.77	$ 476.95	$ 1,907.79
France	HIC	$ 3.15	$ 315.41	$ 1,261.63
Germany	HIC	$ 6.32	$ 632.43	$ 2,529.74
Greece	HIC	$ 3.14	$ 313.66	$ 1,254.65
Hong Kong	HIC	$ 6.36	$ 636.12	$ 2,544.46
Hungary	HIC	$ 2.93	$ 292.53	$ 1,170.12
Ireland	HIC	$ 4.15	$ 414.72	$ 1,658.87
Israel	HIC	$ 3.22	$ 321.92	$ 1,287.68
Italy	HIC	$ 4.48	$ 447.81	$ 1,791.22
Kuwait	HIC	$ 7.50	$ 750.00	$ 3,000.00
Latvia	HIC	$ 4.64	$ 463.61	$ 1,854.44
Netherlands	HIC	$ 4.22	$ 422.04	$ 1,688.15
Norway	HIC	$ 3.14	$ 313.77	$ 1,255.08
Oman	HIC	$ 5.75	$ 575.16	$ 2,300.62
Poland	HIC	$ 2.84	$ 284.42	$ 1,137.68
Qatar	HIC	$ 5.75	$ 575.31	$ 2,301.24
Romania	HIC	$ 2.91	$ 290.87	$ 1,163.48
Saudi Arabia	HIC	$ 5.12	$ 511.82	$ 2,047.27
Slovakia	HIC	$ 2.91	$ 290.70	$ 1,162.81
Slovenia	HIC	$ 4.55	$ 454.96	$ 1,819.84
Spain	HIC	$ 3.81	$ 380.62	$ 1,522.50
Sweden	HIC	$ 3.83	$ 382.89	$ 1,531.57
Switzerland	HIC	$ 4.20	$ 419.95	$ 1,679.80
Taiwan	HIC	$ 2.77	$ 277.25	$ 1,108.99
Türkiye	HIC	$ 5.97	$ 597.20	$ 2,388.80
Egypt	LMIC	$ 1.20	$ 120.18	$ 480.71
Jordan	LMIC	$ 4.26	$ 425.52	$ 1,702.08
Lebanon	LMIC	$ 3.57	$ 356.75	$ 1,427.00
Morocco	LMIC	$ 4.47	$ 447.03	$ 1,788.13
Algeria	UMIC	$ 3.36	$ 336.25	$ 1,345.00
Argentina	UMIC	$ 113.54	$ 11,354.05	$ 45,416.22
Brazil	UMIC	$ 3.00	$ 299.85	$ 1,199.39
Colombia	UMIC	$ 3.35	$ 335.34	$ 1,341.35
Mexico	UMIC	$ 4.07	$ 407.01	$ 1,628.03
South Africa	UMIC	$ 2.28	$ 228.02	$ 912.06

* *Further details on the World Bank Atlas method can be found at their website https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups And technical details are provided in the accompanying Excel sheet https://datacatalogapi.worldbank.org/ddhxext/ResourceDownload?resource_unique_id=DR0090755*

Importance of the WHO EML in driving cost reductions in low- and middle-income countries

In LMICs, cost barriers can be addressed through initiatives such as differential pricing, voluntary licensing agreements, or access programs supported by non-governmental organizations (NGOs) and international health bodies. The cost of panitumumab may be reduced through these mechanisms or through the advent of biosimilars, and cost-effectiveness would be even higher than that described above. Inclusion of panitumumab in the WHO EML will be an important potential driver of access in LMICs. Many experts in HICs and LMICs use cost-effective intervention thresholds of 1 to 3 times the GDP per capita per life year gained, though some question the utility of these thresholds for policy makers and health systems.[90-99] Cost-effectiveness calculations based on list prices may not meet specified thresholds, but applying the term "not cost-effective" in such settings may preclude the engagement necessary to arrive at a price that is suitable for the country's health system budget. For example, the ASCO Resource Stratified Guideline for late-stage colon cancer recommends anti-EGFR therapy only in the "maximal" (high-income country) setting. In RAS wild type mCRC, EGFR inhibitors extend life by many months in some situations; at the right price they could prove cost-effective even in "Enhanced" and "Limited" settings. Placing effective therapies like panitumumab on the WHO EML sets the stage for assessment of value and engagement of stakeholders to bring beneficial therapies to all patients in a cost-effective way.

11. REGULATORY STATUS, MARKET AVAILABILITY AND PHARMACOPOIEAL STANDARDS (NEW MEDICINES)

Availability of Pharmacopeial Standards

Panitumumab is produced and regulated under stringent pharmacopeial standards set by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). These standards ensure the quality, safety, and efficacy of the drug and provide robust guidance for its global manufacture and distribution. International standards for biologic therapies, including monoclonal antibodies like panitumumab, are well established and ensure consistency across different batches and geographies.

