Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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cetuximab, 100mg/20mL and 500mg/100mL solution for infusion (Erbitux®)

SMC No. (1012/14)

Merck Serono Ltd.

05 December 2014

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the end of life medicine process

cetuximab (Erbitux®) is accepted for restricted use within NHS Scotland.

Indication under review: Treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer:

- in combination with irinotecan-based chemotherapy
- in first-line in combination with FOLFOX;
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

SMC restriction: for use in patients with RAS wild-type metastatic colorectal cancer, in combination with irinotecan or oxaliplatin-based chemotherapy, in patients who have not previously received chemotherapy for their metastatic disease (first-line treatment).

Efficacy data for the RAS wild-type population come from post hoc subgroup analyses of two studies that compared cetuximab plus chemotherapy with chemotherapy alone. In the RAS wild-type population, response rates (complete and partial responses) were significantly higher in both studies and overall survival was significantly longer in one study for cetuximab plus chemotherapy than chemotherapy alone.

This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of cetuximab. It is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer:

- in combination with irinotecan-based chemotherapy;
- in first-line in combination with FOLFOX;
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

Dosing Information

Evidence of wild-type RAS (KRAS and NRAS) status is required before initiating treatment with cetuximab. Mutational status should be determined by an experienced laboratory using validated test methods for detection of KRAS and NRAS (exons 2, 3 and 4) mutations.

Cetuximab must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. Close monitoring is required during the infusion and for at least one hour after the end of the infusion. Availability of resuscitation equipment must be ensured.

Prior to the first infusion, patients must receive premedication with an antihistamine and a corticosteroid at least one hour prior to administration of cetuximab. This premedication is recommended prior to all subsequent infusions.

Cetuximab is administered once weekly; the initial dose is cetuximab 400mg/m^2 BSA and all subsequent weekly doses are cetuximab 250mg/m^2. Cetuximab treatment should be continued until progression of the underlying disease.

For the dosage or recommended dose modifications of concomitantly used chemotherapeutic agents, refer to the product information for these medicinal products. They must not be administered earlier than one hour after the end of the cetuximab infusion.

Product availability date

December 2013 (EGFR expressing wild-type metastatic colorectal cancer)

Cetuximab meets SMC end of life criteria in this setting.

Summary of evidence on comparative efficacy

Cetuximab is a chimeric monoclonal immunoglobulin G1 antibody directed against the epidermal growth factor receptor (EGFR). EGFR signalling pathways are involved in the control of cell survival, cell cycle progression, angiogenesis, cell migration and cellular invasion/metastasis. Cetuximab binds to the EGFR which can lead to down-regulation of the receptor and it also targets cytotoxic immune effector cells towards EGFR-expressing tumour cells.[1]

The original marketing authorisation for cetuximab was for the treatment of patients with EGFR-expressing, Kirsten rat sarcoma (KRAS) wild-type (wt) metastatic colorectal cancer in combination with chemotherapy. SMC has previously accepted cetuximab for restricted use in

patients who have not previously received chemotherapy for their metastatic disease, with liver metastases only that are considered non-resectable but in whom potentially curative liver metastasis resection would be undertaken if the lesions became resectable after treatment with chemotherapy and cetuximab. The marketing authorisation for cetuximab was amended by a type II variation in December 2013 following a Committee for Medicinal Products for Human Use request; use is now restricted to patients with RAS wt tumour metastatic colorectal cancer (mCRC). The RAS gene family has three broadly expressed members; KRAS, neuroblastoma RAS viral oncogene homolog (NRAS), and the v-Ha-RAS Harvey rat sarcoma viral oncogene (HRAS). Mutated, activated RAS proteins can bypass inhibition of EGFR resulting in reduced or no treatment effect. [1]

In the current submission, the submitting company has requested that SMC considers cetuximab when positioned for use in patients with RAS wt mCRC, in combination with irinotecan or oxaliplatin-based chemotherapy, in patients who have not previously received chemotherapy for their metastatic disease (first-line treatment).

