AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence Status Report: panitumumab (Vectibix®) for treatment of stage IV metastatic left-sided colorectal cancer with RAS wildtype confirmed by circulating tumour DNA following successful first line treatment with an epidermal growth factor inhibitor and at least one other treatment **(OW29)**

Report prepared by the All Wales Therapeutics and Toxicology Centre
April 2025

Key findings

Licence status
Panitumumab (Vectibix®) is not licensed for treatment of stage IV metastatic left-sided colorectal cancer with RAS (rat sarcoma virus) wild-type confirmed by circulating tumour DNA (ctDNA) following successful first line treatment with an epidermal growth factor inhibitor (EGFRi) (either cetuximab or panitumumab) and at least one other treatment; its use for this indication is off-label.

Clinical evidence
The clinical evidence for the use of panitumumab in this setting comes from a phase II multicentre, open-label, single-arm clinical trial. A total of 36 patients were eligible for panitumumab rechallenge, 27 received treatment per protocol. The trial reported a 30% objective response rate with 8 partial responses, and a median duration of response of 17 weeks. An additional 40% of patients had stable disease, with 82% maintaining it for over 4 months. The disease control rate was 63%, and the median progression-free survival was 16 weeks, while median overall survival was 55 weeks.

Safety
The safety of panitumumab was found to be in line with previous literature; no new safety signals emerged with rechallenge of panitumumab in colorectal cancer compared with its use in other indications.

Patient factors
Panitumumab rechallenge can control tumours without the need for chemotherapy. It targets EGFR in tumours sensitive to this therapy, offering the possibility of renewed responses in patients who previously benefited from panitumumab. Panitumumab is administered through an intra-venous (IV) infusion, as is the preferred third line treatment option of oral trifluridine-tipiracil (Lonsurf®) plus IV bevacizumab. Current fourth line treatment options (regorafenib or trifluridine-tipiracil [Lonsurf®]) are both oral preparations.

Cost effectiveness
An All Wales Therapeutics and Toxicology Centre (AWTTC) literature review did not identify any published studies reporting the cost-effectiveness of panitumumab

in the 3rd or later line in the treatment of stage IV metastatic left-sided colorectal cancer with RAS wildtype.

An AWTTC cost consequence analysis (CCA) compares the costs and outcomes of panitumumab with a range of comparators, according to line of treatment, in the treatment of stage IV metastatic left-sided colorectal cancer with RAS wildtype.

Base case analysis, treatment in the third line, suggests that panitumumab is associated with lower costs and higher overall survival. Scenario analysis finds that panitumumab costs more than the fourth-line (regorafenib) and fifth-line best supportive care (BSC) comparators whilst offering increased overall survival. The cost analysis is limited in scope, as it does not consider full resource costs or the costs of adverse events. It is considered possible that the inclusion of these costs could change the costing conclusion.

A threshold analysis found the quality adjusted life years (QALYs) required range between [commercial in confidence text removed], this is dependent on the willingness-to-pay threshold and treatment line.

Budget impact
For an estimated 30–50 patients eligible for treatment panitumumab is expected to be cost saving as a third line treatment. [commercial in confidence text removed] The budget impact is subject to considerable uncertainty.

Impact on health and social care services
Genomic testing is not routinely available for this indication and may have an impact on laboratory services. Regorafenib is an oral treatment, whereas panitumumab requires bi-weekly intravenous administration until treatment progression or the development of intolerable side effects. However, the overall impact from the administration difference is likely minimal due to the relatively small patient numbers.

Innovation and/or advantages
Clinical experts indicate the main benefit of this treatment is its survival advantage over existing options, whist also providing a chemotherapy-free regimen which may be better tolerated than current treatment options.

Background

Most patients with metastatic colorectal cancer (mCRC) have incurable, unresectable disease. Treatment aims to slow tumour progression, manage symptoms, improve survival, preserve quality of life, and reduce treatment side effects.

Clinicians in Wales have identified a cohort who would benefit from panitumumab re-challenge, providing a survival advantage (compared to current treatment options) and offering a chemotherapy-free regimen. Panitumumab was therefore considered suitable for assessment though the One Wales Medicines process.

[confidential information removed]

Target group

The indication under consideration is stage IV metastatic left-sided colorectal cancer with RAS (rat sarcoma virus) wild-type confirmed by circulating tumour DNA (ctDNA) following successful first line treatment with an epidermal growth factor inhibitor (EGFRi) and at least one other treatment.

Marketing authorisation date: Not applicable, off-label

Panitumumab (Vectibix®) is not licensed for the target group.

Panitumumab (Vectibix®) is indicated for the treatment of adult patients with wild-type RAS mCRC[1]:

- in first line in combination with folinic acid, fluorouracil and oxaliplatin (FOLFOX) or folinic acid, fluorouracil and irinotecan (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.

Dosing information

The licensed dose as monotherapy for colorectal cancer is 6mg/kg administered by IV infusion every two weeks[1],. 6mg/kg is also used for re-challenge in the pivotal CHRONOS clinical trial[2]. Treatment is continued until treatment progression or the development of intolerable side effects.

Clinical background

Colorectal cancer develops in the lining of the large intestine (colon and rectum). When it spreads beyond the large intestine and nearby lymph nodes, it is referred to as metastatic colorectal cancer[3]. Colon cancer can be further categorised based on its location: left-sided colorectal cancer originates in the descending colon, sigmoid colon, and rectum, while right-sided colorectal cancer arises from the cecum, ascending colon, and transverse colon[4]. Stage IV mCRC refers to cancer that has spread beyond the colon or rectum to distant parts of the body, such as the liver, lungs, or other organs[5].

The assessment of tumour histology, including both the primary location and any metastases, is necessary before initiating a systemic therapy[6]. Individuals with left-sided tumours are more likely to respond well to EGFRi therapy[7]. RAS wild-type means that the cancer cells have normal, unmutated RAS genes (Kirsten RAS [KRAS] or Neuroblastoma RAS [NRAS]), which makes the tumour sensitive to treatment with an EGFRi such as cetuximab or panitumumab[7,8]. RAS mutations are negative predictive factors for the use of anti-EGFR monoclonal antibodies, and therefore RAS testing is mandatory before treatment is initiated[6].

CtDNA consists of small DNA fragments found in the bloodstream, originating from cancerous cells and tumours. As tumours grow, cells die and are replaced, the dead cells release their contents, including DNA, into the bloodstream. By analysing ctDNA, it is possible to detect the tumour type, aiding in diagnosis and treatment decisions[9]. A well-established mechanism of acquired resistance to anti-EGFR monoclonal antibodies is the development of RAS mutations in tumours that were initially RAS wild-type. However, it is still unclear whether these mutations result from

late-stage acquisition of subclones or from the progressive selection of previously undetectable mutated subclones[10,11]. In patients who initially respond to anti-EGFR therapy but later experience disease progression, switching to an alternative treatment may allow the RAS mutations to subside, potentially providing an opportunity to reintroduce an EGFRi therapy in a later treatment line, known as a rechallenge[10].

Panitumumab is a fully human monoclonal antibody that specifically targets the human epidermal growth factor receptor (EGFR), a protein involved in cell growth in normal epithelial tissues and various tumour cells[1]. By binding to EGFR's ligand-binding domain, panitumumab inhibits receptor activation, leading to receptor internalisation, reduced cell growth, apoptosis, and lower production of interleukin 8 and vascular endothelial growth factor[1].

Both panitumumab and cetuximab are licensed as monotherapy options for the treatment of mCRC but neither are specifically licenced for rechallenge[1,12].

Incidence/prevalence

Colon cancer makes up 72% of colorectal cancer cases, while rectal cancer accounts for 28%[13]. In the UK, around 44,000 new cases are diagnosed annually, representing 12% of all cancers[14], with 666 Stage IV cases in Wales in 2021[15]. Stage IV mCRC has a poor prognosis, with 1-year survival rates of about 44% and 5-year survival rates under 10%[16].

