National Institute for Health and Care Excellence

Health Technology Evaluation

Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Servier Laboratories	Appropriate	Thank you for your comment. No action required.
	Bowel Cancer UK	As a patient organisation, we welcome the evaluation of this treatment, particularly as treatment options are severely limited on the NHS for metastatic colorectal cancer patients who have found previous treatments unsuccessful. Treatment options outside of the NHS remain hugely expensive and inaccessible for most patients and therefore the evaluation of this technology is highly important. After reaching out to patients in our community who have metastatic colorectal cancer and have undergone 2 systemic treatments, the following points were raised that demonstrate the appropriateness of this evaluation:	Thank you for your comment. No action required.

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		• One individual shared that in her husband's case, trifluridine–tipiracil with bevacizumab was the first treatment that had any 'noticeable impact' on his lung metastases. After 3 months undergoing this treatment, they had shrunk by about 20-25%. He had previously received treatment with Folfiri, Capox and Folfox, all of which failed. This demonstrates that trifluridine–tipiracil with bevacizumab has provided an extended period of survival for some patients and could therefore provide the same for other metastatic CRC patients as a third-line treatment. • One patient shared that she had received 46 rounds of Cetuximab and Folfiri, all of which failed to stop her lung nodes growing. She is now receiving Folfox and is living with neuropathy and fatigue. Her next treatment option will be Lonsurf and she shared that she will have to look into self-funding bevacizumab alongside this to have any chance of pro-longing her survival. The financial stress of having to consider self-funding has caused 'extreme anxiety', which would be alleviated if this treatment were available on the NHS. After undergoing so many failed chemotherapies, the provision of trifluridine–tipiracil with bevacizumab on the NHS could potentially offer hope of extended survival for this patient. • One patient highlighted the inaccessibility of this treatment, sharing that they fortunately had private healthcare through Bupa. This trifluridine–tipiracil with bevacizumab, without which 'the quote was c£5000 per month'. The patient went on to explain that they are in the top 1-5% of earners and have no children and yet even they would not be able to cover this cost of treatment. Similarly, a second patient explained that she is unable to afford bevacizumab privately. She finds it difficult knowing that if she was able to,	

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		she could have 'remarkable success' with this treatment, as others have done. She stressed that the NHS needs to 'remove the postcode lottery so there is one standard of care'. She also stated that this treatment 'could give [her] months or even longer' and yet it is currently only available to those who can afford it privately. As a result, she feels like her 'life isn't worth anything' and feels hopeless given her lack of other treatment options at this time. The availability of trifluridine–tipiracil with bevacizumab on the NHS could therefore give her another treatment option, possibly extending her survival and providing hope during a time that otherwise feels 'hopeless'.	
Wording	Servier Laboratories	Yes	Thank you for your comment. No action required.
	Bowel Cancer UK	Yes	Thank you for your comment. No action required.
Timing Issues	Servier Laboratories	Urgent	Thank you for your comment. No action required.
	Bowel Cancer UK	Clinical oncologists who are also members of our Medical Advisory Board have expressed the urgency of this evaluation to the NHS. One oncologist based in Wales expressed that at present, this treatment is only available in some areas of the UK. Standardisation with formal appraisal is therefore urgently needed to enhance equality of access. Another clinician, based in Scotland, agreed, and explained that whilst they have access to this combination 'fairly easily' in Glasgow, other Scottish and English sites don't. She explained that without NICE approval, patients are	Thank you for your comment. No action required.

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		paying high fees for bevacizumab top ups, which are extremely variable. In some areas, patients are even being made to pay for 'the whole package' and not just the bevacizumab top up. She went on to state that this is 'very unfair and a postcode lottery'. This appraisal is therefore urgently needed to standardise the availability of this treatment and reduce the postcode lottery of care.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Servier Laboratories	Yes	Thank you for your comment. No action required.
	Bowel Cancer UK	Upon checking the reference (1) cited for the incidence of colorectal cancer in the UK, the publication cited estimates that there were 52,128 cases of colorectal cancer rather than 42,900 as written on the background section of the draft scope. However, CRUK report the 42,900 figure written. CRUK data is the gold standard, and therefore it would be best to change the incidence of colorectal cancer citation to reference them not only to align with what has been written but to be using the best standard of data. Additionally, the background information would be more complete if it considered the current quality of life and expected survival amongst the patient indication pool in the UK. Furthermore, the background information would also be more complete if it considered available trial data such the SUNLIGHT trial to inform of the clinical and cost effectiveness of comparator treatments for this indication and the treatment under evaluation in more detail. For example, factors effecting	Thank you for your comment. The references have been updated to reflect this. The background section acts as a brief overview of the disease area and current treatments available.

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		quality of life such as the range and incidence of side effects, and a comparison of progression-free survival statistics.	
Population	Servier Laboratories	Yes	Thank you for your comment. No action required.
	Bowel Cancer UK	Yes	Thank you for your comment. No action required.
Subgroups	Servier Laboratories	There is a clear difference between the population in the trial and the population relevant to England. The Sunlight study, which forms the basis of the submission, mainly includes patients who have had prior bevacizumab. This is not the situation in NHS practice as it is not available. There was a prespecified subgroup in the SUNLIGHT trial looking at the survival benefits in patients with/without prior bevacizumab. To note that 72% of the population received previous anti-VEGF therapy. The subgroup without prior bevacizumab reflects even better the UK population and as such, it might be relevant to evaluate the whole population as well as the population without prior bevacizumab.	Thank you for your comment. The subgroup 'people without prior bevacizumab' has been added to the scope as it is more reflective of the current NHS population.
	Bowel Cancer UK	Patients with Kirsten rat sarcoma (KRAS) mutations. KRAS mutations exist in around 40% of CRC cases and 'colorectal tumors bearing KRAS mutations are associated with advanced disease status, poor tumor differentiation, distant metastasis and inferior survival in patients'.	Thank you for your comment. If the data are available subgroup analysis can be