Efficacy data for this indication, following the type II variation, come from post hoc analyses of RAS wt patients from two pivotal studies (CRYSTAL and OPUS).[1-8] Both studies were of open-label, randomised, design and recruited patients aged ≥18 years with histologically confirmed adenocarcinoma of the colon or rectum which expressed EGFR. Patients had first occurrence of metastatic disease which was not curatively resectable with at least one bi-dimensionally measurable index lesion. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, a life expectancy of at least 12 weeks and adequate haematologic, hepatic, and renal function. In both studies patients were treated until progressive disease was diagnosed or unacceptable toxicity occurred.

The phase III study (CRYSTAL) recruited 1,217 patients who were randomised equally to: cetuximab (400mg/m^2 intravenous [iv] infusion on day one then a 250mg/m^2 iv infusion every seven days thereafter) plus FOLFIRI (fluorouracil 400mg/m^2 iv bolus followed by a 46-hour continuous iv infusion of 2,400mg/m^2, folinic acid 400mg/m^2 iv (racemic) or 200mg/m^2 iv (L-form) plus irinotecan 180mg/m^2 iv infusion, all on day one every two weeks); or FOLFIRI alone.[1-6] The primary outcome was progression free survival (PFS) in the intention to treat (ITT) population, defined as the time in months from randomisation until progressive disease was first observed or death occurred due to any cause within 60 days of the last tumour assessment or randomisation. Secondary outcomes included response rate and overall survival. The RAS wt tumour subgroup included 178 and 189 of patients in the cetuximab + FOLFIRI and FOLFIRI groups respectively.

OPUS, a phase II study, recruited 344 patients who were randomised equally to: cetuximab (400mg/m^2 iv infusion on day one then a 250mg/m^2 iv infusion every seven days thereafter) plus FOLFOX-4 (fluorouracil 400mg/m² iv bolus, followed by a 22-hour continuous infusion of 600mg/m² iv and folinic acid 200mg/m^2 iv infusion on days 1 and 2, plus oxaliplatin 85mg/m^2 iv infusion on day one, every two weeks); or FOLFOX-4 alone.[1,2,7,8] The primary outcome was response rate in the ITT population, defined as the proportion of patients with confirmed complete response (CR) or partial response (PR), as best overall response, according to radiological assessments. Secondary outcomes included PFS and overall survival. The RAS wt tumour subgroup included 38 and 49 patients in the cetuximab + FOLFOX-4 and FOLFOX-4 groups respectively.

An additional study (FIRE-3) of phase III, open-label design recruited 592 patients with KRAS exon 2 wild-type mCRC who has not received previous treatment.[9,10] Other recruitment criteria

were similar to the previous studies. Patients were randomised equally to cetuximab iv + FOLFIRI iv (doses as for CRYSTAL study, except only racemic folinic acid was used) or bevacizumab 5mg/kg iv (over 30 to 60 minutes) every two weeks + FOLFIRI. The primary endpoint of the study was overall response rate. A total of 342 patients had RAS wild-type tumours (n=171 in each group).

In the RAS wt population, overall survival was significantly longer for cetuximab plus FOLFIRI versus FOLFIRI alone (in the CRYSTAL study), and versus bevacizumab plus FOLFIRI (in the FIRE-3 study). Results for PFS, response rate and overall survival for the RAS wt populations only of the studies are presented in the table below.

Table: Results of primary and some secondary endpoints for the CRYSTAL, OPUS and FIRE-3 studies in the RAS wt tumour populations

	N (RAS wt)	**Median progression free survival (months)***		**Response rate (%)****		**Median overall survival (months)**	
CRYSTAL							
Cetuximab + FOLFIRI	178	11.4	HR 0.56, 95% CI 0.41 to 0.76, p=0.0002	66%	OR 3.11, 95% CI 2.03 to 4.78; p<0.0001	28.4	HR 0.69, 95% CI 0.54 to 0.88; p=0.0024
FOLFIRI	189	8.4		39%		20.2	
OPUS							
Cetuximab + FOLFOX-4	38	12.0	HR 0.53, 95% CI, 0.27 to 1.04; p=0.06.	58%	OR 3.33, 95% CI 1.38 to 8.17, p=0.0084	19.8	HR 0.94, 95% CI, 0.56 to 1.56; p=0.80
FOLFOX-4	49	5.8		29%		17.8	
FIRE-3							
Cetuximab + FOLFIRI	171	10.4	HR 0.93, 95% CI, 0.74 to 1.17; p=0.54	66%	OR 1.28, 95% CI, 0.83 to 1.99; p=0.32	33.1	HR 0.70, 95% CI, 0.53 to 0.92; p=0.011
Bevacizumab + FOLFIRI	171	10.2		60%		25.6	