Clinicians consulted by the (AWTTC estimate that there are around 200-250 metastatic patients each year, with 60% having left-sided tumours and 50% of those being RAS wild-type. Approximately 50-80 patients annually will undergo ctDNA testing, with 60% of them being eligible for rechallenge. This results in an estimated 30 to 50 patients per year in Wales who would qualify for treatment with an EGFRi.

Current treatment options and relevant guidance

Patients with mCRC have disease that is incurable; treatment goals are focused on delaying tumour progression, alleviating tumour-related symptoms, optimising survival, preserving quality of life (QoL), and minimising treatment-related toxicity[16].

First-line treatment involves targeted biologic therapy tailored to the mutation profile and tumour location, such as cetuximab or panitumumab combined with chemotherapy (FOLFOX or FOLFIRI) for left-sided RAS wild-type tumours[17]. Second-line treatment usually involves chemotherapy, with the specific regimen chosen based on the patient's first line therapy[18]. The proposed treatment under consideration would be third line or later with the current treatment pathway based on Welsh clinical expert clinical advice and current NICE TA-approved treatments.

Third line treatment for RAS wild-type mCRC

In the third line setting, after progression following second line treatment, patients with RAS wild-type mCRC are often treated with targeted therapies. Key options include:

- Trifluridine-tipiracil (Lonsurf®) (administered orally) with IV bevacizumab is licensed and NICE approved after the failure of two lines of treatment[16]

- Trifluridine-tipiracil (Lonsurf®) alone is NICE approved at this line of treatment[19]
- Regorafenib (administered orally) is similarly NICE approved[19]

Fourth line treatment for RAS wild-type mCRC

In the fourth line setting, treatment options are more limited, but there are still effective therapies:

- Regorafenib: In accordance with NICE TA866[16], regorafenib can continue to be an option in the fourth line setting for patients who have failed earlier treatments and have not received regorafenib.
- Trifluridine-tipiracil (Lonsurf®): if trifluridine-tipiracil was not used in the third line setting, it can still be considered in the fourth line setting for patients with progressive disease, in accordance with NICE TA405[20]. However, clinical expert opinion is that in practice patients will have been treated with trifluridine-tipiracil (Lonsurf®) plus bevacizumab at third line therefore regorafenib would be the treatment of choice.
- Best Supportive Care (BSC): In cases where all available treatments have been exhausted and the patient has a poor performance status, the focus may shift toward BSC, which aims to improve the patient's quality of life.

Panitumumab monotherapy for mCRC that has progressed after first line chemotherapy was appraised by NICE in 2012. At the time NICE decided not to recommend panitumumab in this setting stating that it did not provide enough benefit to patients to justify its high cost even when the special considerations were applied[21]. However, the marketing authorisation holder has informed AWTTC that rechallenge falls outside the marketing authorisation for this medicine and therefore this NICE recommendation would not apply as NICE advice does not include off-label use of a medicine.

Fruquintinib for previously treated mCRC is currently undergoing NICE TA, publication date is to be confirmed at the time of writing this report[22].

The European Society for Medical Oncology (ESMO) has recently updated its treatment guidelines for unresectable mCRC in the third-line setting and beyond[6]. For patients with RAS wild-type, ESMO recommends several third-line and later treatment options, including trifluridine-tipiracil with or without bevacizumab, panitumumab, irinotecan with cetuximab and regorafenib.

Summary of evidence on clinical effectiveness

A literature search was conducted in February 2025 by the All Wales Therapeutics and Toxicology Centre (AWTTC) relating to panitumumab as rechallenge monotherapy in metastatic colorectal cancer with RAS wild-type identified on circulating tumour DNA testing. Searches were performed using Cochrane, Central Register of Controlled Trials, EMBASE, MEDLINE and TRIP database. The primary outcomes were overall survival (OS), progression-free survival (PFS), objective response rate (ORR), adverse events (AE), health related quality of life (HRQoL) and resource use. A literature search identified 268 records which were assessed for eligibility, with 80 excluded following removal of duplicates and screening of title and abstracts. Following eligibility screening, three publications were included in the

report covering one clinical trial, and two meta-analyses and systematic reviews. The remaining records were excluded due to small patient numbers, incorrect cohort or unsuitable study design (see Appendix 1). The company also provided information that contributed to the development of the findings in this report.

Efficacy

The main source of evidence comes from the CHRONOS trial (Sartore-Bianchi et al, 2022) which was a phase II multicentre, open-label, single-arm clinical trial that aimed to evaluate the use of ctDNA to guide rechallenge with panitumumab in patients with mCRC[2]. The trial included mCRC patients who had previously received an EGFRi either in combination with chemotherapy or as monotherapy, followed by at least one additional line of therapy, and had either progressed or experienced relapse. The primary endpoint was objective response rate (percentage of patients achieving a partial response) in patients who received panitumumab rechallenge based on ctDNA detection[2]. Secondary end points were progression-free survival, overall survival, safety and tolerability of this strategy.

A total of 36 patients were eligible for panitumumab rechallenge based on molecular criteria. Of these, 27 received the treatment according to the trial protocol, six did not meet the clinical inclusion criteria, and three were treated at the discretion of the physician[2]. Among the 27 patients enrolled, the median age was 64 years (range 42–80), and 15 (56%) were stage IV at initial diagnosis. Primary tumour location was right side in 5 (18%) patients, left side in 17 (63%) and rectum in 5 (18%) patients. Patients had a median of three prior therapies (range 2–6). All received oxaliplatin-based regimens, 93% had irinotecan-based regimens, and 59% had anti-vascular endothelial growth factor (VEGF) therapies. Additionally, 26% had received regorafenib, 22% had trifluridine-tipiracil, and 100% had anti-EGFR combined with chemotherapy, with 7% having previously undergone rechallenge and 26% having received reintroduction. None of the patients had received anti-EGFR monotherapy. Anti-EGFR therapy was first line in 75% of patients, the previous EGFRi was either cetuximab (41%), panitumumab (55%) or both (4%)[2].

The trial met its primary endpoint with an objective response rate (ORR) of 30%, consisting of 8 partial responses, 6 of which were confirmed and 2 unconfirmed according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria[2]. The median duration of response was 17 weeks. Additionally, 11 of the 27 patients (40%) achieved stable disease (SD), and 9 of these 11 (82%) maintained SD for more than 4 months. The disease control rate, defined as partial response plus SD lasting more than 4 months, was 63% (17 patients). The median PFS was 16 weeks, while the median OS was 55 weeks[2].

Supplemental data provided results by location of tumour. For patients with left-sided (including rectal) disease (n = 22): 7 (ORR, 32%) achieved partial responses (including 1 unconfirmed); 10 (45%) achieved SD, 8 (80%) of whom maintained stable disease for more than 4 months.

Meta-analyses and systematic reviews

The literature search and the company-submitted information pack identified two systematic reviews and meta-analyses. The studies by de Moraes et al. (2024, 14 studies, 520 patients) and da Silva et al (2024, 13 studies, 402 patients) both

evaluated the efficacy and safety of anti-EGFR rechallenge in mCRC, specifically in RAS wild-type patients[23,24]. In both meta-analyses, EGFRi rechallenge demonstrated modest clinical efficacy. Pooled analyses were performed to calculate ORR and disease control rate (DCR). De Moraes et al reported an ORR of 17.7% and DCR of 61.7% (516 patients), the da Silva analysis reported an ORR of 20.5% and DCR of 67.4% (285 patients)[23,24]. De Moraes et al performed sub-group analyses by EGRFi and reported ORR of 18.3% for cetuximab and 10.9% for panitumumab, the DCR was 62.1% and 63.1% respectively (313 and 148 patients, respectively)[24]. Da Silva et al pooled results of 3 studies (all combination treatment with cetuximab) which had analysed RAS status by ctDNA analysis; the pooled HR for OS showed a greater benefit with EGFRi for patients with RAS wild-type (HR:0.41; 95% CI 0.28–0.6)[23]. It is important to note that both reviews reported significant heterogeneity between studies. EGFRi rechallenge included use both as monotherapy or in combination with other treatments and CHRONOS was the only study included for panitumumab monotherapy alone.