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		(BMC, Molecular Cancer volume 20, Article number: 143, 2021). Patients with this mutation often have limited treatment options. One respondent from our patient forum shared that her husband has KRAS G12D and 'benefited tremendously' from this treatment, after previous treatments including Folfiri, Capox and Folfox failed. Given this patient's experience and due to no immunotherapy being available for his mutation (KRAS G12D), we believe further investigation into the effectiveness of this treatment for CRC patients with KRAS mutations is warranted and should be considered as part of this assessment. As another patient expressed, '[we] strongly believe everybody should have the option' of trifluridine–tipiracil with bevacizumab, not just those with KRAS or other mutations. However, we believe further investigations into the effectiveness of this treatment for those with mutations would be beneficial to this assessment.	included in the company's submission and they will be considered during the appraisal. The list in the scope is not intended to be exhaustive. No action needed.
Comparators	Servier Laboratories	Servier do not believe all comparators listed in the scope to be appropriate. • Single-agent irinotecan (after FOLFOX) • Raltitrexed (if 5-FU/FA are not suitable) In technology appraisal ID4036 with Pembrolizumab, the company stated that irinotecan and raltitrexed were excluded based on clinical feedback that they are rarely used in practice unless other treatments are contraindicated. The clinical expert and Cancer Drugs Fund lead both confirmed that irinotecan and raltitrexed monotherapy are rarely used in clinical practice • FOLFIRI (after either FOLFOX or CAPOX) • FOLFOX (after either FOLFIRI or CAPOX)	Thank you for your comments. Stakeholders can provide justification for the most appropriate comparators and the committee will consider this during the appraisal. The list of comparators in the scope is kept inclusive.

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		These are second line settings so should not be used as a comparator to Trifluridine/tipiracil + bevacizumab as SmPC states for the treatment of adult patients with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens. Both the inclusion criteria of SUNLIGHT and the proposed SmPC (approved by EMEA) mentions; including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents. • Nivolumab with ipilimumab (where high microsatellite instability or mismatch repair deficiency is present) Technology appraisal ID4036 with Pembrolizumab states 4-8% of patients with colorectal cancer have MSI-H tumours. CHECKMATE 142 publication, references "patients with DNA mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) mCRC to ≈4% to 5% of patients." However, only around 35 people per year are expected to have nivolumab with ipilimumab for colorectal cancer with high MSI or MMR deficiency. This number is small because pembrolizumab is already available as a first-line therapy and people can only have a checkpoint inhibitor at 1 point in the treatment pathway. An advisory board carried out by Servier Laboratories in July 2023 found that clinicians would use Nivolumab with ipilimumab in the second line setting prior to the use of Trifluridine tipiracil + bevacizumab, and therefore earlier in the treatment pathwayA	

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		This regimen is used if genetic testing indicates high microsatellite instability or mismatch repair deficiency. If genetic testing is positive these agents provide targeted therapy and are the treatment of choice. Trifluridine tipiracil + bevacizumab would not be considered an alternative option in the presence of such positive genetic tests and is not a comparator to these regimens. • Encorafenib with cetuximab An advisory board carried out by Servier Laboratories in July 2023 found that clinicians would use encorafenib with cetuximab in the second line setting prior to the use of Trifluridine tipiracil + bevacizumab, and therefore earlier in the treatment pathway. This regimen is used if genetic testing indicates BRAF V600E mutation-positive. If genetic testing is positive these agents provide targeted therapy and are the treatment of choice. Trifluridine tipiracil + bevacizumab would not be considered an alternative option in the presence of such positive genetic tests and is not a comparator to these regimens. • Best Supportive Care Servier believes BSC would only be offered for those patients with ECOG 2+ In addition, the most recent ESMO guidelines does not mention the use of BSC here https://www.esmo.org/living-guidelines/esmo-metastatic-colorectal-cancer-living-guideline/advanced-and-metastatic-disease-without-potential-conversion/advanced-and-metastatic-disease-without-potential-conversion/third-and-further-lines Servier considers the following comparators to be appropriate:	

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		• Trifluridine–tipiracil monotherapy • Regorafenib	
	Bowel Cancer UK	Yes	Thank you for your comment. No action required.
Outcomes	Servier Laboratories	Appropriate	Thank you for your comment. No action required.
	Bowel Cancer UK	Yes	Thank you for your comment. No action required.
Other considerations	Bowel Cancer UK	One clinician from our Medical Advisory Board shared that the assessment of Fruqutinib has significant relevance for the positioning and approval of these different Systematic Anti-Cancer Therapy approaches.	Thank you for your comment. As fruquintinib has yet to be assessed by NICE, it cannot be considered as a comparator for this evaluation.
Questions for consultation	Servier Laboratories	• Where do you consider trifluridine–tipiracil with bevacizumab will fit into the existing care pathway for metastatic colorectal cancer? Based on the ESMO updated GL, and the experts ad boards, the combination is applicable to 3L patients irrespective of RAS and BRAF status.	Thank you for your comment. No action required.

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		Cervantes A et al. Ann Oncol 2023;34(1):10-32. and ESMO Metastatic Colorectal Cancer Living Guidelines, v1.1 July 2023. https://www.esmo.org/living-guidelines/esmo-metastatic-colorectal-cancer-living-guideline/advanced-and-metastatic-disease-without-potential-conversion/advanced-and-metastatic-disease-without-potential-conversion/third-and-further-lines	

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

British Society of Gastroenterology
Crohn's and Colitis UK
Roche