Table 4. Countries in which panitumumab has regulatory approval and current indications (listed by date of initial approval)

Country	Date of Initial Approval	Current Indications
United States	27-Sep-06	mCRC (1st/3rd lines w/*RAS*)
European Union[a]	3-Dec-07	mCRC (1st/2nd/3rd lines w/*RAS*)
United Kingdom	3-Dec-07	mCRC (1st/2nd/3rd lines w/*RAS*)
Canada	3-Apr-08	mCRC (1st/3rd lines w/*RAS*)
Australia	23-May-08	mCRC (1st/2nd/3rd lines w/*RAS*)
Switzerland	14-Oct-08	mCRC (1st/2nd/3rd lines w/*RAS*)
Russia	1-Oct-09	mCRC (1st/2nd/3rd lines w/*RAS*)
Israel	4-Mar-10	mCRC (1st/2nd/3rd lines w/*RAS*)
Japan 100mg	16-Apr-10	mCRC (1st/2nd/3rd lines w/*KRAS*)
Japan 400mg	27-Jun-11	mCRC (1st/2nd/3rd lines w/*KRAS*)
Ukraine	21-Jul-10	mCRC (1st/2nd/3rd lines w/*RAS*)
Brazil	16-Nov-10	mCRC (1st/2nd/3rd lines w/*RAS*)
Argentina	24-Jan-11	mCRC (1st/2nd/3rd lines w/*RAS*)
Jordan	20-Mar-11	mCRC (1st/2nd/3rd lines w/*RAS*)
Mexico	18-Apr-11	mCRC (all lines w/*RAS*)
Serbia	19-Jul-11	mCRC (1st/2nd/3rd lines w/*RAS*)
Chile	17-Oct-11	mCRC (1st/2nd/3rd lines w/*RAS*)
Macau	27-Apr-12	mCRC (1st/2nd/3rd lines w/*RAS*)
Colombia	4-Jun-12	mCRC (1st/3rd lines w/*RAS*)
Kuwait	4-Jul-12	mCRC (1st/2nd/3rd lines w/*RAS*)
Bosnia and Herzegovina	25-Jul-12	mCRC (1st/2nd/3rd lines w/*RAS*)
Hong Kong	14-Aug-12	mCRC (1st/2nd/3rd lines w/*RAS*)
Bahrain	23-Dec-12	mCRC (1st/2nd/3rd lines w/*RAS*)
Egypt	17-Jan-13	mCRC (1st/2nd/3rd lines w/*RAS*)
Qatar	24-Jan-13	mCRC (1st/2nd lines w/*RAS*)
Philippines	4-Apr-13	mCRC (1st/2nd/3rd lines w/*RAS*)
Oman	8-May-13	mCRC (1st/2nd/3rd lines w/*RAS*)
Saudi Arabia	12-May-13	mCRC (1st/2nd/3rd lines w/*RAS*)
Türkiye	24-May-13	mCRC (1st/2nd lines w/*RAS*)
Lebanon	5-Jun-13	mCRC (1st/2nd/3rd lines w/*RAS*)
United Arab Emirates	16-Jun-13	mCRC (1st/2nd/3rd lines w/*RAS*)
Taiwan	20-Jun-13	mCRC (1st/3rd lines w/*RAS*)
Guatemala	9-Jul-13	mCRC (1st/2nd/3rd lines w/*RAS*)
Kazakhstan	19-Jul-13	mCRC (1st/2nd/3rd lines w/*RAS*)
Malaysia	25-Jul-13	mCRC (1st/2nd/3rd lines w/*RAS*)
Ecuador	31-Jul-13	mCRC (1st/2nd/3rd lines w/*RAS*)
India	19-Dec-13	mCRC (1st/2nd/3rd lines w/*RAS*)
Morocco	30-Dec-13	mCRC (1st/2nd/3rd lines w/*RAS*)
Singapore	27-Jan-14	mCRC (1st/2nd/3rd lines w/*RAS*)
Costa Rica	12-May-14	mCRC (1st/2nd/3rd lines w/*RAS*)
Panama	5-Sep-14	mCRC (1st/2nd/3rd lines w/*RAS*)

Peru	7-Nov-14	mCRC (1st/2nd/3rd lines w/*RAS*)
Algeria	9-Aug-15	mCRC (1st/2nd/3rd lines w/*RAS*)
Indonesia	13-Jul-16	mCRC (1st/2nd/3rd lines w/*KRAS*)
Thailand	15-Jul-16	mCRC (1st/2nd/3rd lines w/*RAS*)
South Africa	29-Jul-16	mCRC (3rd line w/*KRAS*)
Montenegro	6-Dec-17	mCRC (1st/2nd/3rd lines w/*RAS*)
Belarus	31-Jan-18	mCRC (1st/2nd/3rd lines w/*RAS*)
Iran	15-Apr-18	mCRC (1st/2nd/3rd lines w/*RAS*)
Brunei	16-Jul-19	mCRC (1st/2nd/3rd lines w/*RAS*)
Libya	17-Jul-22	mCRC (1st/2nd/3rd lines w/*RAS*)

mCRC = metastatic colorectal cancer; w/KRAS = wild-type Kirsten rat sarcoma 2 viral oncogene homologue; w/RAS = wild-type rat sarcoma viral oncogene homologue

[a] *Includes 27 European Union members (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the Netherlands) + 3 further European Economic Area countries (Iceland, Liechtenstein, and Norway). Approved in Croatia on 01 August 2011 (not approved through European Union centralized procedure).*

Conclusion

Metastatic colon cancer is a common global problem, and with demographic shifts and ageing populations will only increase in prevalence. It is often KRAS/RAS wild type and BRAF wild type, and therefore potentially responsive to EGFR inhibitors like panitumumab. Panitumumab extends life in patients with frontline, second line, and third line therapy, has few severe toxicities, and can feasibly be administered in LMICs.