Safety

In the CHRONOS trial, panitumumab rechallenge was generally well-tolerated[2]. Results were collated to include patients treated with panitumumab monotherapy according to previous protocol version 2.1 dated 2017 (n =32). No patients required permanent treatment interruptions, and there were no treatment withdrawals due to adverse events. Grade 3/4 adverse event (AE) toxicities were seen in 22% of patients, including skin rash (9%), folliculitis (6%), and paronychia (3%). Twelve patients (37%) received tetracycline antibiotics as prophylaxis for skin reactions, though this did not significantly impact the rate of cutaneous events[2].

The adverse events reported in the CHRONOS trial are consistent with those outlined in the Summary of Product Characteristics (SmPC) for panitumumab[1,2]. Both sources highlight skin-related reactions, hypomagnesemia, and diarrhoea as common adverse effects associated with panitumumab therapy. The CHRONOS findings support the overall safety profile described in the SmPC, with most adverse events being manageable and not leading to discontinuation of treatment.

Discussion

Panitumumab is licensed as monotherapy for later treatment of mCRC, although to be included in the two randomised controlled trials (RCTs) on which the licence is based, participants must have been naïve to prior treatment with panitumumab. The first was a Phase III trial comparing panitumumab monotherapy with BSC versus BSC alone in 463 patients with chemorefractory, wild-type KRAS mCRC, who had a median of two prior treatments[25]. Panitumumab showed significant benefits over BSC, improving OS (10.0 vs. 7.4 months), PFS (3.7 vs.1.9 months), and achieving a 10% response rate[25]. The second Phase III, randomised, open label, non-inferiority trial compared panitumumab with cetuximab in 1,010 patients with wild-type KRAS mCRC, also with a median of two prior treatments[26]. The results showed no significant difference in OS (10.0 vs. 9.9 months) or PFS (3.7 months for both treatments), with comparable response rates[26]. Overall these studies demonstrate a similar response rate to CHRONOS, however the main difference being that CHRONOS patients were not naïve to EGFRi treatment and the CHRONOS trial aimed to improve patient selection using molecular profiling through ctDNA, targeting

those less likely to have developed resistance mutations, potentially leading to better outcomes.

CHRONOS was a phase II multicentre, open-label, single-arm clinical trial[2]. All patients had received an EGFRi plus chemotherapy (as per UK clinical practice) and prior treatments received were relevant to those used in UK clinical practice. Patients had received a median of three prior treatments, almost all patients had an eastern cooperative oncology group (ECOG) status of 0 or 1 and most patients had left-sided disease (63%) which is most likely to reflect the population eligible for this treatment. However, the study lacked a formal comparison between retreatment with anti-EGFR therapy and standard later line treatments. The trial also lacked long-term follow-up, preventing assessment of treatment durability and safety[2].

Over the last ten years there have been a number of medicines approved for third-line or later treatment of mCRC (see current treatment section above) which have improved survival rates in this clinical setting. The median OS for third-line treatment with trifluridine-tipiracil plus bevacizumab was 10.8 months in the SUNLIGHT study with a PFS of 5.6 months[27]. Regorafenib has been studied in two main clinical trials: CONCUR and CORRECT[28,29]. In CONCUR, OS was 8.8 months[28]. In CORRECT, participants were heavily pre-treated, with approximately 50% having received four or more lines of prior treatment, which may have in part accounted for the lower OS of 6.4 months[29]. RAS wild-type status was not tested in either of the regorafenib trials. CONCUR and CORRECT were both placebo-controlled trials with a control arm of best supportive care alone. Overall survival in the control groups were 6.3 and 5 months respectively[28,29].

In their submission to NICE (TA1008, published September 2024)[19], the manufacturers of trifluridine-tipiracil conducted a network meta-analysis (NMA) to provide an indirect comparison of the relative treatment effectiveness for OS and PFS of trifluridine-tipiracil plus bevacizumab with regorafenib. The NMA results favoured trifluridine-tipiracil plus bevacizumab over regorafenib for both OS (Hazard ratio [HR] 0.60, 95% CI 0.38 to 0.95) and PFS (HR 0.49, 95% CI 0.31 to 0.84)[19]. For NICE TA866[16], the company reported similar efficacy between regorafenib and trifluridine-tipiracil based on a fixed-effect network meta-analysis model, with an OS HR of 0.99 (95% CI 0.84 to 1.17)[16]. Although the NICE commented on the heterogeneity between trials, the Committee concluded that regorafenib was likely to provide similar benefits in terms of PFS and OS to trifluridine-tipiracil.

It is difficult to draw any firm conclusions or undertake an indirect analysis between panitumumab and the relevant comparators due to heterogeneity between studies in terms of number and type of prior treatments, differences in study design and characteristics of study participants. Many of the comparator studies also did not test RAS status or RAS status was known for only a proportion (30.7% of patients in SUNLIGHT had RAS wild-type disease[27]) of the study population.

The conclusions of two meta-analyses by de Moraes et al (2024) and da Silva et al (2024) are supportive of the findings of the CHRONOS trial, as well as the use of ctDNA as a guide for treatment[23,24] They are however limited by the heterogenous nature of the studies included and the fact that most participants received combination treatment. This could potentially limit the generalisability of the results to patients receiving panitumumab as a single-agent therapy.

The biological rationale behind rechallenging is not entirely understood, and clinical data supporting efficacy of panitumumab rechallenge are still lacking. While some studies have shown that rechallenge can be beneficial for certain patients[2], long-term outcomes remain uncertain.

Panitumumab is commonly associated with skin reactions, including acneiform rash, dry skin, pruritus, and paronychia, affecting up to 90% of patients[1]. Other commonly reported adverse events include fatigue, diarrhoea, and infusion-related reactions. While dose adjustments or interruptions can help manage side effects, they may reduce the drug's effectiveness. Overall, the available information suggests that panitumumab safety is consistent with the profile known for its pharmacological class and no new signals have been identified[1]. Data available, although limited in size and long-term exposure, appear acceptable and suggest a tolerable profile.

Cost-effectiveness evidence

A literature review conducted by AWTTC did not identify any studies relevant to the cost-effectiveness of panitumumab in third-line or later-line treatment of stage IV metastatic left-sided colorectal cancer with RAS wildtype. The lack of cost-effectiveness evidence for the indication is not unexpected given the paucity of clinical trial data for panitumumab in third-line or later-line treatment of stage IV metastatic left-sided colorectal cancer with RAS wildtype.

An AWTTC cost consequence analysis (CCA) compares selected resource use and clinical outcomes associated with panitumumab (6mg/kg once every two weeks) with a range of comparators in the treatment of stage IV metastatic left-sided colorectal cancer with RAS wildtype. The analysis adopts a lifetime horizon and an NHS Wales/Personal and Social Services perspective. Costs are discounted at 3.5% per annum.

Cost of intervention

The administration of panitumumab is displayed in Table 1, the per cycle dose of 6 mg/kg every two weeks is informed by the SmPC. The average weight of the patient cohort is calculated at 79.7 kg, this equates a cycle dose of 478 mg. An 8-cycle administration is used for the per person panitumumab cost, this aligns with the 17-week median progression free survival from the CHRONOS study[2].