HR=hazard ratio, CI=confidence interval, OR=odds ratio

*primary endpoint for CRYSTAL study; ** primary endpoint for OPUS and FIRE-3 studies

There are no quality of life (QoL) data for the RAS wt population from any of the studies. In the CRYSTAL study, the European Organization for Research and Treatment of Cancer QoL questionnaire-core 30 (QLQ-C30) was used to assess QoL in patients with KRAS wt tumours.[6] The QLQ-C30 is a cancer specific self-administered questionnaire incorporating five functional scales, three symptom scales, six symptom single-item scales and one global health status (GHS)/QoL scale. QoL was evaluable in 94% (627/666) of patients with KRAS wt tumours; of these, 52% received FOLFIRI, and 48% FOLFIRI plus cetuximab. There was no significant difference between groups for GHS/QoL and social functioning scores. Early skin reactions in patients receiving cetuximab did not significantly affect the QoL scores.

Summary of evidence on comparative safety

In the overall CRYSTAL study population, grade 3/4 adverse events (AE) were significantly more common in the cetuximab + FOLFIRI group (79% [476/600]) than in the FOLFIRI group (61% [367/602]), p<0.001. The incidence of treatment-related serious AE was 26% with cetuximab + FOLFIRI and 19% with FOLFIRI alone. The main reason for treatment discontinuation was due to AE in 8.7% (52/599) of patients in the cetuximab + FOLFIRI group and 5.2% (31/599) of patients in the FOLFIRI alone group.

In the RAS wt population of CRYSTAL, any grade 3/4 AE occurred in 81% versus 58% of patients in the cetuximab + FOLFIRI and FOLFIRI groups respectively. Grade 3/4 AE (occurring in ≥5% of patients in either group) included neutropenia (31% in the cetuximab + FOLFIRI group versus 20% in the FOLFIRI group), diarrhoea (15% versus 9%), rash (9% versus none), leukopenia (8% versus 4%), fatigue (7% versus 5%), deep vein thrombosis (6% versus 0.5%), dermatitis acneiform (5% versus none). Grade 3/4 skin reactions (any) occurred in 21% versus 0.5% of patients, acne-like rash in 17% versus none, and infusion related reactions in 2% versus none in the cetuximab + FOLFIRI versus FOLFIRI alone group, respectively.

In the overall OPUS study population, grade 3/4 AE occurred in a higher proportion of patients in the cetuximab + FOLFOX-4 group (76% [129/170]) than in the FOLFOX-4 alone group (70% [117/168]). In the cetuximab plus FOLFOX-4 group, cetuximab was discontinued in 23% (39/169) of patients, chemotherapy was discontinued 30% (51/169), and both were discontinued in 9.5% (16/169) of patients due to AEs. Chemotherapy was discontinued in 25% (42/168) of patients in the FOLFOX-4 alone group due to AEs. Skin reactions occurred in 18% (30/170) of cetuximab + FOLFOX-4 patients and 0.6% (1/168) of FOLFOX-4 alone patients and infusion-related reactions in 4.7% (8/170) versus 1.8% (3/168) of patients respectively.

In the RAS wt population of OPUS, any grade 3/4 AE occurred in 78% (28/36) of patients in the cetuximab + FOLFOX-4 group and 63% (29/46) of patients in the FOLFOX-4 alone group. Any serious AE occurred in 42% (15/36) of patients in the cetuximab + FOLFOX-4 group and 15% (7/46) of patients in the FOLFOX-4 alone group.

Summary of clinical effectiveness issues

Recent studies have shown that patients with RAS wt may respond to anti-EGFR treatment and, conversely, patients with KRAS and NRAS mutated tumours do not respond to anti-EGFR treatment. The RAS wt population is approximately 50% of the mCRC patient population.

