MABp1 (Xilonix) for metastatic colorectal cancer – third line

SUMMARY

MABp1 is intended to be used as a third line therapy for the treatment of metastatic colorectal cancer in patients experiencing disease related symptoms. If licensed, it would offer a novel treatment option designed to control the spread of advanced disease while at the same time offering symptom relief in such patients, a group who currently have few well tolerated effective therapies available. MABp1 does not currently have Marketing Authorisation in the EU for any indication.

Colorectal cancer is the fourth most common cancer in the UK, accounting for 13% of all new cases in 2011. Between 20% and 55% of people presenting with colorectal cancer have metastatic disease and the 5-year survival rate for such patients is 6.6%. Approximately half of all patients with cancer lose some body weight, and it has been estimated that 55–60% of patients with colorectal cancer experience weight loss due to cancer cachexia. In addition, more than 75% of patients undergoing cancer-related treatments experience cancer-related fatigue.

The majority of patients with colorectal cancer have metastatic disease that initially is not suitable for potentially curative resection; therefore the aim of treatment is either to convert initially unresectable disease to resectable disease, or is palliative, to control symptoms, extend survival and improve quality of life. Treatment may include chemotherapy or biological agents (alone or in combination with chemotherapy). Treatment for cancer cachexia may include oral, enteral or parenteral nutrition, treatment of secondary gastrointestinal symptoms, nutritional counselling, psychotherapeutic interventions, physical training, and short term use of corticosteroids or progestational agents. Patients with cancer-related fatigue can benefit from both pharmacologic and non-pharmacologic interventions such as psychostimulants, exercise, cognitive-behavioural strategies, and sleep therapy. MABp1 is currently in two phase III clinical trials comparing its effect on the objective response rate and overall survival against treatment with placebo. These trials are expected to complete in October 2015 and December 2016 respectively.
**TARGET GROUP**

- Colorectal cancer: metastatic or unresectable; patients experiencing disease related symptoms – third line; after failure of oxaliplatin and irinotecan based regimens.

**TECHNOLOGY**

**DESCRIPTION**

MABp1 is a first-in-class true human monoclonal antibody targeting anti-interleukin-1-alpha (IL-1α). MABp1 targets an inflammatory cytokine that is essential for tumour growth and spread, and is responsible for symptoms commonly observed in advanced cancer, such as weight loss, fatigue, and appetite loss. In the phase III clinical trial, MABp1 is administered intravenously (IV) at a dose of 7.5mg/kg every 2 weeks until evidence of clinical progression.

MABp1 does not currently have Marketing Authorisation in the EU for any indication. MABp1 is currently in phase II clinical trials for the treatment of acne vulgaris, non-small cell lung cancer (late-stage disease, second-line therapy or greater), plaque psoriasis, pyoderma, type 2 diabetes mellitus, and vascular restenosis.

**INNOVATION and/or ADVANTAGES**

If licensed, MABp1 will offer a novel treatment option designed to control the spread of advanced disease while at the same time offering symptom relief in patients with metastatic or unresectable colorectal cancer who are refractory to standard treatments, a group who currently have few well tolerated effective therapies available.

**DEVELOPER**

XBiotech.

**AVAILABILITY, LAUNCH OR MARKETING**

MABp1 is in phase III clinical trials.

**PATIENT GROUP**

**BACKGROUND**

Colorectal cancer, or cancer of the large bowel, is a malignant tumour arising from the lining of the large intestine (colon and rectum); almost two-thirds (66%) of all bowel cancers arise from the colon and over one-third (34%) arise from the rectum (including the anus). There are a number of different histological types of colorectal cancer including: adenocarcinoma, squamous cell carcinoma, carcinoid tumour, sarcoma, and lymphoma.

Symptoms of colorectal cancer may include: bleeding from the rectum or blood in the stools, a change in normal bowel habits (e.g. diarrhoea or looser stools lasting longer than four to six weeks), a lump in the rectum or abdomen, a feeling of needing to strain to pass a bowel motion, weight loss, pain in the abdomen or rectum, and anaemia. Sometimes a tumour may
obstruct the bowel, which can result in symptoms including abdominal pain, feeling bloated, constipation, and vomiting4,5.

The cause of colorectal cancer in most people remains unknown, although factors such as age (over 65 years), obesity, smoking and high alcohol intake are believed to increase risk6,7. A diet high in fibre and low in saturated fat may reduce risk, whilst a diet high in red or processed meats may increase risk6,7. Family history and inherited conditions or related bowel conditions may greatly increase an individual’s risk of colorectal cancer6,7.

Individuals with colorectal cancer may exhibit a number of disease related symptoms such as weight loss, fatigue, and appetite loss; with research suggesting that such symptoms may predict shortened survival8. Loss of appetite and subsequent weight loss may be due to cancer cachexia, which is defined as a multifactorial syndrome that is characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment9. Patients with cancer cachexia generally display severe weight loss from both fat and muscle tissue10. Cancer cachexia is associated with poor quality of life, increased risk of dose-limiting chemotherapy toxicities, and poor survival11,12. Anorexia (the loss of the desire to eat), inflammation, insulin resistance, and increased muscle protein breakdown are frequently associated with cachexia12,13. Although anorexia is common in patients with advanced cancers, cachexia may develop in the absence of anorexia13. In patients with cancer cachexia, loss of respiratory muscle function may lead to death from hypostatic pneumonia, which is most likely to occur following 25–30% total body weight loss13.