Resource use following treatment is described as BSC, cost inputs for this were identified from the literature. An AWTTC targeted literature search was undertaken to identify published figures reporting resource use and costs associated with BSC for patients with mCRC. One applicable estimate was identified within NICE Evidence Review Group report for TA405[20], inflated to £260 in 2025 (supplementary Table 1.a). The drug acquisition cost is based on patient access scheme (PAS) price and does not include VAT. For the lifetime horizon the duration of BSC is calculated as the OS minus PFS reported in the CHRONOS study, the total intervention cost of panitumumab is [commercial in confidence text removed].

Table 1. Panitumumab: diagnostic, procurement, and administration costs.

	Figure	Reference
100 mg vial	¶¶	PAS
400 mg vial	¶¶	PAS
Administration schedule	6 mg/kg once every two weeks	SmPC[1]
Average patient weight (kg)	79.67	NHS digital with gender distribution from CHRONOS[30]
Single dose amount	478 mg	
Single dose cost (400 mg vial + 100 mg vial)	¶¶	
Doses per patient	8	CHRONOS PFS duration[2]
Delivery simple chemotherapy first	£418	National schedule of reference costs 2023/24[31]
Delivery simple chemotherapy subsequent	£426	National schedule of reference costs 2023/24[31]
Total acquisition and administration cost	¶¶	
Duration of best supportive care	39 weeks	CHRONOS OS - PFS[2]
Total cost of best supportive care	£2,326	NICE TA405[20]
ctDNA cost per test	£150	AWMGS
Weighted ctDNA test cost for positives	£250	60% inclusion rate. Clinical expert opinion
Total cost per patient	¶¶	
AWMSG: All Wales Medical Genomics Service; OS: overall survival; PAS: Patient Access Scheme; PFS: progression-free survival ¶¶ commercial in confidence figure removed		

Cost of comparators

The analysis includes the costs considerations for the third-line, fourth-line, and fifth-line treatments reflecting the current use within the NHS in Wales as informed by clinical experts. Patients are modelled to receive treatment with either panitumumab or the appropriate comparator according to the line of treatment. Table 2 reports the range of comparators and the total per patient cost. The comparator for third-line therapy is trifluridine-tipiracil plus bevacizumab; fourth-line is regorafenib; and fifth-line is BSC. BSC costs are applied to each line of treatment following the median treatment duration up until death. The cost of comparators and the relative cost compared to panitumumab is reported in Table 2. Treatment durations have been based on OS data from SUNLIGHT, CORRECT and CONCUR clinical trials (Table 3)[27-29]. Cost details for the range of comparators is offered in Appendices 2.a–c.

Table 2. Comparator costs

Line in therapy	Cost	Relative cost of panitumumab compared to comparators
3rd line: Trifluridine-tipiracil* + bevacizumab	¶¶	¶¶
4th line: Regorafenib*	¶¶	¶¶
5th line: Best supportive care	¶¶	¶¶
*Patient Access Scheme price †All Wales drug contract price ¶¶ commercial in confidence figure removed		

Clinical outcomes

The clinical outcomes and health-related quality of life effects captured in the cost-consequence analysis are informed by the literature where possible, and by clinical expert opinion where published evidence is lacking. The summary of evidence on clinical effectiveness section provides greater detail on the sources of the primary and secondary clinical outcomes included, and the rationale for apportioning applicability to the targeted population. The key clinical outcomes, progression free survival, overall survival, and treatment emergent adverse events of grade three or higher are reported according to treatment line are reported in Table 3. Clinical experts have reported that the distribution of patients for this indication within the Welsh NHS is likely to be 56% third-line, 31% fourth-line and 13% fifth-line (supplementary Table 1.d).

Table 3. Progression free survival, overall survival and adverse events

	Panitumumab	Trifluridine-tipiracil + bevacizumab	Regorafenib	Best supportive care
	Intervention	Comparator 3rd line	Comparator 4th line	Comparator 5th line
Progression free survival (months)	3.69	5.60	2.18	unknown
Overall survival (months)	12.67	10.80	6.91	4
Adverse events ≥ grade 3* (% patients)	22.0%	72.4%	51.6%	unknown
References	CHRONOS[2]	SUNLIGHT[27]	CORRECT and CONCUR[28,29]	Clinical expert opinion
*The cost of adverse events is not included in the cost analysis.				

Results

In the base case analysis panitumumab was found to cost [commercial in confidence text removed] less than trifluridine-tipiracil plus bevacizumab in the third line of therapy and is associated with higher overall survival and reduction of adverse events (Table 4); progression-free survival, however, was shorter.

Table 4. Base case analysis

	Panitumumab	Trifluridine-tipiracil + bevacizumab
	Intervention	Comparator 3rd line
Costs/resource use		
Medicine acquisition	¶¶	¶¶
Administration	£3,400	£4,252
ctDNA screening	£250	
Best supportive care	£2,326	£1,505
total	¶¶	¶¶
Net cost		¶¶
Clinical outcomes		
Overall survival (months)		1.87
Progression free survival (months)		-1.68
Adverse events ≥ grade 3		-50.4%
¶¶ commercial in confidence figure removed		

Scenario analysis

Clinical experts have reported that approximately 44% of patients treated would be in later lines (fourth and fifth). Comparison of panitumumab to regorafenib as a fourth-line therapy and best supportive care as a fifth-line approach is detailed in Table 5. Panitumumab was found to be more costly than both the fourth-line and fifth-line options whilst offering improved overall survival. Progression free survival was higher in the panitumumab group with a lower adverse event rate compared with regorafenib.

Table 5. Fourth-line and Fifth-line cost consequence analyses

	Panitumumab	Regorafenib	Best supportive care
	Intervention	Comparator 4th line	Comparator 5th line
Costs/resource use			
Medicine acquisition	¶¶	¶¶	
Administration	£3,400		
ctDNA screening	£250		
Best supportive care	£2,326	£1,089	£1,038
total	¶¶	¶¶	¶¶
Net cost		¶¶	¶¶
Clinical outcomes			
Overall survival (months)		5.76	8.67
Progression free survival (months)		1.74	NA
Adverse events ≥ grade 3		-29.6%	NA
¶¶ commercial in confidence figure removed			

Threshold analysis

To characterise the scale of the differences in costs and overall survival a range of threshold analyses are undertaken at the willingness-to-pay values of £20,000 and £30,000 per quality adjusted life year (QALY). In the base case analysis panitumumab costs less and increases survival. Table 6 reports the threshold QALYs required, and the potential average health-related quality of life (HRQoL) required, over the additional overall survival, for the two alternative scenarios. The required HRQoL average for panitumumab to reach the £20,000 threshold is highest [commercial in confidence figure removed] when compared to the fifth-line option of BSC, this is due to the high net cost.

Table 6. Threshold analysis

	Trifluridine-tipiracil + bevacizumab	Regorafenib	Best supportive care
	Comparator 3rd line	Comparator 4th line	Comparator 5th line
Net cost	¶¶	¶¶	¶¶
Threshold QALYs required (£20,000 per QALY)	¶¶	¶¶	¶¶
Threshold QALYs required (£30,000 per QALY)	¶¶	¶¶	¶¶
Overall survival difference (months)	1.87	5.76	8.67
Threshold quality of life given overall survival (£20,000 per QALY)	¶¶	¶¶	¶¶
Threshold quality of life given overall survival (£30,000 per QALY)	¶¶	¶¶	¶¶
QALY: quality adjusted life year ¶¶ commercial in confidence figure removed			

To inform and contextualise the threshold analysis an AWTTC targeted literature review sought disease specific HRQoL for patients with stage IV left-sided mCRC cancer with RAS wildtype, Odom et al. (2011) was chosen due to the closeness of patient match and study size[32]. Odom et al. report a baseline weighted HRQoL figure of 0.71. Clinical experts have reported that HRQoL is expected to reduce in a linear trend across the overall survival duration. Applying the overall survival durations with the baseline HRQoL of 0.71, calculations offered in supplementary Table 1.e, that declines linearly results in area under the curve QALYs which are reported in Table 7.

