Regorafenib for metastatic colorectal cancer

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This technology summary is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes.

The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Regorafenib for metastatic colorectal cancer

Target group
- Colorectal cancer: metastatic – third or fourth line.

Technology description
Regorafenib (BAY 73-4506) is a multi-kinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases. Regorafenib inhibits angiogenic kinase receptors, such as the VEGF and the TIE2 receptor, which play a central role in angiogenesis. It also inhibits various oncogenic kinases such as RAF, RET and c-KIT, thereby preventing the proliferation of cancer cells. It is intended as a third or fourth line treatment option for patients with metastatic colorectal cancer (CRC) who have progressed after standard therapies. In phase III trials, regorafenib was administered orally at 160mg once daily for three weeks of a four week cycle.

Regorafenib is also in phase III trials for gastrointestinal stromal tumours and in phase II trials for liver and renal cancer.

Innovation and/or advantages
If licensed, regorafenib will offer a new treatment option for a group of patients for whom there are currently only limited effective pharmacological treatments available.

Developer
Bayer plc.

Availability, launch or marketing dates, and licensing plans
In phase III clinical trials.

NHS or Government priority area
This topic is relevant to Improving Outcomes: A Strategy for Cancer (2011).

Relevant guidance
- NICE technology appraisal. Cetuximab, bevacizumab and panitumumab monotherapy for the treatment of metastatic colorectal cancer that has progressed after first line chemotherapy. Expected date of issue to be confirmed\(^1\).
- NICE technology appraisal. Panitumumab in combination with chemotherapy within its licensed indication for the treatment of metastatic colorectal cancer. Suspended April 2011\(^2\).
- NICE technology appraisal. Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer. December 2010\(^3\).
- NICE technology appraisal. Cetuximab for the first line treatment of metastatic colorectal cancer. August 2009\(^4\).
- NICE technology appraisal. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. 2007\(^5\).
- NICE technology appraisal. Irinotecan, oxaliplatin and ralitrexed (review) for colorectal cancer. 2005\(^6\).
- NICE technology appraisal. Capecitabine and tegafur with uracil for metastatic colorectal cancer. 2003\(^7\).
- NICE clinical guideline. Diagnosis and management of colorectal cancer. Expected October 2011\(^8\).


Clinical need and burden of disease
CRC is the third most common cancer in the UK. In 2008, there were 34,944 new cases recorded in England and Wales of which 20-55% presented with metastatic disease. In 2008, there were 14,233 registered deaths in England and Wales, the second most common cause of death from cancer. The occurrence of CRC is strongly related to age, with 83% of cases arising in people who are 60 years or older. The 5-year survival rate for patients with advanced CRC is less than 5%, and without treatment, survival after diagnosis of metastatic disease is 6-9 months.

In England there were 133,705 admissions for malignant neoplasm of the colon, rectosigmoid junction and rectum (ICD C18-C20), resulting in 471,393 bed days and 148,804 finished consultant episodes in 2009-10.

Existing comparators and treatments
Treatments for metastatic CRC are mainly palliative and aim to increase both the duration and quality of the patients’ remaining life whilst controlling symptoms. This involves a combination of specialist treatments (such as surgery, chemotherapy and radiation), symptom control and psychosocial support.

First line chemotherapy options include:
- Oxaliplatin plus 5FU/FA (FOLFOX).
- Capecitabine plus oxaliplatin (XELOX).
- Irinotecan plus 5FU/FA (FOLFIRI).
- 5FU plus folinic acid (5FU/FA).
- Oral analogues of 5FU (capecitabine and tegafur with uracil).
- Raltitrexed for palliation of advanced colorectal cancer when 5FU/FA cannot be used (not recommended by NICE).
- Irinotecan plus capecitabine (XELIRI).

Second line chemotherapy options include:
- Irinotecan.
- FOLFOX.
- FOLFOX and irinotecan.
- XELIRI.
- XELOX.

Third line chemotherapy options include:
- Panitumumab as monotherapy in EGFR-expressing non-mutated KRAS metastatic colorectal cancer.

Cetuximab, in combination with irinotecan, is licensed for first or second line treatment in patients with tumours expressing epidermal growth factor receptor (not recommended by...
NICE). Although not licensed for this indication, bevacizumab may also be used in combination with a second line chemotherapy regimen (not recommended by NICE).^{a}

**Efficacy and safety**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01103323, 14387, EudraCT: 2009-012787-14; regorafenib vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Bayer plc.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry&quot;, manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU, USA, Canada and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants and schedule</td>
<td>n=751; adults; CRC; metastatic; progression during or within 3 mths following last administration of standard therapies. Randomised to regorafenib 160mg tablet once daily for 3 weeks of a 4 week cycle; or placebo, both with best supportive care. Patients continue with treatment until one of the following: disease progression, death, toxicity, non-compliance investigator decision or withdrawal of consent.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Follow-up 32 mths.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Overall survival.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Progression free survival; tumour response rate; disease control rate; adverse events; health-related quality of life.</td>
</tr>
<tr>
<td>Expected completion date</td>
<td>June 2013.</td>
</tr>
</tbody>
</table>

**Estimated cost and cost impact**

The cost of regorafenib is not yet known. The costs of other selected treatments for patients with metastatic colorectal cancer are as follows^{20,b}.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost for 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin</td>
<td>85mg/m^2 IV every 2 weeks</td>
<td>£2,700</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>10mg/kg IV every 2 weeks</td>
<td>£11,100</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>350mg/m2 every 3 weeks</td>
<td>£2,880</td>
</tr>
</tbody>
</table>

**Claimed or potential impact – speculative**

Patients

- ☑ Reduced mortality or increased length of survival
- ☑ Reduction in associated morbidity or improved quality of life for patients and/or carers
- ☐ Quicker, earlier or more accurate diagnosis or identification of disease
- ☐ None identified
- ☐ Other:

Services

- ☐ Increased use
- ☐ Service organisation
- ☐ Staff requirements
- ☐ Decreased use
- ☐ Other:
- ☑ None identified
- ☐ Other:

^{a} Expert opinion.

^{b} Costs based on average adult bodyweight 76.9kg and average surface area 1.7m^2.
Costs

- Increased unit cost compared to alternative
- Increased costs: more patients coming for treatment
- Increased costs: capital investment needed
- New costs:
- Savings:
- Other: uncertain unit cost compared to alternative therapies.

Other issues

- Clinical uncertainty or other research question identified: None identified

References

1. National Institute for Health and Clinical Excellence. Cetuximab, bevacizumab and panitumumab monotherapy for the treatment of metastatic colorectal cancer that has progressed after first line chemotherapy. Technology appraisal in development. London: NICE; Expected date of issue to be confirmed.