National Institute for Health and Care Excellence

Health Technology Evaluation

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

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	Takeda	For the reasons outlined below around the innovative nature of fruquintinib and the unmet need for patients with previously treated metastatic colorectal cancer (mCRC), Takeda believe this is an appropriate referral to NICE.	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 that has been previously treated we received the following response, which illustrates the need for additional treatment options within this population:	Thank you for your comment. No action required.

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		One patient stated they were diagnosed with stage 4 colorectal cancer that had metastasised to their liver. Following an emergency right hemi colostomy they underwent one round of chemotherapy. The second round was halted for a period of 7 weeks due to severe burn blisters after which the went back onto CAPOX. The patient was then moved into the BEACON CRC trial but their treatment within this trial stopped working after 3 months. They are now in the process of acquiring treatment oversees “given my cancer type is a rare mutation and not so much (available) in the UK for BRAF mutations.”	
Wording	Takeda	The draft remit should be updated to align with the expected marketing authorisation for fruquintinib: “*To appraise the clinical and cost effectiveness of fruquintinib within its marketing authorisation for treating* [redacted]” Takeda request that the intervention is referred to as fruquintinib, and the brand name be removed from any publicly available documents until marketing authorisation is granted.	Thank you for your comment. The remit is kept broad until marketing authorisation is granted. No action required.
	Bowel Cancer UK	Yes	Thank you for your comment. No action required.
Timing Issues	Takeda	Outcomes for patients with mCRC who have been previously treated with or are not considered candidates for available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy are extremely poor. These patients	Thank you for your comment. No action required.

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		face an overall survival of only 5–7 months (1-3), and therefore there is an urgent need for alternative treatment options.	
	Bowel Cancer UK	With few options available to this patient population, it is important that this treatment is evaluated thoroughly and efficiently to fully understand and deliver benefits to patients in this indication.	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Takeda	Takeda suggest the wording describing the clinical trial populations for fruquintinib on page 2 be adjusted to the below for clarity: *"It has been studied in clinical trials compared with best supportive care in adults with advanced, metastatic colorectal cancer who had progressed after second line or above standard chemotherapy and those who have progressed on, or were intolerant to chemotherapy, anti-VEGF and anti-EGFR biologics, and TAS-102 (trifluridine-tipiracil) or regorafenib."*	Thank you for your comment. This section has been updated.
	Bowel Cancer UK	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. The background information would also be more complete if it considered available trial data such as the FRESCO-2 trial. While this trial does not compare fruquintinib to other treatment options available to previously treated metastatic colorectal cancer patients, it could contribute to a broader understanding of the clinical effectiveness of fruquintinib.	Thank you for your comment. The background section acts as a brief overview of the disease area and current treatments available. A systematic review of all available evidence for the clinical effectiveness of

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		Additional information regarding the efficacy and safety of this treatment when compared to regorafenib may also be useful in the absence of clinical trials.	fruquintinib and its effect on quality of life will be carried out as part of the evaluation. No action required.
Population	Takeda	Takeda request that the population is updated to align with the anticipated marketing authorisation of fruquintinib: "[redacted]".	Thank you for your comment. Confidential information cannot be included in the scope. The population is kept broad until marketing authorisation is granted. No action required.
	Bowel Cancer UK	Yes	Thank you for your comment. No action required.
Subgroups	Takeda	No subgroups are planned to be considered separately.	Thank you for your comment. No action required.
	Bowel Cancer UK	The current list is appropriate.	Thank you for your comment. No action required.
Comparators	Takeda	Takeda agree that trifluridine-tipiracil monotherapy and regorafenib are appropriate comparators for fruquintinib, based on the anticipated marketing authorisation and UK clinical expert opinion obtained by Takeda at an advisory board in September 2023. Best supportive care (BSC) is also	Thank you for your comments. Nivolumab plus ipilimumab and