Table 7. Potential QALY by treatment line

	Panitumumab	trifluridine-tipiracil + bevacizumab	regorafenib	BSC
	Intervention	Comparator 3rd line	Comparator 4th line	Comparator 5th line
QALYs	0.37	0.32	0.20	0.12
Net QALYs		0.06	0.17	0.26
QALY: quality adjusted life year				

Cost-effectiveness evidence limitations

- There are no published cost-effectiveness studies for this intervention.
- The analysis adopts a limited cost approach which doesn't consider the cost of adverse events and ongoing resource use. It is unknown what impact this has on the analysis aside from an increase in uncertainty.
- The clinical inputs from the CHRONOS trial are not specific to one line of therapy. Whilst the range of lines within this analysis (third, fourth and fifth) are observed within the trial, the lack of line specific overall survival, progression free survival and adverse event rate reduces the robustness of the analysis. A negative relationship between OS and lines of therapy may result in underestimating relative overall survival in earlier lines of therapy whilst overestimating relative overall survival in later lines.
- The comparative clinical effectiveness trials are not restricted to administration in single lines of therapy. Evidence sourced from trials where treatment is delivered in a range of lines of therapy may induce bias.
- The patient characteristics of the CHRONOS trial vary from the comparator evidence trials. Patients in latter lines of therapy may achieve worse health outcomes, the single estimate for panitumumab lacks this detail.
- The evidence used to inform line specific clinical outcomes for the comparators is sourced from trials which include patients with a range of prior lines of therapy. This lack of patient/line matching may induce bias to the analysis in cases where there is a correlation between prior lines of therapy and clinical outcomes.
- The mapping of QoL over time is informed by experts, the simplistic linear slope may underestimate the benefits of extensions to progression-free and overall survival.
- The comparator clinical evidence is sourced from separate studies to that of the intervention, the lack of directly comparative evidence limits the certainty of the findings.
- The simple approaches used in this analysis may lack the accuracy and nuance of a full partitioned survival model, however, the clinical evidence was insufficiently detailed to undertake such analysis.
- The targeted literature searches used to identify resource use and utility data are inferior to undertaking full systematic reviews for these inputs, the confidence and robustness of the conclusions are subsequently limited.

Table 8. Examples of medicine acquisition costs

Regimens	Unit cost	Example doses	Approximate costs per patient
Panitumumab*	¶¶ per 100mg vial ¶¶ per 400mg vial	6 mg/kg IVI once every two weeks [β].	¶¶
Trifluridine-tipiracil*	¶¶ per 20 tablet pack of 15mg ¶¶ per 20 tablet pack 20mg	35 mg/m^2/dose twice daily (10 days per month)[π]	¶¶
Bevacizumab[†]	¶¶ per 400mg vial	5 mg/kg IVI twice monthly[β].	¶¶
Regorafenib*	¶¶ per 84 tablet pack of 40mg	160 mg daily for 3 weeks, 1 week off	¶¶

Costs of administration are not included. VAT is not included.
This table does not imply therapeutic equivalence of medicines or the stated doses.
*Patient Access Scheme (PAS) price
[†]All Wales drug contract price
[β] Dose calculated using an average patient weight of 79.67kg[30]
[π] Dose calculated using an average patient surface area of 1.79 m^2 [40]
¶¶ commercial in confidence figure removed

Table 9. Severity modifier considerations for One Wales Medicines Assessment Group (OWMAG)

AWMSG criteria for applying a severity modifier weight	New medicine considerations
OWMAG can: • apply a QALY weight of 1 if the medicine is indicated for patients with a condition associated with an absolute QALY shortfall < 12 and/or a proportional QALY shortfall < 0.85. • apply a QALY weight of 1.2 if the medicine is indicated for patients with a condition associated with an absolute QALY shortfall ranging between 12 and 18 and/or a proportional QALY shortfall ranging between 0.85 and 0.95. • apply a QALY weight of 1.7 if the medicine is indicated for patients with a condition associated with an absolute QALY shortfall >18 and/or a proportional QALY shortfall ≥ 0.95. If the absolute and proportional QALY shortfalls imply different levels of severity, QALY weighting selection is guided by the shortfall that shows greatest severity.	The general population expected life-year and expected total QALY estimates are taken from the pooled 2017–2019 population health state profiles offered by the health survey 2014[33] in combination with the valuation model of Hernandez et al.(2022)[34,35]. The median age of 64 and the gender distribution are taken from the CHRONOS study (59% male)[2]. The general population is estimated to achieve 11.28 QALYs. Expected life-year and expected total QALY estimates for patients being treated with the current standard of care is estimated according to the line of therapy. The quality of life estimate of 0.71 is sourced from Odom et al[36]., this is used across each line of therapy. There is a linear reduction in QoL modelled across OS, this is informed by clinical expert opinion. Patients treated with a third line therapy of trifluridine-tipiracil plus bevacizumab are estimated to achieve 0.32 QALYs. The fourth line of regorafenib is estimated to achieve 0.20 QALYs. Fifth line therapy consists of BSC which is associated with an OS of 4 months resulting in 0.12 QALYS. AWTTC considers the QALY shortfall estimates to be informed by recent and robust data sources. AWTTC considers the most plausible absolute QALY loss to be around 10.96 in the 3rd line, 11.08 in the 4th line and 11.16 in the fifth line. The relative reduction in QALYs exceeds 95% in all lines of treatments. Due to the high relative shortfall, each line meets the AWMSG criteria for the 1.7 QALY modifier weight. This estimate is deemed plausible due to the very low overall survival expected for this patient cohort.
AWTTC: All Wales Therapeutics and Toxicology Centre; BSC: best supportive care; OS: overall survival; QALY: quality-adjusted life-year	

If OWMAG conclude that panitumumab should be considered under the AWMSG policy for appraising medicines for severe conditions, OWMAG will need to consider:

- the effect of the severity QALY weight applied, and whether the weighted QALY benefits in this patient group result in a most plausible ICER that falls within the current cost-effectiveness threshold range.

In addition, OWMAG will need to be satisfied that:

- The estimates of the expected life years and total QALYs for the general population and for patients being treated with the comparator medicines(s) are sourced from recent and robust data sources.
- The assumptions used in the economic modelling are plausible, objective and robust.

Budget impact

The Patient Access Scheme (PAS) price of panitumumab (Vectibix®) is [commercial in confidence text removed]. Clinical experts estimate that patients will receive a maximum of 6 months treatment (12 cycles).

Medicine acquisition costs for panitumumab and comparators for one month of treatment are provided in Table 10. NHS Wales secondary care prescribing figures from 2024 for bevacizumab have been used to calculate a weighted average procurement cost (supplementary Table 1.b).

Table 10. Cost of panitumumab and comparators in Wales (per patient)

	Cost	Regimen	Comments
Panitumumab (Vectibix®) per 2 cycles (1 month)	¶¶	6 mg/kg IV infusion* every 2 weeks[1]	PAS price Assumes vial wastage Excludes VAT
Regorafenib (Stirvaga®) per cycle (1 month)	¶¶	160 mg daily for 3 weeks, 1 week off[37]	PAS price Excludes VAT
Trifuridine-tipiracil (Lonsurf®) per cycle (1 month)	¶¶	35 mg/m^2/dose† twice daily on days 1-5 and 8-12[38]	PAS price Excludes VAT
Bevacizumab per 2 cycles (1 month)	¶¶	5 mg/kg IV infusion* every 2 weeks[39]	Assumes vial wastage Weighted average. All Wales drug contract procurement cost. Excludes VAT
*Average adult weight 79 kg[30] †Mean body surface area 1.79 m^2[40] IV: intra-venous; PAS: patient access scheme ¶¶ commercial in confidence figure removed			

Associated resource costs for panitumumab and comparators are defined in Table 1. Clinical experts estimate that 50 to 80 patients per year would be suitable for ctDNA

testing and 60% of them would be identified as RAS wild-type and be eligible for treatment with panitumumab as re-challenge (30 to 50 patients in Wales). Resource costs for these lower and upper estimates are provided in Table 11.