In the current submission, the submitting company has requested that SMC considers cetuximab when positioned for use in EGFR-expressing, RAS wt mCRC, in combination with irinotecan or oxaliplatin-based chemotherapy, in patients who have not previously received chemotherapy for their metastatic disease (first-line treatment within the amended licensed indication). Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area in terms of effective first-line treatments. Cetuximab meets SMC end of life criteria.

The pivotal studies compared cetuximab + FOLFIRI with FOLFIRI alone (CRYSTAL) and cetuximab + FOLFOX-4 with FOLFOX-4 alone (OPUS) for the first-line treatment of mCRC. At the time the pivotal studies were conducted, tumour biomarkers had not been identified. Therefore, post hoc subgroup analyses in patients with RAS wt tumours provide efficacy data for the amended indication currently under review. Baseline characteristics of the subgroups were generally similar to the whole populations, although initial randomisation was not stratified by tumour mutational status which could have resulted in imbalances between treatment groups. Response rates were significantly higher for cetuximab + chemotherapy than chemotherapy alone for both studies, and PFS significantly longer for cetuximab + FOLFIRI than FOLFIRI alone, in the CRYSTAL study. Overall survival, a secondary endpoint for both studies, was significantly longer for cetuximab + chemotherapy than chemotherapy alone in the CRYSTAL study only. Both studies were of open-label design, although used an independent review committee to determine the day of progression and the best overall response. The RAS wt tumour subgroups are small, particularly for the OPUS study and there are no QoL data in this population. In patients with RAS mutations (i.e. patients with known KRAS exon 2 mutations as well as additionally identified RAS mutations) in the OPUS and CRYSTAL studies, outcomes were poorer in those treated with cetuximab + chemotherapy versus chemotherapy alone.[1,2]

The European Medicines Agency notes that restricting the use of cetuximab to patients with metastatic colorectal cancer carrying RAS wt tumours (i.e. KRAS and NRAS) improves the benefit without increasing the risk.[1] The availability of cetuximab (when used with FOLFIRI) will provide clinicians with a treatment regimen for patients that may extend median overall survival compared to FOLFIRI alone.

Additional efficacy data come from a phase III study where cetuximab + FOLFIRI was superior to bevacizumab + FOLFIRI for overall survival only. However, bevacizumab was not recommended by SMC for first line treatment of mCRC so this study is of less relevance to clinical practice in NHS Scotland.

Clinical experts consulted by SMC reported the use of CAPOX (capecitabine orally for 14 days plus oxaliplatin iv on day one of a three weekly cycle) for the first-line treatment of mCRC. However, the submitting company did not present direct comparative efficacy data for cetuximab in combination with FOLFOX or FOLFIRI versus CAPOX. The non-inferiority or CAPOX with FOLFOX has been demonstrated[11] but a network meta-analysis of cetuximab plus chemotherapy versus CAPOX was not possible due to the differing patient populations (RAS wt population for cetuximab versus non-selective population for CAPOX). Therefore, comparative efficacy data of cetuximab plus chemotherapy versus CAPOX is limited to naive indirect comparisons.

Clinical experts consulted by SMC considered that cetuximab is a therapeutic advancement due to evidence of prolongation of progression free survival and overall survival. They also noted that its introduction would impact on service delivery (including clinic and pharmacy aseptic time) as it requires weekly iv infusions and is used with the FOLFOX or FOLFIRI chemotherapy regimens (which require central lines). The current first-line treatment is CAPOX, which requires considerably fewer iv infusions.

Mutational status should be determined by an experienced laboratory using validated test methods for detection of KRAS and NRAS (exons 2, 3, and 4) mutations before cetuximab is considered.[2] Patients require premedication with an antihistamine and a corticosteroid at least

one hour prior to administration of each infusion of cetuximab, and resuscitation equipment must be available.[2]

Summary of patient and clinician engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of cetuximab, as an end of life medicine, in the context of treatments currently available in NHS Scotland, specifically in the first-line treatment of metastatic colorectal cancer.

