**National Institute for Health and Care Excellence**

**Health Technology Evaluation**

**Tucatinib with trastuzumab for previously treated HER2-positive colorectal cancer [ID6227]**

**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 |
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| Appropriateness of an evaluation and proposed evaluation route | Seagen | Yes, we consider the intention of NICE to evaluate tucatinib in combination with trastuzumab within its anticipated marketing authorisation for previously treated HER2 positive colorectal cancer through its Single Technology Appraisal process to be appropriate. | Thank you for your comment. No further action needed. |
| Bower cancer UK | As a patient focused organisation, we welcome the evaluation of this treatment, particularly due to the lack of NICE recommended treatment options for patients with previously treated HER2 positive colorectal cancer. After reaching out to our patient community who have HER2-positive colorectal cancer, the following points were highlighted that demonstrate the appropriateness of this evaluation.- One patient reported that this treatment would ‘Open up another potential line of treatment’. This patient is 35 years old, making this a clear demonstration of how the evaluation of this treatment could provide another option and potentially an extended period of survival when all other options have been explored.- One patient reported that her consultant felt her chemotherapy was not working, and that as a result she has self-funded trastuzumab. She stated that she was in a ‘fortunate position’ to do this, highlighting that accessing these kinds of treatments should not be an issue of equality or wealth. Similarly, a second patient stated, ‘I believe it [this treatment] should be made available to anyone who qualifies for it.’- One patient responded that she was ‘surprised to learn that herceptin [Trastuzumab] is available on the NHS for breast cancer and gastric cancer patients but not for bowel cancer patients.’ This highlights a feeling of surprise amongst this indication that there is no targeted treatment for patients with HER2- positive colorectal cancer, but there is for HER2-positive cancers of other primary source. Similarly, another patient reported that ‘This kind of treatment is extremely tailored to fit a specific type of BC [bowel cancer] and I believe that the more precise the treatment, the better the outcome, hopefully this will be the future of treatment for individuals.’ | Thank you for your comment. No further action needed. |
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| Wording | Seagen | Tucatinib in combination with trastuzumab is intended for patients with unresectable or metastatic colorectal cancer. As the draft scope states the broader colorectal cancer population, please amend the wording to include “unresectable or metastatic” in the remit as follows:  “To appraise the clinical and cost effectiveness of tucatinib with trastuzumab within its anticipated marketing authorisation for treating previously treated HER2-positive unresectable or metastatic colorectal cancer.” | Thank you for your comment. This has been amended. |
| Bower cancer UK | When looking at comparators for this treatment, it would be more accurate to consider the clinical and cost effectiveness of these treatments specifically for the indication that would benefit from the treatment under evaluation – patients who have HER2 positive colorectal cancer who have previously received treatment. | Thank you for your comment, the appraisal will be specific to people with previously treated HER-2 positive colorectal cancer. |
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| Additional comments on the draft remit | Seagen | Colorectal cancer is the 4th most common cancer in the UK, with 20% of patients metastatic at diagnosis and a further 20% of non-metastatic colorectal cancer patients developing metastases (1-3). Only 3–5% of patients with metastatic colorectal cancer are HER2 positive; however, this is associated with a greater number of metastatic sites (4, 5).  Among patients with metastatic colorectal cancer, 5-year survival is only 10%, with 43% of patients receiving second line therapy and beyond. There are also no NICE recommended treatments for patients with HER2-positive metastatic colorectal cancer (6, 7). Furthermore, as described in the draft scope section “Background”, current treatments for metastatic colorectal cancer can be unsuccessful, not tolerated, or contraindicated. These patients instead receive best supportive care to manage the symptoms and complications of the condition.  As a result, there is a high unmet need for effective therapies for patients with previously treated HER2 positive metastatic colorectal cancer. | Thank you for your comment. The unmet need in this area will be explored during the appraisal process. No further action needed. |
| Bower cancer UK | approximately 3-5% of colorectal cancers are HER2 positive (Djaballah et al., 2022), and in the UK approximately 42,900 people will be diagnosed with colorectal cancer every year (Cancer Research UK, 2016-2018). With no targeted alternative treatment for patients with previously treated HER2 positive colorectal cancer available in England and Wales, and low efficacy amongst the treatment that is offered at this point (National Cancer Institute US, 2023), this is a significant number of patients who could benefit from an additional period of disease progression-free time with family, friends and loved ones. Therefore, we believe that this evaluation is of some urgency. | Thank you for your comment. The unmet need in this area will be explored during the appraisal process. No further action needed. |
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Comment 2: the draft scope