Table 11. Net resource costs for upper and lower patient number estimates for panitumumab and comparator treatments

	Cost per patient	80 patients*	30 patients	50 patients
Panitumumab				
Circulating tumour DNA liquid biopsy	£150	£12,000	£4,500	£7,500
Resource costs for 1st month (2 cycles)	**£844**		**£25,320**	**£42,200**
Resource cost per month for subsequent cycles	**£852**		**£25,560**	**£42,600**
Trifuridine-tipiracil (Lonsurf®) with bevacizumab				
Resource cost for 1 month (2 cycles)	**£844**		**£25,320**	**£42,200**
Best supportive care				
Resource cost for 1 month (1 cycles)	**£260**		**£7,800**	**£13,000**
*60 to 80 patients are estimated to be eligible for ctDNA, 60% of whom will be RAS wild-type and eligible for panitumumab re-challenge				

Clinical expert opinion is that the current available preferred treatment option at third line would be for trifluridine-tipiracil (Lonsurf®) with bevacizumab. For patients not fit enough to receive bevacizumab, trifluridine-tipiracil (Lonsurf®) alone is an option for use. At fourth line regorafenib or BSC are the current treatment options and fifth line and beyond is BSC. Median progression free survival for patients receiving panitumumab in the CHRONOS study and treatment duration for trifluridine/tipiracil with bevacizumab in the SUNLIGHT trial and for regorafenib in the CONCUR and CORRECT trials have been used to inform the treatment duration for the panitumumab and comparators for the budget impact calculations shown in Tables 12 and 13[2,27-29]. It is assumed that patients progressing on active treatment would go on to receive BSC therefore where the duration of treatment is less than 4 months, the remainder of the treatment would be BSC.

The budget impact for panitumumab versus trifluridine-tipiracil (Lonsurf®) with bevacizumab as third line treatment is detailed in Table 12. In this setting panitumumab is overall cost saving based on medicine acquisition cost alone. The table shows costs for the lower and upper estimates of patient numbers for 4 months of treatment, as per the progression free survival in the CHRONOS trial[2]. Table 13 details the budget impact for panitumumab used as a fourth line treatment versus regorafenib or best supportive care. If panitumumab is used as fifth line treatment or above the comparator treatment is BSC, which is predominately primary healthcare resource cost with no significant medicine acquisition costs. From fifth-line onwards the budget impact will equal the acquisition cost of panitumumab, [commercial in confidence text removed].

Table 12. Budget impact for four months panitumumab as third line treatment

	30 patients	50 patients
Comparator: trifluridine-tipiracil (Lonsurf®) with bevacizumab		
Panitumumab total medicines acquisition cost*	¶¶	¶¶
Trifluridine-tipiracil (Lonsurf®)† with bevacizumab§ total medicines acquisition cost	¶¶	¶¶
Overall net cost	**¶¶ Cost saving**	**¶¶ Cost saving**
Costs exclude VAT Average adult weight 79 kg[30] Mean body surface area 1.79 m^2[40] *6 mg/kg IV infusion every 2 weeks[1] †35 mg/m^2/dose twice daily on days 1-5 and 8-12[38] §5 mg/kg IV infusion every 2 weeks[39] ¶¶ commercial in confidence figure removed		

Table 13. Budget impact for four months panitumumab as fourth line treatment

	30 patients	50 patients
Comparator: regorafenib		
Panitumumab total medicines acquisition cost*	¶¶	¶¶
Regorafenib (Stirvaga®) 2 months†§ + 2 months BSC¶ total medicines acquisition cost	¶¶	¶¶
Overall net cost	¶¶	¶¶
Costs exclude VAT Average adult weight 79 kg[30] Mean body surface area 1.79 m^2[40] *6 mg/kg IV infusion every 2 weeks[1] †160 mg daily for 3 weeks, 1 week off[37] §Mean of median treatment durations in CORRECT (1.7 months) and CONCUR (2.4 months)[28,29] ¶Two months of comparator medicine costs only, no medicine acquisition costs are provided for BSC BSC: best supportive care ¶¶ commercial in confidence figure removed		

Budget impact discussion

- The budget impact shows that panitumumab re-challenge is likely to be cost saving as a third line treatment for this small sub-group of patients. This assumes the current favoured option for third line treatment is trifluridine/tipiracil plus bevacizumab. [commercial in confidence text removed].
- There is considerable uncertainty as to the number of patients treated at each line respectively. In the CHRONOS study the median number of previous treatments was three, in SUNLINGHT the majority of patients (93%) had received two prior treatments[2,27]. In CONCUR and CORRECT the majority of

patients had received three or more previous treatments[28,29]. If these studies reflect real world practice then fourth- and fifth-line budget impact estimates are likely to be more plausible. However, if this were the case then patient numbers may be expected to be towards the lower end of the estimate due to the poor overall survival of this patient group.

- The duration of treatment is subject to significant uncertainty. CHRONOS did not report a median treatment duration, PFS was used as a proxy so may be an over estimate[2]. Median treatment duration from study results were used for the comparator medicines. The results of the studies used to estimate treatment duration were not stratified by the number of previous treatments. It would be reasonable to assume that treatment duration would be longer for those patients who had received fewer treatments.
- The weighted average procurement cost for bevacizumab may fall slightly if biosimilar uptake increases in Wales. This is unlikely to affect future budget impacts significantly as the bevacizumab acquisition cost is not the main driver for the total cost for trifluridine/tipiracil plus bevacizumab.
- Monitoring costs are not included, clinical experts state that monitoring is the same for panitumumab as for comparator treatments.
- Treatment of adverse event costs have not been included however are expected to be similar for each treatment arm and small in comparison to drug acquisition costs[19,21].
- Administration costs are higher for subsequent treatment cycles than for the initial administration costs for bevacizumab and panitumumab. The NHS cost code SB15Z for delivery of subsequent chemotherapy covers a range of subsequent chemotherapy regimens from simple to highly complex[41]. It is therefore likely to be an overestimation of the costs for these more simple, single agent regimens with short infusion times after the first dose (30 to 60 minutes)[1,39].
- The resource costs associated with BSC is subject to significant uncertainty. There are very limited data available for BSC in mCRC which would be classed as palliative care for this indication. Gardiner et al (2018) performed a systematic review to explore activity and unit cost data for palliative care and concluded that due to limited data and heterogeneity it was not possible to provide an aggregate cost of palliative care in the UK[42]. We report costs provided for the appraisal of NICE TA405, trifluridine-tipiracil for previously treated mCRC inflated to 2025 prices. The costs comprise primary care costs only so may be someway reflective of BSC for comparison to active treatment with patients receiving support at home rather than in a hospice or as a hospital in-patient.

Equality and health impact assessment

AWTTC have completed an Equality and Health Impact Assessment in parallel with each development stage of the project. This follows the five ways of working for public bodies, and work to achieving the wellbeing goals, outlined in the Well-Being of Future Generations (Wales) Act 2015.

It is not expected that panitumumab will have significant potential negative impact on people based on the protected characteristics of the Equality Act 2010.