The key points expressed by the group were:

- Metastatic colorectal cancer is a devastating disease and has a huge psychological impact on patients and their families. Patients in Scotland do not have access to any other antibody treatment so have very limited treatment options; prognosis with currently approved medicines is around 12-20 months.

- PACE participants highlighted that patients with mCRC are generally fit and robust through much of the duration of their illness, becoming symptomatic in last month or so. They cope well with their treatment so the extension of life with cetuximab can be of very high quality. Cetuximab can enable patients to maintain a normal life, contribute to the economy and the community and spend valuable time with family and friends.

- There is now a much better understanding of targeting cetuximab in RAS wild-type patient groups (about 50% of all patients with metastatic disease), improving outcomes for patients who will gain most benefit. It avoids exposing patients who will not benefit which is a huge step forward.

- PACE participants expressed strong support for the availabilty of cetuximab in Scotland in the RAS wild-type population. They noted that there is an equity issue that can be distressing for patients and can impact on NHS Scotland's ability to participate in clinical research.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis of the addition of cetuximab to chemotherapy with either FOLFIRI or FOLFOX regimens in patients with RAS wt mCRC. The economic model consisted of first, second and third line treatment states, and a curative liver resection health state that patients could enter during first line treatment, and had a base case time horizon of 10 years. The comparators considered were FOLFIRI or FOLFOX chemotherapy alone. Based on SMC clinical expert feedback, CAPOX chemotherapy represents a regimen used in the first line treatment of mCRC in Scotland, but was not considered as a comparator in the economic analysis.

The clinical data used in the economic analysis were derived from the CRYSTAL study for the comparison with FOLFIRI, and the OPUS study for the comparison with FOLFOX-4. The second line treatment was assumed to be either FOLFOX or FOLFIRI, and third line was assumed to consist of best supportive care (BSC). Extrapolation of PFS data from these

studies was performed fitting the best fitting parametric function (the Weibull) according to AIC and BIC criteria, and it was assumed that PFS benefits for cetuximab translated to overall survival benefits; hence, second and third line extrapolation was applied equally to each treatment arm. Estimates of resection rates were based on emerging data from further analysis of the CRYSTAL study showing curative resection rates for RAS wt patients specifically of 7.3% and 2.1% for cetuximab + FOLFIRI and FOLFIRI respectively. [16] Outcomes for curative resection were based on a published study that modelled survival associated with rescue surgery for unresectable colorectal liver metastases.[12]

The utility estimates for each treatment line state (0.778, 0.769 and 0.663 for first, second and third line BSC respectively) and the post-curative resection health state (0.789) were largely based on published EQ 5D values,[13-15] or by assumption for post-resection progressive disease (0.68). Disutilities for grade 3 or 4 adverse events were derived from a range of published sources. Drug costs were based on a treatment duration for cetuximab + FOLFIRI or FOLFOX estimated to be 5.8 and 5.5 months respectively, and a BSA of 1.79m^2.

Resource use and cost estimates for RAS screening, drug administration, adverse event management, liver resection and post resection management were based on published sources and Scottish expert opinion. Medicines costs were calculated assuming no vial sharing for cetuximab.

The base case results were an incremental cost-effectiveness ratio (ICER) of £72,846 per quality adjusted life year (QALY) gained for cetuximab + FOLFIRI vs. FOLFIRI, based on an incremental cost of £17,540, incremental life years of 0.32 (or 3.8 months), and incremental QALYs of 0.24. The ICER for the comparison of cetuximab + FOLFOX vs. FOLFOX was estimated to be £71,481/QALY, with incremental cost of £16,751, incremental life years of 0.31 (or 3.7 months), and incremental QALYs of 0.23.

A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple confidential discount was offered on the list price of the medicine. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the decision but is unable to do so as the company has indicated that they should remain commercial in confidence. Therefore, only the without-PAS cost-effectiveness estimates can be presented.

Scenario and sensitivity analysis indicated that the results were sensitive to the duration of treatment with cetuximab + chemotherapy, the hazard ratio for first line PFS, and the difference in curative resection rates estimated. As the differences in resection rates were small and not based on a statistically significantly difference, assuming the same resection rates across treatment arms produced without PAS ICERs of £129,650 and £129,190/QALY vs. FOLFIRI and FOLFOX respectively.

