

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Proposed Health Technology Appraisal**

**Trifluridine in combination with tipiracil hydrochloride for previously treated metastatic colorectal cancer**

**Draft scope (pre-referral)**

**Draft remit/appraisal objective**

To appraise the clinical and cost effectiveness of trifluridine in combination with tipiracil hydrochloride within its marketing authorisation for treating metastatic colorectal cancer after at least 2 prior chemotherapy regimens.

**Background**

Colorectal cancer is a malignant tumour arising from the lining of the large intestine (colon and rectum). Metastatic colorectal cancer refers to disease that has spread beyond the large intestine and nearby lymph nodes. This type of cancer most often spreads first to the liver, but metastases may also occur in other parts of the body including the lungs, brain and bones.

In 2012, there were 34,322 people diagnosed with colorectal cancer<sup>1</sup> and 13,236 deaths<sup>2</sup>. Between 10% and 25% of people with colorectal cancer have metastatic disease when first diagnosed<sup>3,4</sup>, and approximately 50% of people who have surgery for early stage disease will eventually develop metastases<sup>5</sup>. The overall 5 year survival rate for metastatic colorectal cancer is around 7%<sup>6</sup>.

Treatment of metastatic colorectal cancer may involve a combination of surgery, chemotherapy, radiotherapy and supportive care. When possible, surgical removal (resection) or destruction of the primary tumour and metastases may be considered. For people with metastases only in their livers, complete resection appears to offer the best chance of long-term survival, providing 5 year survival rates ranging from 25% to 44%<sup>5</sup>.

Chemotherapy is an option to prolong survival and/or to make the primary tumour or metastases suitable for resection. NICE clinical guideline (CG) 131 recommends the following sequences of chemotherapy for people with metastatic colorectal cancer: folinic acid plus fluorouracil plus oxaliplatin (FOLFOX) as first line treatment followed by either single agent irinotecan or folinic acid plus fluorouracil plus irinotecan (FOLFIRI) as second-line treatment, or capecitabine plus oxaliplatin (XELOX) as first-line treatment then FOLFIRI as second-line treatment. For people who are intolerant to 5-fluorouracil and folinic acid, or for whom these drugs are not suitable, raltitrexed may be considered. CG131 also recommends capecitabine or tegafur with uracil (in combination with folinic acid) as an option for the first-line treatment of metastatic colorectal cancer. Chemotherapy may be combined with biological agents such as cetuximab (recommended as a first line treatment for some people in technology appraisal 176, and available

through the Cancer Drugs Fund), panitumumab (available through the Cancer Drugs Fund for treating metastatic colorectal cancer first, third or fourth line) and bevacizumab (available through the Cancer Drugs Fund for use in combination with oxaliplatin-based chemotherapy in the second- and third-line settings). Cetuximab or panitumumab alone may also be considered in clinical practice, in the third- or fourth-line settings (available through the Cancer Drugs Fund; not recommended by NICE).

### The technology

Trifluridine in combination with tipiracil hydrochloride (Lonsurf, Taiho Pharmaceuticals) is an anti-cancer treatment comprising a nucleoside analogue and a thymidine phosphorylase inhibitor. The nucleoside analogue (trifluridine) is incorporated into the DNA of tumour cells and inhibits tumour growth, whereas the thymidine phosphorylase inhibitor (tipiracil hydrochloride) slows the breakdown of trifluridine to prolong its action. It is administered orally as a fixed-dose combination.

Trifluridine in combination with tipiracil hydrochloride does not currently have a marketing authorisation in the UK. It has been studied in clinical trials, compared with placebo, for treating metastatic colorectal cancer in adults for whom 2 or more chemotherapy regimens have failed.

<b>Intervention(s)</b>	Trifluridine in combination with tipiracil hydrochloride
<b>Population(s)</b>	Adults with metastatic colorectal cancer, after at least 2 prior chemotherapy regimens
<b>Comparators</b>	<ul style="list-style-type: none"> <li>• Raltitrexed</li> <li>• Bevacizumab in combination with oxaliplatin-based chemotherapy (not recommended by NICE but funded via the CDF)</li> <li>• Cetuximab (not recommended by NICE but funded via the CDF)</li> <li>• Best supportive care</li> </ul>
<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• overall survival</li> <li>• progression-free survival</li> <li>• response rates</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>

<b>Economic analysis</b>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>Biosimilars are not expected to be in established NHS practice at the time of appraisal and are not included as comparators.</p> <p>Where comparator technologies are available through the Cancer Drug Fund, the cost incurred by the Cancer Drug Fund should be used in any economic analyses, rather than the list price.</p>
<b>Other considerations</b>	<p>Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.</p>
<b>Related NICE recommendations and NICE Pathways</b>	<p>Related Technology Appraisals:</p> <p>‘Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy’ (2014). NICE Technology Appraisal No. 307. Review date August 2016.</p> <p>‘Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of TA150 and part review of TA118)’ (2012). NICE Technology Appraisal No. 242. Guidance on static list.</p> <p>‘Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer’ (2010). NICE Technology Appraisal No. 212. Guidance on static list.</p> <p>‘Cetuximab for the first-line treatment of metastatic colorectal cancer’ (2009). NICE Technology Appraisal No. 176. Currently under review [ID794].</p> <p>‘Bevacizumab and cetuximab for the treatment of</p>