Among all cancer-related symptoms, fatigue is likely to exert the greatest influence on patients’ quality of life, often interfering with their physical and social activities14. The National Comprehensive Cancer Network defines cancer related fatigue as “a distressing persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning”14. Fatigue is the most common symptom of patients with cancer who receive radiation therapy, cytotoxic chemotherapy, or biological response modifiers; additionally individuals who survive cancer often report fatigue as a problem months to years after their treatment has ended15.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:


**CLINICAL NEED and BURDEN OF DISEASE**

Colorectal cancer is the fourth most common cancer in the UK, accounting for 13% of all new cases in 20112. In England there were 34,044 cases of bowel cancer in 2011 (representing 46 cases per 100,000 population) (ICD-10 C18-C20)16. In metastatic colorectal cancer the tumour has spread beyond the confines of the bowel and locoregional lymph nodes to other parts of the body1. Between 20%-55% of people presenting with colorectal cancer have metastatic disease, and an estimated 50-60% of patients who have undergone surgery for early stage colorectal cancer with apparently complete excision will eventually develop advanced disease and distant metastases (typically presenting within 2 years of initial diagnosis)1. The 5-year survival rate for metastatic colorectal disease is 6.6%1. In
2013-14 there were 137,937 admissions for colorectal cancer (ICD-10 C18-C20) in England, resulting in 379,266 bed days and 153,062 finished consultant episodes. In England and Wales 13,939 deaths from colorectal cancer (ICD-10 C18-C20) were registered during 2013.

Weight loss in patients with cancer is rarely recognised, assessed, or managed actively but research indicates that approximately half of all patients with cancer lose some body weight, and one-third of patients lose more than 5% of their original body weight. It is estimated that up to 20% of all cancer deaths are directly caused by cachexia through immobility and cardiac or respiratory failure. It has been estimated that 55–60% of patients with colorectal cancer experience weight loss due to cancer cachexia. It is thought that more than 75% of patients undergoing cancer-related treatments experience cancer-related fatigue. The population likely to be eligible to receive MABp1 could not be estimated from available published sources.

### PATIENT PATHWAY

#### RELEVANT GUIDANCE

**NICE Guidance**


**Other Guidance**

- Scottish Intercollegiate Guidelines Network. Diagnosis and management of colorectal cancer. 2011.
CURRENT TREATMENT OPTIONS

The management of metastatic colorectal cancer is largely palliative, combining specialist treatments (palliative surgery, chemotherapy and radiation) with control of symptoms and psychosocial support29. However, approximately 8% of people with metastatic colorectal cancer have potentially resectable liver metastases, and in some, chemotherapy may make these liver metastases operable29. The majority of patients have metastatic disease that initially is not suitable for potentially curative resection; therefore the aim of treatment is to convert initially unresectable disease to resectable disease, and where this is not possible to control symptoms, extend survival and improve quality of life21.

Treatment may include29,30,31,32,33,34:

Chemotherapy
- FOLFOX (folinic acid, 5-fluorouracil and oxaliplatin) as first or second line treatment.
- XELOX (capecitabine and oxaliplatin) as first line or second line treatment.
- Irinotecan as second line treatment.
- FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first or second line treatment.
- Raltitrexed – only for patients who are intolerant to folinic acid, 5-fluorouracil, or for whom these drugs are not suitable.

Biological agents
Current NICE guidance recommends cetuximab as a first line treatment – in combination with FOLFIRI or FOLFOX within its licensed indication for patients in whom29,31:
- The primary colorectal tumour has been resected or is potentially operable.
- The metastatic disease is confined to the liver and is unresectable.
- The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment.

Expert opinion suggests that cetuximab is rarely used in the UK in this situation, as emerging research indicates that adding cetuximab may result in reduced survival post-operatively34.

In England, the remaining biological options for patients include34:
- Bevacizumab as a second or third line treatment, in combination with an oxaliplatin containing regimen.
- Cetuximab as first-line treatment with either FOLFOX or an irinotecan containing regimen.
- Panitumab as a first line treatment, in combination with FOLFOX.
- Panitumumab (single agent) as a third or fourth line treatment.
- Cetuximab (single agent) as a third or fourth line treatment.

In patients with metastatic or unresectable colorectal cancer, the options for treating cancer cachexia are limited. Treatment is multimodal and may include27: oral, enteral or parenteral nutrition, treatment of secondary gastrointestinal symptoms and other causes for decreased nutritional intake, nutritional counselling, psychotherapeutic interventions, physical training, and short term use of corticosteroids or progestational agents (megestrol and progestins). For refractory cachexia the primary treatment goal should not be reversal of weight loss, but rather alleviation of disease-related symptoms and an overall increase of quality of life27. For such patients the provision of appetising food and enteral nutritional support in a context that does not add to eating-related distress is recommended27.
Patients with moderate or severe cancer-related fatigue can benefit from both pharmacologic and non-pharmacologic interventions, while those with mild fatigue that does not interfere with quality of life may be treated with non-pharmacologic measures alone. Pharmacologic options for the treatment of cancer-related fatigue include psychostimulants such as methylphenidate and modafinil, or erythropoietin-stimulating agents for the treatment of anaemia. Non-pharmacologic interventions for the treatment of cancer-related fatigue may include exercise, cognitive-behavioural strategies such as progressive muscle relaxation or relaxation breathing, and sleep therapy.