Additional factors

Prescribing unlicensed medicines

Panitumumab (Vectibix®) is not licensed to treat this indication and is therefore 'off label'. Providers should consult the relevant guidance on prescribing unlicensed medicines before any off-label medicines are prescribed.

Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content. An Equality and Health Impact Assessment (EHIA) has been completed in relation to the medicine and has been published on the AWTTC website.

Information presented in this document can be reproduced using the following citation: All Wales Therapeutics & Toxicology Centre. Evidence Status Report. Panitumumab (Vectibix®) for treatment of stage IV metastatic left-sided colorectal cancer with RAS wildtype confirmed by circulating tumour DNA following successful first line treatment with an epidermal growth factor inhibitor and at least one other treatment. Reference number: OW29. 2025.

References

1. Amgen Ltd. Vectibix 20 mg/mL concentrate for solution for infusion. Summary of Product Characteristics. July 2023. Available at: https://www.medicines.org.uk/emc/product/6178/smpc#gref. Accessed March 2025.
2. Sartore-Bianchi A, Pietrantonio F, Lonardi S et al. Circulating tumor DNA to guide rechallenge with panitumumab in metastatic colorectal cancer: the phase 2 CHRONOS trial. *Nature Medicine.* 2022;28(8):1612-1618.
3. Cancer Research UK. What is metastatic bowel cancer? Available at: https://www.cancerresearchuk.org/about-cancer/bowel-cancer/advanced/about-metastatic-bowel-cancer. Accessed March 2025.
4. Janssens K, Fransen E, Van Camp G et al. A Belgian Population-Based Study Reveals Subgroups of Right-sided Colorectal Cancer with a Better Prognosis Compared to Left-sided Cancer. *The Oncologist.* 2023;28(6):e331-e340.
5. Cancer Research UK. Stage 4 bowel cancer. Available at: https://www.cancerresearchuk.org/about-cancer/bowel-cancer/stages-types-and-grades/stage-four. Accessed March 2025.
6. Cervantes A, and Martinelli E. Updated treatment recommendation for third-line treatment in advanced colorectal cancer from the ESMO Metastatic Colorectal Cancer Living Guideline. *Annals of Oncology.* 2024;35(2):241-243. Available at: https://www.sciencedirect.com/science/article/pii/S0923753423043351.
7. Dean L, and Kane M. Medical Genetics Summaries [Internet]. Cetuximab Therapy and RAS and BRAF Genotype. In: Pratt VM, Scott SA, Pirmohamed M, et al. 2020. Available at: https://www.ncbi.nlm.nih.gov/books/NBK564547/.
8. Ciardiello D, Martinelli E, Troiani T et al. Anti-EGFR Rechallenge in Patients With Refractory ctDNA RAS/BRAF wt Metastatic Colorectal Cancer: A Nonrandomized Controlled Trial. *JAMA Network Open.* 2024;7(4):e245635-e245635.
9. Wen X, Pu H, Liu Q et al. Circulating Tumor DNA-A Novel Biomarker of Tumor Progression and Its Favorable Detection Techniques. *Cancers (Basel).* 2022;14(24).
10. Misale S, Yaeger R, Hobor S et al. Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. *Nature.* 2012;486(7404):532-536.

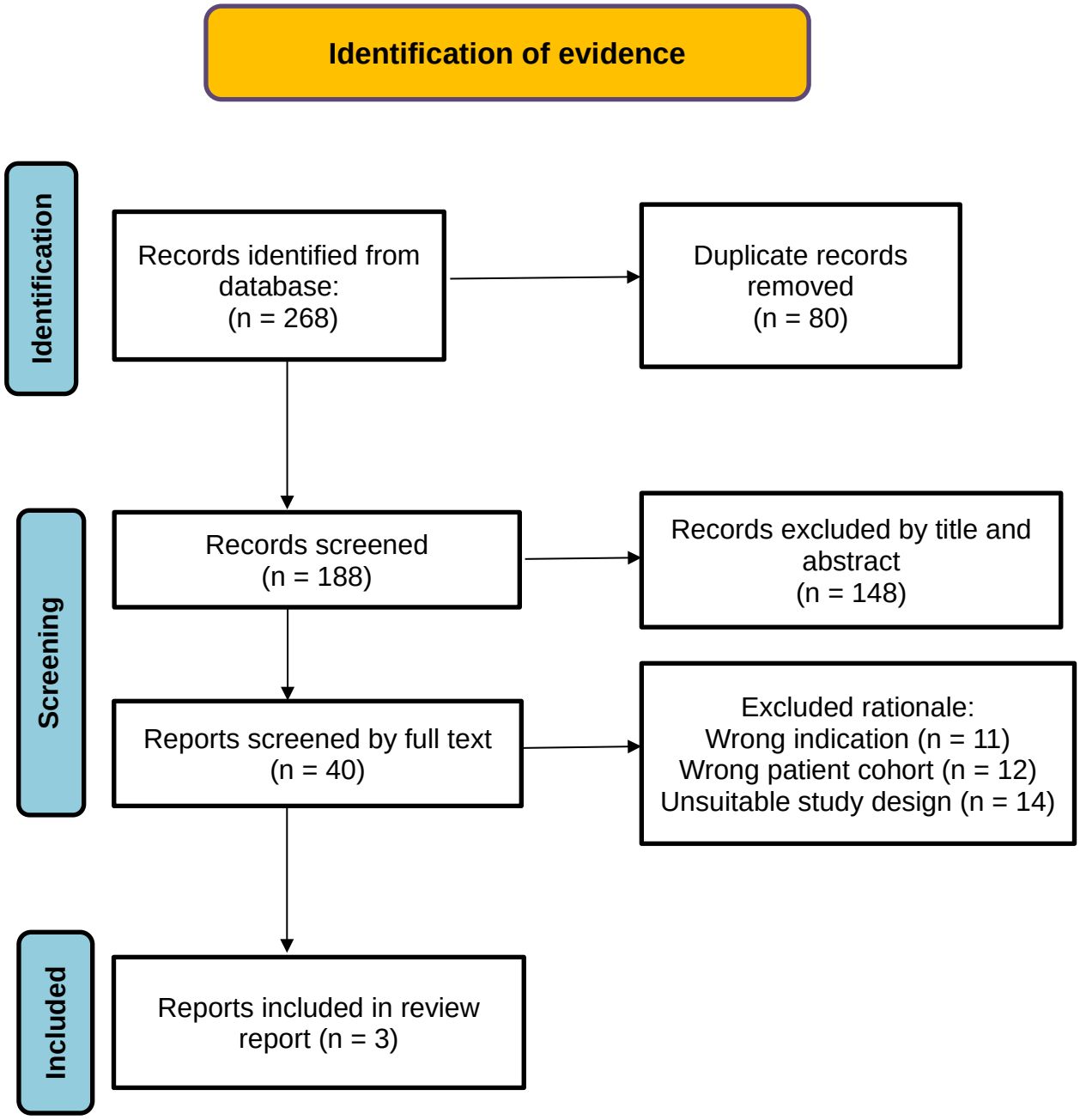
11. Lièvre A, Bachet JB, Le Corre D et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Research.* 2006;66(8):3992-3995.
12. Merck. Erbitux 5 mg/mL solution for infusion. Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/317/smpc#companyDetails. Accessed March 2025.
13. Marcellinaro R, Spoletini D, Grieco M et al. Colorectal Cancer: Current Updates and Future Perspectives. *Journal of Clinical Medicine.* 2023;13(1).
14. Cancer Research UK. Bowel cancer incidence statistics. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence. Accessed March 2025.
15. Welsh Cancer Intelligence and Surveillance Unit (WCISU). Cancer Incidence in Wales, 2002-2021. September 2024. Available at: https://phw.nhs.wales/services-and-teams/welsh-cancer-intelligence-and-surveillance-unit-wcisu/cancer-reporting-tool-official-statistics/cancer-incidence/. Accessed March 2025.
16. National Institute for Health and Care Excellence. Technology appraisal guidance TA866: Regorafenib for previously treated metastatic colorectal cancer. Feburary 2023. Available at: https://www.nice.org.uk/guidance/ta866. Accessed March 2025.
17. National Institute for Health and Care Excellence. Technology appraisal guidance TA439: Cetuximab and panitumumab for previously untreated metastatic colorectal cancer. September 2017. Available at: https://www.nice.org.uk/guidance/ta439. Accessed March 2025.
18. Cervantes A, Adam R, Roselló S et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology.* 2023;34(1):10-32.
19. National Institute for Health and Care Excellence. Technology appraisal guidance TA1008: Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments. September 2024. Available at: https://www.nice.org.uk/guidance/ta1008. Accessed March 2025.
20. National Institute for Health and Care Excellence. Technology appraisal guidance TA405: Trifluridine–tipiracil for previously treated metastatic colorectal cancer. August 2016. Available at: https://www.nice.org.uk/guidance/ta405. Accessed March 2025.
21. National Institute for Health and Care Excellence. Technology appraisal guidance TA242: Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy. Last review March 2015. Available at: https://www.nice.org.uk/guidance/ta242. Accessed March 2025.