	<p>metastatic colorectal cancer' (2007). Technology Appraisal No. 118. Guidance on static list. Partially reviewed as part of TA242.</p> <p>Terminated appraisals</p> <p>'Regorafenib for metastatic colorectal cancer after treatment for metastatic disease' (terminated appraisal) (2015). NICE Technology Appraisal No. 334.</p> <p>'Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer' (terminated appraisal) (2011). NICE Technology Appraisal No. 240. Currently under review [ID794].</p> <p>Appraisals in development</p> <p>'Colorectal cancer (metastatic) - cetuximab (review TA176) and panitumumab (part review TA240) (1st line)'. NICE technology appraisals guidance [ID794]. Publication expected April 2016.</p> <p>Proposed Appraisals</p> <p>'Ramucirumab in combination with FOLFIRI for treating metastatic colorectal cancer after progression with bevacizumab, oxaliplatin and fluoropyrimidine'. Proposed NICE technology appraisal [ID867]. Publication date to be confirmed.</p> <p>Related Guidelines:</p> <p>'The diagnosis and management of colorectal cancer' (2011, partially updated December 2014). NICE Clinical Guideline No. 131. Review date to be confirmed.</p> <p>Related Interventional Procedures:</p> <p>'Selective internal radiation therapy for non-resectable colorectal metastases in the liver' (2011). Interventional Procedures Guidance No. 401</p> <p>'Radiofrequency ablation for colorectal liver metastases' (2009) Interventional Procedures Guidance No. 327.</p> <p>'Preoperative high dose rate brachytherapy for rectal cancer' (2006). Interventional Procedures Guidance No. 201.</p> <p>Related Quality Standards:</p> <p>'Colorectal cancer (2012). Quality Standard No. 20.  <a href="http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp">http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp</a></p> <p>Related NICE Pathways:</p>
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	<p>'Colorectal cancer' (2011). NICE Pathway.  <a href="http://pathways.nice.org.uk/pathways/colorectal-cancer">http://pathways.nice.org.uk/pathways/colorectal-cancer</a></p>
<b>Related National Policy</b>	<p>Department of Health, 2013, <a href="#">NHS Outcomes Framework 2014-2015</a>. Domains 1, 2, 4 and 5.</p> <p>Department of Health, 2011, <a href="#">Improving outcomes: a strategy for cancer</a></p> <p>Department of Health, 2009, <a href="#">Cancer commissioning guidance</a></p> <p>Department of Health, 2007, <a href="#">Cancer reform strategy</a></p> <p>NHS England, 2014, <a href="#">Manual for prescribed specialised services 2013/14</a>. Chapter 10.</p> <p>NHS England, 2015, <a href="#">Cancer Drugs Fund list</a></p> <p>Public Health England, 2011, <a href="#">National Screening Committee policy on bowel cancer screening in adults</a>.</p>

### Questions for consultation

How is trifluridine in combination with tipiracil hydrochloride expected to be used in clinical practice? Is it expected to be used after specific chemotherapy regimens or lines of treatment?

Have all relevant comparators for trifluridine in combination with tipiracil hydrochloride been included in the scope?

- Which treatments are considered to be established clinical practice in the NHS for metastatic colorectal cancer in people after at least 2 prior chemotherapy regimens?
- Are any other chemotherapy regimens or biological agents (such as FOLFOX, FOLFIRI, XELOX, panitumumab or aflibercept) used in this population?
- Which oxaliplatin-based combination regimens are used?
- Is raltitrexed used in this population?
- How should best supportive care be defined?

Are there any subgroups of people in whom trifluridine in combination with tipiracil hydrochloride is expected to be more clinically effective and cost effective or other groups that should be examined separately?

- Should consideration be given to RAS mutation status or any other biological markers?
- Should subgroups based on the location of metastases (inside and/or outside the liver) be considered?

Where do you consider trifluridine in combination with tipiracil hydrochloride will fit into the existing NICE pathway, [Colorectal cancer](#)?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which trifluridine in combination with tipiracil hydrochloride will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider trifluridine in combination with tipiracil hydrochloride to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of trifluridine in combination with tipiracil hydrochloride can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at <http://www.nice.org.uk/article/pmg19/chapter/1-Introduction>)

### References

1. Office for National Statistics (2012) '10 most common cancers in males and females'. Accessed June 2015.
2. Cancer Research UK (2014) 'Bowel cancer mortality statistics'. Accessed June 2015.
3. Bowel Cancer UK (2014) 'Bowel cancer statistics'. Accessed June 2015.

4. Association of Coloproctology of Great Britain and Ireland (2007) 'Guidelines for the Management of Colorectal Cancer'. Accessed June 2015.
5. Garden OJ, Rees M, Poston GJ et al. (2006) Guidelines for resection of colorectal cancer liver metastases. *Gut* 55 (Suppl III) iii1–iii8.
6. Cancer Research UK (2014b) 'Bowel cancer survival statistics'. Accessed June 2015.