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02138422, EUCTR2014-000550-12; MABp1 vs placebo; phase III.</th>
<th>NCT01767857; MABp1 vs placebo; phase III.</th>
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<td>Sponsor</td>
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<td>XBiotech, Inc.</td>
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<td>Status</td>
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<td>Source of information</td>
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<td>Worldwide (incl. UK).</td>
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<td>Design</td>
<td>Randomised, placebo-controlled</td>
<td>Randomised, placebo-controlled</td>
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<td>Participants</td>
<td>n=276 (planned); aged ≥18 years; metastatic or unresectable colorectal carcinoma refractory to standard therapy; failed both an oxaliplatin (may have been in the adjuvant setting) and an irinotecan based regimen; symptomatic disease, one symptom from each domain (metabolic and functional) must be present; evidence of metabolic dysfunction, defined as the presence of ≥1 of the following: any degree (≤20%) of unintentional total body weight loss within 6 months, or serum interleukin 6 levels ≥10pg/ml; evidence of reduced function or presence of cancer related symptoms as determined by EORTC QLQ-C30a: appetite reduction, with a score of &gt;10, presence of fatigue, with a score of &gt;10, presence of pain, with a score of &gt;10, decreased role, or emotional and social function, with a score of &lt;90; Eastern Cooperative Oncology Group (ECOG) performance status 1 or 2; no mechanical obstruction that would prevent adequate oral nutritional intake; no weight loss &gt;20% total body weight within 6 months; no relevant significant co-morbid disorder; no subjects who have not recovered from the adverse effects of prior therapy at the time of enrolment (excluding alopecia and grade 2 neuropathy); no extensive prior radiation therapy to the bone marrowb; no known brain metastases.</td>
<td>n=600 (planned); aged ≥18 years; metastatic or unresectable colorectal carcinoma refractory to standard therapy; experienced progression (or intolerance) after treatment with standard approved regimens including, oxaliplatin, irinotecan fluoropyrimidine, bevacizumab, and cetuximab or panitumumab if KRAS wildtype; no planned radiation therapy, chemotherapy, or investigational agents while enrolled in protocol; ECOG performance status 0-2; ≥2 weeks since previous cancer treatment; serum potassium and magnesium levels within institutional normal limits; adequate renal, hepatic, and bone marrow function; patients enrolled must, in the investigator's judgment, be healthy enough to stay in trial for 3 months; no weight loss &gt;20% within 6 months; no mechanical obstruction that would prevent adequate oral nutritional intake; no relevant significant co-morbid disorder; no subjects who have not recovered from the adverse effects of prior therapy (excluding alopecia and grade 2 neuropathy); no immunocompromised subjects.</td>
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a European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) Questionnaire.

b Extensive radiation therapy is defined as treatment of more than one axial bony metastasis. However for subjects with rectal cancer, pelvic irradiation is acceptable in addition to treatment of one axial bony metastasis.
Randomised to MABp1 7.5mg/kg IV every 2 weeks; or placebo 7.5mg/kg IV every 2 weeks.

Randomised to MABp1 7.5mg/kg IV every 2 weeks; or placebo 7.5mg/kg IV every 2 weeks; both with best supportive care.

Active treatment for 8 weeks, thereafter MABp1 is provided to all patients in an open label extension, follow-up until clinical progression.

Active treatment until clinical or radiographic progression, follow-up for up to 18 months.

Objective response rate (ORR),

Overall survival (OS).

AEs; pharmacodynamics; quality of life (QoL) as assessed by the EORTC QLQ-C30 questionnaire; serum IL-6; platelet count.

Change in lean body mass; QoL as assessed by the EORTC QLQ-C30 questionnaire; progression free survival; ORR.

Study completion date reported as Oct 2015.

Study completion date reported as Dec 2016.

The cost of MABp1 is not yet known.

Reduced mortality/increased length of survival

Reduced symptoms or disability

No impact identified

Increased use of existing services: IV administration every two weeks.

Decreased use of existing services

Need for new services

None identified

Increased drug treatment costs

Reduced drug treatment costs

Other increase in costs: additional costs for IV administration in clinic.

Other reduction in costs:

None identified

Other: uncertain unit cost compared to existing treatments.

None identified

ORR is defined as a stabilisation or positive (≥0kg) change in lean body mass (LBM) — as assessed by dual-energy X-ray absorptiometry (DEXA) scan and improvement or no worsening (≥0 score point change) on any two of the three symptom scale measures (fatigue, pain, appetite) of EORTC QLQ-C30.
Clinical uncertainty or other research question  None identified

REFERENCES