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		considered a treatment option in patients who are not candidates for or are intolerant to trifluridine-tipiracil or regorafenib and is therefore an appropriate comparator. However, based on existing NICE guidance for mCRC and clinical expert opinion elicited to-date (including an advisory board held in September 2023), Takeda believe the following treatments are not relevant comparators, and would like to request their removal from the final scope: • Nivolumab plus ipilimumab is only recommended by NICE in patients with tumours positive for high microsatellite instability or mismatch repair deficiency. Clinical expert opinion elicited at the advisory board stated that biomarker-dependent treatments, such as nivolumab plus ipilimumab, are used following genetic testing of the tumour (4) and earlier in the treatment pathway than the proposed positioning of fruquintinib. In relation, TA866 did not include nivolumab plus ipilimumab as a relevant comparator (5). As such, nivolumab plus ipilimumab should not be considered an appropriate comparator for fruquintinib. • Encorafenib plus cetuximab is only recommended by NICE in patients with tumours positive for the *BRAF* V600E mutation. Clinical expert opinion elicited at the advisory board stated that biomarker-dependent treatments, such as encorafenib plus cetuximab, are used following genetic testing of the tumour (4) and earlier in the treatment pathway than the proposed positioning of fruquintinib. In relation, TA866 did not include encorafenib plus cetuximab as a relevant comparator (5). As such, encorafenib plus cetuximab should not be considered an appropriate comparator for fruquintinib.	encorafenib plus cetuximab have been removed as comparators from the scope.

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	Bowel Cancer UK	Yes	Thank you for your comment. No action required.
Outcomes	Takeda	No comments, Takeda agree with the proposed outcomes.	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 member of our Medical Advisory Board shared that the NICE assessment of trifluridine-tipiracil with bevacizumab has significant relevance for the positioning and approval of these different Systematic Anti-Cancer Therapy approaches.	Thank you for your comment. As trifluridine-tipiracil with bevacizumab has yet to be assessed by NICE, it cannot be considered as a comparator for this evaluation.
Questions for consultation	Takeda	**Where do you consider fruquintinib will fit into the existing care pathway for metastatic colorectal cancer?** Takeda anticipate that fruquintinib will be used in the same position as trifluridine-tipiracil (6) and regorafenib (5) for patients with previously treated mCRC. Fruquintinib is also anticipated to be used in patients who are not considered candidates for, or have been previously treated with trifluridine-tipiracil and/or regorafenib.	Thank you for your comments. Nivolumab plus ipilimumab and encorafenib plus cetuximab have been removed as

		Which treatments do you consider to be the comparators of fruquintinib? As per the proposed positioning of fruquintinib above, trifluridine-tipiracil monotherapy (6) and regorafenib (5) are considered to be the only relevant active comparators. In patients where standard therapies have been unsuccessful, not tolerated or contraindicated, BSC is the only remaining option and is therefore also considered to be a comparator for fruquintinib. **Would fruquintinib be used as an alternative treatment option to nivolumab with ipilimumab for people with high microsatellite instability or where high mismatch repair is present?** As noted above, biomarker-dependent treatments such as nivolumab plus ipilimumab would be expected to be used earlier in the treatment pathway than the positioning of fruquintinib, and only in patients where genetic testing has indicated high microsatellite instability or mismatch repair deficiency. In relation, TA866 did not include nivolumab + ipilimumab as a relevant comparator. As such, nivolumab plus ipilimumab should not be considered an appropriate comparator for fruquintinib.. **Would fruquintinib be used as an alternative treatment option to encorafenib plus cetuximab for people with *BRAF* V600E mutation-positive metastatic colorectal cancer?** As noted above, biomarker-dependent treatments such as encorafenib plus cetuximab would be expected to be used earlier in the treatment pathway than fruquintinib, and only in patients where genetic testing has identified a *BRAF* V600E mutation. In relation, TA866 did not include encorafenib plus cetuximab as a relevant comparator. As such, encorafenib plus cetuximab should not be considered an appropriate comparator for fruquintinib. **When would best supportive care be used in the treatment of metastatic colorectal cancer?**	comparators from the scope.