Perhaps the most important question for the Expert Committee to consider in this instance is not the clinical benefit or place in therapy of the medicine, which are clear and well-established, but the importance of improving access to effective medicines like panitumumab where the patent has expired, but there is no biosimilar competition (as yet). It is a weighty responsibility to make a decision that may ultimately benefit (or prevent benefit to) large swathes of the population who already have unequal access to medicines of any kind, and for whom ironically a rejection for inclusion in the EML could delay access even longer.

Maurel et al.[52] make the important point that the inclusion of newer agents for the management of mCRC in the guidelines are based on robust data and "…*would be put into practice by most oncologists working in LMICs, where EGFR antibodies are accessible*". They further note that "…*as a starting point, making these chemotherapy agents more widely available in LMICs would significantly impact outcomes in mCRC*" but that currently *'…[t]he high cost of targeted agents and the molecular testing necessary to select them mean that they are only used in a very small proportion of patients in LMICs…*". An important point about reviews of medicine prices, especially when related to consideration of addition of those medicines to the Essential Medicines List, is that they are often biased towards the pricing of medicines in high-income country contexts (where they are generally available and often reimbursed by national governments following cost effectiveness reviews). Such pricing may then be cited as a reason for non-recommendation. Using high-income country pricing (and the basis of those prices being related to the relative cost effectiveness of those medicines in a national context) as a proxy for

unaffordability in LMICs may perjure the possibility of earlier access to more advanced therapies in the LMIC context, especially when license holders are willing to radically reduce prices via pooled procurement contracts, global access platforms, and other mechanisms that meet the needs of patients in LMICs.

Medicines can exist simultaneously in both HIC and LMIC contexts, and in the latter environment, this is far more likely when national reimbursement/UHC schemes exist to support the health of their populations. In the absence of UHC, catastrophic out-of-pocket spending is a widely cited concern, including by the WHO on the release of the 2023 UHC Global Monitoring Report; https://www.who.int/news/item/18-09-2023-billions-left-behind-on-the-path-to-universal-health-coverage. Even where UHC exists, it may be suboptimal and medicines affordability can be a concern with current medicines on National Medicines Lists. To address these important issues, some medicines sponsors are demonstrating that they are far more attuned to the needs of differential pricing for LMICs – some sponsors have declared specific LMIC pricing policies; others make more general statements acknowledging the need for a population's access to innovation while recognizing the different budget circumstances in LMICs; still others are developing alternatively branded medicines specifically for discounted sales in LMICs. In 2022, Hwang and colleagues'[100] provocative article in JAMA called for a separation of the clinical and economic components of the EML review, arguing that two-stage process could "…*help alleviate lingering concerns among public health advocates that reliance on cost-effectiveness analyses could block recommendations for inclusion of important innovations in the list and, consequently, access to them in resource-limited settings*…". In the case of medicines like panitumumab, which has a a clearly established place in therapy (developed over the 17 years since first introduction), is referenced in all major clinical guidelines across multiple lines of therapy, and has proven its cost-effectiveness serially in multiple national health settings, a positive recommendation for addition to the Essential Medicines List will send a signal to both national governments and medicines sponsors that medicines with appropriately beneficial clinical impact can be considered essential for health systems in LMICs. This will allow those who are formally charged with accountability for affordability the opportunity to negotiate on price and population and allow some LMIC governments to subsequently add such medicines to their National Medicines List under the right circumstances after appropriate negotiation. After all, health is a member state responsibility.

In their 2022 paper assessing access to and affordability of WHO essential medicines for cancer in sub-Saharan Africa, Kizub and colleagues[101] note the following:

> *"…[our analysis] provides further justification for including cancer treatment coverage as part of a UHC program, since our analysis supports that no cancer drugs or treatment regimens are affordable through OOP purchasing by individual patients. In fact, a recent study of 148 countries showed that one of the predictors of improved breast cancer survival was the increased coverage of essential health services for cancer care…".*

In conclusion, panitumumab is a highly effective and safe treatment for patients with metastatic colorectal cancer with wild-type KRAS/NRAS. Its inclusion on the WHO Essential Medicines

List would significantly improve access to this life-extending therapy in LMICs, where the burden of colorectal cancer is rising, and access to modern targeted therapies is limited. With the potential to reduce mortality and enhance the quality of life for patients, panitumumab is an important tool in the global fight against cancer and aligns with WHO's mission to achieve universal health coverage and equity in cancer care.

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