The main weaknesses with the economic evaluation were:

- Lack of comparison with CAPOX, which is used in clinical practice for the first line treatment of mCRC and represents a relevant comparator. On request, the company provided an analysis comparing cetuximab + FOLFOX vs. CAPOX whereby it was assumed the outcomes associated with CAPOX would be the same as for FOLFOX based on a study demonstrating non-inferiority of CAPOX to FOLFOX.[11] The costs of CAPOX were applied with the resulting without PAS ICER estimated to be £70,029/QALY.

- Limitations in the clinical data, in particular small patient numbers with RAS wt mCRC especially from the OPUS trial for the comparison with FOLFOX.
- There are several uncertainties in the extrapolation of survival outcomes; in particular, the approach adopted assumes the PFS benefit translates into a direct overall survival (OS) benefit, which is uncertain. The submitting company presented an alternative trial based overall survival modelling approach with ICERs ranging from being lower than the figures above to scenarios where cetuximab was dominated (less effective and more expensive). However, these results appeared to have a number of limitations which made the results unreliable.
- The resection rates estimated in the RAS wt patient population are low and the ICERs are very sensitive to varying these proportions or assuming no difference.

The Committee considered the benefits of cetuximab in the context of its decision modifiers that can be applied when encountering high cost-effectiveness ratios and concluded that the criterion for a substantial improvement in survival was met.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate modifiers, the Committee accepted cetuximab for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

A Patient Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guideline Network published guideline number 126; Diagnosis and management of colorectal cancer, in December 2011.[17] The following advice is included for patients with mCRC.

- Surgical resection should be considered for all patients with resectable liver metastases.
- Patients with resectable liver metastases should be considered for perioperative chemotherapy with a combination of oxaliplatin and 5-fluorouracil/leucovorin [folinic acid] for a total period of six months.
- Patients with unresectable liver metastases should be considered for downstaging chemotherapy using a combination of oxaliplatin (or irinotecan) and 5-fluorouracil/leucovorin.
- All patients with mCRC should be considered for chemotherapy.
- Combination treatment with 5-fluorouracil/leucovorin/oxaliplatin or capecitabine and oxaliplatin or 5-FU/leucovorin/irinotecan are the preferred options in patients with good performance status and organ function.
- Second line chemotherapy should be considered for patients with mCRC with good performance status and adequate organ function.
- Irinotecan should be used as second line therapy following first line oxaliplatin (or vice versa).

The National Institute for Health and Care Excellence (NICE) published clinical guideline number 131; Colorectal cancer: the diagnosis and management of colorectal cancer, in November 2011. [18]

When offering multiple chemotherapy drugs to patients with advanced and mCRC, consider one of the following sequences of chemotherapy unless they are contraindicated:

- FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) as first-line treatment then single agent irinotecan as second-line treatment or
- FOLFOX as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment or
- XELOX (capecitabine plus oxaliplatin) as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment
- Consider raltitrexed only for patients with advanced colorectal cancer who are intolerant to 5-fluorouracil and folinic acid, or for whom these drugs are not suitable (for example, patients who develop cardiotoxicity). Fully discuss the risks and benefits of raltitrexed with the patient.
- Oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid) is recommended as an option for the first-line treatment of mCRC.
- The choice of regimen (intravenous 5-fluorouracil and folinic acid or one of the oral therapies) should be made jointly by the individual and the clinician(s) responsible for treatment. The decision should be made after an informed discussion between the clinician(s) and the patient; this discussion should take into account contraindications and the side-effect profile of the agents as well as the clinical condition and preferences of the individual.
- Refer to technology assessment for biological agents

NICE published technology appraisal number 242; Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy, in January 2012.[19]

- Cetuximab monotherapy or combination chemotherapy is not recommended for the treatment of people with mCRC that has progressed after first-line chemotherapy.
- Bevacizumab in combination with non-oxaliplatin (fluoropyrimidine-based) chemotherapy is not recommended for the treatment of people with mCRC that has progressed after first-line chemotherapy.
- Panitumumab monotherapy is not recommended for the treatment of people with mCRC that has progressed after first-line chemotherapy.
- People currently receiving cetuximab monotherapy or combination chemotherapy, bevacizumab in combination with non-oxaliplatin chemotherapy, or panitumumab monotherapy for the treatment of mCRC that has progressed after first-line chemotherapy should have the option to continue treatment until they and their clinician consider it appropriate to stop.