22. National Institute for Health and Care Excellence. Fruquintinib for previously treated metastatic colorectal cancer ID6274. TBC. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta11280. Accessed March 2025.
23. da Silva LFL, Saldanha EF, da Conceição LD et al. Anti-EGFR Rechallenge in Metastatic Colorectal Cancer and the Role of ctDNA: A Systematic Review and Meta-analysis. *Journal of Gastrointestinal Cancer.* 2024;56(1):28.
24. de Moraes FCA, de Oliveira Rodrigues ALS, Priantti JN et al. Efficacy and Safety of Anti-EGFR Therapy Rechallenge in Metastatic Colorectal Cancer: A Systematic Review and Meta-Analysis. *Journal of Gastrointestinal Cancer.* 2024;56(1):9.
25. Kim TW, Elme A, Kusic Z et al. A phase 3 trial evaluating panitumumab plus best supportive care vs best supportive care in chemorefractory wild-type KRAS or RAS metastatic colorectal cancer. *British Journal of Cancer.* 2016;115(10):1206-1214.
26. Price TJ, Peeters M, Kim TW et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol.* 2014;15(6):569-579.
27. Prager GW, Taieb J, Fakih M et al. Trifluridine-Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer. *The New England Journal of Medicine.* 2023;388(18):1657-1667.
28. Li J, Qin S, Xu R et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncology.* 2015;16(6):619-629.
29. Grothey A, Van Cutsem E, Sobrero A et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381(9863):303-312.
30. NHS England. Health Survey for England, 2021 Part 4: Trends height and weight. December 2022. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2021/part-4-trends. Accessed March 2025.
31. NHS England. National schedule of NHS costs 23/24. Available at: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/. Accessed March 2025.
32. Odom D, Barber B, Bennett L et al. Health-related quality of life and colorectal cancer-specific symptoms in patients with chemotherapy-refractory metastatic disease treated with

panitumumab. *International Journal of Colorectal Disease.* 2011;26(2):173-181.
33. Hernández AM, Pudney S, and Wailoo A. Estimating EQ-5D by Age and Sex for the UK. NICE DSU Report. 2022. Accessed March 2025.
34. National life tables: England. Office for National Statistics Life tables: England, 2017-2019 (pooled). Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandreferencetables. Accessed March 2025.
35. NatCen Social Research, University College London, and Department of Epidemiology and Public Health. Health Survey for England, 2014. [data collection]. 4th Edition. UK Data Service. SN: 7919,. 2023. Available at: http://doi.org/10.5255/UKDA-SN-7919-4. Accessed March 2025.
36. Odom D, Barber B, Bennett L et al. Health-related quality of life and colorectal cancer-specific symptoms in patients with chemotherapy-refractory metastatic disease treated with panitumumab. *International Journal of Colorectal Disease.* 2011;26(2):173-181.
37. Bayer plc. Stivarga 40 mg film-coated tablets. Summary of Product Characteristics. May 2023. Available at: https://www.medicines.org.uk/emc/product/1263/smpc. Accessed March 2025.
38. Servier Laboratories Limited. Lonsurf 20 mg/8.19 mg film-coated Tablets. Summary of Product Characteristics. August 2024. Available at: https://www.medicines.org.uk/emc/product/10731/smpc. Accessed March 2025.
39. Roche Products Limited. Avastin 25mg/ml concentrate for solution for infusion. Summary of Product Characteristics. December 2022. Available at: https://www.medicines.org.uk/emc/product/3885/smpc. Accessed March 2025.
40. Sacco JJ, Botten J, Macbeth F et al. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. *PLoS One.* 2010;5(1):e8933.
41. NHS England. NHS Payment Scheme: 2024/25 pay award prices. March 2024. Available at: https://www.england.nhs.uk/publication/2023-25-nhs-payment-scheme/#heading-2.
42. Gardiner C, Ryan T, and Gott M. What is the cost of palliative care in the UK? A systematic review. *BMJ Support Palliative Care,.* 2018;8(3):250-257.

43. Haddaway NR, Page MJ, Pritchard CC et al. PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. *Campbell Systematic Reviews.* 2022;18(2):e1230.

Appendix 1 PRISMA flow diagram[43]



Appendix 2.a. Cost of trifluridine-tipiracil and bevacizumab followed by best supportive care

trifluridine-tipiracil	Figure	Reference
Dose of trifluridine-tipiracil mg/m^2	35 mg/m^2	SmPC[38]
Average body size	¶¶	Sacco et al 2010[40]
Single administration amount	62.65 mg	3*15 mg + 1*20 mg (Rounded to the nearest 5 mg as per SmPC)
Administration schedule	twice daily (10 days per month)	
15 mg*20	¶¶	PAS
20 mg*20	¶¶	PAS
5-month treatment from SUNLIGHT optimal procurement approach	¶¶	15*15mg*20 + 5*20mg*20
Bevacizumab		
Dose mg/kg	5 mg/kg	SmPC[39]
Average weight (kg)	79.67 kg	average weight (kg)
Dose amount (mg)	398.35	Calculation (5* 79.67kg)
Optimal administration (400mg)	¶¶	Calculations reported in supplementary table 1.b
Total cost of procurement (10 deliveries)	¶¶	5 months, 2 cycles per month
Administration (sb12z + 9* sb15z)	£4,252	National schedule of reference costs 2023/24
Total bevacizumab cost	¶¶	
Best supportive care		
BSC costs	£1,505	10.8 months OS - 5 months treatment (*£260 BSC month)[20]
Total cost		
Total cost	¶¶	
Treatment duration based on figure from SUNLIGHT trial ¶¶ commercial in confidence figure removed		

Appendix 2.b. Cost of regorafenib followed by best supportive care

Regorafenib		
Regorafenib	¶¶	84*40 mg tablets
Administration schedule	160 mg (4*40 mg) daily for 3 weeks, 1 week off	SmPC[37]
Monthly cost	¶¶	
Median treatment duration (months)	2.72	
Total 2.72-month cost	¶¶	3 packs of 84*40mg
Best supportive care		
BSC	£1,089	6.91 months OS - 2.72 months treatment (*£260 BSC month)[20]
Total cost		
Total cost	¶¶	
Duration of treatment based on crude PFS average from the CORRECT and CONCUR trails, details offered in supplementary table 1.c. ¶¶ commercial in confidence figure removed		

Appendix 2.c. Cost of best supportive care for fifth-line.

Best supportive care		
BSC costs	£1,038	4 months (*£260 BSC month)[20]