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		BSC is used to manage the symptoms and complications of mCRC in patients where standard therapies have been unsuccessful, not tolerated or contraindicated. **Would fruquintinib be a candidate for managed access?** The preferred funding of fruquintinib for patients with previously treated mCRC is through routine NHS funding via baseline commissioning. If the NICE committee feels unable to make a positive recommendation for routine NHS funding, then Takeda would be open to discussions with NICE and NHS England around potential inclusion in the CDF. **Do you consider that the use of fruquintinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** The addition of fruquintinib to the treatment pathway would expand choice for this patient population. Fruquintinib offers a favourable safety profile, and would provide a new, oral treatment option which does not negatively impact quality-of-life, for patients unable to receive trifluridine-tipiracil or regorafenib, and for patients who have progressed on either or both of these therapies. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** To support the benefits of fruquintinib which may not be captured by the QALY calculation, Takeda will provide information from the scientific literature and expert clinical input from advisory board meetings.	

		Is the technology likely to be similar in its clinical effectiveness and resource use to any of the comparators? Or in what way is it different to the comparators? While Takeda expects the efficacy profile of fruquintinib to be similar to regorafenib and trifluridine–tipiracil, the key differentiation is based on the relative toxicity profiles of the three treatments: • The key toxicity for trifluridine–tipiracil is myelosuppression, and based on feedback received from clinical expert opinion, Takeda believes that approximately 20% of patients will have complicated myelosuppression for which they will receive G-CSF (4). In FRESCO and FRESCO-2, fruquintinib was associated with low rates of haematological toxicities, which were predominantly low-grade (7, 8) • The key toxicities for regorafenib are fatigue and hand-foot syndrome, which can be difficult to manage. At a medical advisory board conducted by Takeda in September 2023, clinical experts advised that the tolerability profile of fruquintinib could be more manageable in clinical practice than that of regorafenib (4). **Will the intervention be used in the same place in the treatment pathway as the comparator(s)? Have there been any major changes to the treatment pathway recently? If so, please describe.** Yes, it is anticipated that fruquintinib will be licensed for use in a similar position to the comparators regorafenib and trifluridine-tipiracil. The most recent change in the treatment pathway for previously treated mCRC was the positive NICE recommendation for regorafenib in December 2022 (5). **Will the intervention be used to treat the same population as the comparator(s)?** Yes, fruquintinib is anticipated to be licensed for use in the same population as the comparators trifluridine-tipiracil and regorafenib. Fruquintinib is also anticipated to be licensed for use in patients who have already been treated	

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		with, or are unable to receive trifluridine-tipiracil and/or regorafenib. For these patients, the comparator would be BSC. **Overall is the technology likely to offer similar or improved health benefits compared with the comparators?** Currently there are no head-to-head data available comparing fruquintinib with regorafenib or trifluridine-tipiracil. Therefore, Takeda will conduct an indirect treatment comparison (ITC) to inform comparative efficacy estimates within the economic analysis. Therefore, no definitive conclusions regarding the similarity of health benefits vs trifluridine-tipiracil and regorafenib can be made at this time. As previously noted, in both the FRESCO and FRESCO-2 clinical trials, fruquintinib was generally well tolerated, with a toxicity profile consistent with the established monotherapy safety profile observed in other studies. **Would it be appropriate to use the cost-comparison methodology for this topic?** As noted above, in the absence of head-to-head data between fruquintinib and its comparators, and with ITC results not yet available, it is uncertain whether fruquintinib would be considered to offer similar health benefits vs the comparators. Therefore, Takeda plan to submit via the single technology appraisal (STA) process using cost-utility methods but would be open to potential discussions with NICE around this topic.	

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

BMS