The European Society for Medical Oncology (ESMO) published clinical practice guidelines; Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up in September 2014.[20] The guidelines note that treatment strategies for unresectable mCRC are rapidly evolving. Treatment options for four clinically defined groups are included in the guidance and factors include tumour- and disease-related characteristics, such as clinical presentation, resectablility and patterns of tumour biology as well as patient-related factors. First-line treatment options include chemotherapy doublet (fluoropyrimidine plus oxaliplatin or irinotecan) plus bevacizumab or an anti-EGFR antibody depending on the clinical scenario. The guidance notes the importance of determining RAS status before initiating an anti-EGFR

antibody. The guidance also notes the importance of "the concept of the continuum of care in the strategic choice of a regimen or sequence in the different lines".

Additional information: comparators

Chemotherapy regimens; FOLFIRI, FOLFOX, CAPOX (XELOX), for details see table below.

Cost of relevant comparators

Drug	Dose Regimen	Cycle length	Cost per cycle (£)	Cost per 26 weeks (£)
Cetuximab + FOLFOX-4	**cetuximab 400mg/m^2 iv for first dose, then 250mg/m^2 thereafter, D1 and D8 oxaliplatin 85mg/m^2 iv, D1 folinic acid 200mg/m^2 iv, D1 and D2 fluorouracil 400mg/m^2 iv bolus then 600mg/m^2 iv, D1 and D2**	**2 weeks**	Cycle 1: £3,076 Subsequent cycles: £2,542	£33,580 (£33,046)
Cetuximab + FOLFIRI	**cetuximab 400mg/m^2 iv for first dose, then 250mg/m^2 thereafter, D1 and D8 irinotecan 180mg/m^2 iv, D1 folinic acid 400mg/m^2 iv, D1 fluorouracil 400mg/m^2 iv bolus then 2400mg/m^2 iv, D1**	**2 weeks**	Cycle 1: £3108 Subsequent cycles: £2,574	£33,996 (£33,462)
FOLFOX-4	oxaliplatin 85mg/m^2 iv, D1 folinic acid 200mg/m^2 iv, D1 and D2 fluorouracil 400mg/m^2 iv bolus then 600mg/m^2 iv, D1 and D2	2 weeks	£761	£9,893
FOLFIRI	irinotecan 180mg/m^2 iv, D1 folinic acid 400mg/m^2 iv, D1 fluorouracil 400mg/m^2 iv bolus then 2400mg/m^2 iv, D1	2 weeks	£793	£10,309
CAPOX (also known as XELOX)	oxaliplatin 130mg/m^2 iv, D1 capecitabine 1,000mg/m^2 orally twice daily, D1 to 14	3 weeks	£972	£5,832*

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis, MIMs and BNF on 10 September 2014. Costs are based on a body surface area of 1.8m^2. Costs per 26 weeks are calculated for complete cycles administered during this period. Calculations assume that unused drug will be discarded and a whole number of vials will be used. Costs calculated for the racemic form of folinic acid where appropriate. Costs do not take any patient access schemes into consideration.
D=day, iv=intravenous. *Experts advise that this treatment is only given for 6 cycles for mCRC.

Additional information: budget impact

The submitting company estimated there to be 682 patients in year 1, rising to 731 patients in year 5 eligible for treatment with cetuximab added to FOLFIRI or FOLFOX chemotherapy regimens, with an estimated uptake rate of 20% in year 1 (136 patients) and 85% in year 5 (585 patients).

Without PAS:
The submitting company estimated the gross medicines budget impact to be £2.72 million in year 1 and £11.68 million in year 5. The company assumed displacement of the use of FOLFIRI, FOLFOX regimens used alone and CAPOX, resulting in a net medicines budget impact estimated to be £2.52 million in year 1 and £8.18 million in year 5.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

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This assessment is based on data submitted by the applicant company up to and including 17 October 2014.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.