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Background information | Seagen | With regards current treatments/treatment pathway, [NICE technology appraisal 866](https://www.nice.org.uk/guidance/ta866) recommends regorafenib for patients with previously‑treated metastatic colorectal cancer ([8](#_ENREF_8)). Regorafenib is positioned similarly to the proposed positioning for tucatinib in combination with trastuzumab in the treatment pathway and is considered a comparator of the intervention. Please include regorafenib as a treatment option in the “Background” section.  Please note that in section “The technology”, the trial/study information included for tucatinib in combination with trastuzumab is incorrect where it states: “It is being studied in a randomized phase III study in combination with a FOLFOX regimen compared to a FOLFOX regimen alone or in combination with bevacizumab or cetuximab in people with HER2‑positive metastatic and/or unresectable colorectal cancer that has not been treated in the metastatic stage.” Please amend the wording to instead state that: “It has been evaluated in a Phase 2, open label, investigator sponsored trial (MOUNTAINEER; NCT03043313 ([9](#_ENREF_9))) in combination with trastuzumab in patients with HER2-positive metastatic cancer who have received previous treatment.”  **Please note:** A Phase 3 study of tucatinib in combination with trastuzumab (MOUNTAINEER‑03; NCT05253651 ([10](#_ENREF_10))) is ongoing. However, as this trial investigates the use of tucatinib in combination with trastuzumab and mFOLFOX6, and in a different patient population to that of the Phase 2 MOUNTAINEER trial, MOUNTAINEER‑03 is not considered relevant to the decision problem. | Thank you for your comment. TA866 has been added to the background section and the trial information has been updated accordingly. |
| Bower cancer UK | Furthermore, the background information would also be more complete if it considered available trial data 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 quality of life such as the range and incidence of side effects, and a comparison of progression-free survival statistics. | Thank you for your comment. The background section is intended to give a brief overview of the disease area and not explore the clinical/cost effectiveness of comparator treatments, which will be explored later on in the appraisal process. |
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| Population | Seagen | Tucatinib in combination with trastuzumab is intended for patients with unresectable or metastatic colorectal cancer, whereas the draft scope states the broader colorectal cancer population. Please amend the population wording to incorporate the following text: \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* | Thank you for your comment. The population in the scope has been updated to be specific to people with unresectable or metastatic disease. |
| Bower cancer UK | yes | Thank you for your comment. No further action needed. |
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| Subgroups | Seagen | There are no subgroups that should be considered separately. | Thank you for your comment. No further action needed. |
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| Comparators | Seagen | Regorafenib and trifluridine‑tipiracil, which are available for patients with metastatic colorectal cancer who have received prior therapy, are positioned similarly to the proposed positioning for tucatinib in combination with trastuzumab and are therefore considered suitable comparators of the intervention.  As previous treatment with single‑agent irinotecan (after FOLFOX), FOLFIRI (after either FOLFOX or CAPOX), FOLFOX (after either FOLFIRI or CAPOX), and raltitrexed (if 5-FU/FA are not suitable) was required prior to initiation of tucatinib and trastuzumab in the Phase 2 MOUNTAINEER trial, we recommend these are not included in the scope as they are not relevant comparators. Clinicians have indicated that they would only consider using tucatinib in combination with trastuzumab after these treatments have failed or in patients for whom they are unsuitable.  Finally, we do not consider best supportive care as a direct comparator of tucatinib in combination with trastuzumab and recommend it is not considered in the scope. Best supportive care is a treatment option typically given later in the treatment pathway after failure of regorafenib and/or trifluridine‑tipiracil. Tucatinib in combination with trastuzumab will be positioned alongside regorafenib and trifluridine‑tipiracil and would therefore be positioned before best supportive care in the treatment pathway. | Thank you for your comment, the committee will consider which comparators are relevant during the appraisal. |
| Bower cancer UK | As there currently is no NICE recommended treatment for patients with previously treated HER2-positive colorectal cancer, this treatment is best compared with best supportive care. However, when looking at treatments that patients at this stage may currently be accessing, this is likely to be Regorafenib and Trifluridine-tipiracil. The other comparators listed may be used earlier in the pathway. | Thank you for your comment, the committee will consider which comparators are relevant during the appraisal. |
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| Outcomes | Seagen | Yes. The outcomes listed in the draft scope are considered relevant to the intervention.  Please also include “Duration of response” as this was a key secondary endpoint in the MOUNTAINEER study and is an outcome that has been included in previous NICE technology appraisals of oncology products. | Thank you for your comment. This has been added to the scope. |
| Bower cancer UK | yes | Thank you for your comment. No further action needed. |
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| Equality | Seagen | No issues have been identified. | Thank you for your comment. No further action needed. |
| Bower cancer UK | When considering the promotion of equality of opportunity from a patient perspective, it is apparent that in order for this treatment to be equally available to all, the standardisation of HER2 testing for colorectal cancer is key. | Thank you for your comment. The committee will consider any relevant equalities issues during the appraisal process, along with the costs and availability of HER2 testing. No further action needed. |
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| Other considerations |  |  |  |
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| Questions for consultation | Seagen | ***Q1.*** *Where do you consider tucatinib with trastuzumab will fit into the existing care pathway for unresectable or metastatic HER2‑positive colorectal cancer?*  We consider tucatinib in combination with trastuzumab as a treatment option \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*, in line with the proposed indication.  ***Q2.*** *When would best supportive care be used in the treatment of unresectable or metastatic HER2-positive colorectal cancer?*  Best supportive care is a treatment option typically given later in the treatment pathway, after where tucatinib in combination with trastuzumab will be placed. As treatment with tucatinib in combination with trastuzumab would be used before best supportive care, we believe best supportive care is not a direct comparator of the intervention.  ***Q3.*** *Are there any subgroups for which tucatinib with trastuzumab would be expected to be more clinically and cost effective?*  No, we do not consider there to be any subgroups for which tucatinib in combination with trastuzumab would be expected to be more clinically and/or cost effective.  ***Q4.*** *Do you consider tucatinib with trastuzumab to be appropriate for people with RAS wild-type and BRAF 600 metastatic colorectal cancer?*  \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  HER2 is a known actionable target, so any patient with a HER2-postive colorectal cancer could receive benefit from tucatinib and trastuzumab. This includes patients with MSI high/MMR and BRAF/ RAS mutations. We would propose that tucatinib and trastuzumab is positioned after the current NICE approved therapies for these indications (MSI/MMR and BRAF).  \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*  ***Q5.*** *Which treatments do you consider to be the comparators of tucatinib with trastuzumab?*  We consider both regorafenib and trifluridine‑tipiracil as direct comparators of tucatinib in combination with trastuzumab. Both regorafenib ([8](#_ENREF_8)) and trifluridine‑tipiracil ([11](#_ENREF_11)) are NICE‑recommended available treatment options for patients with metastatic colorectal cancer who have received prior therapy and are positioned similarly to where tucatinib in combination with trastuzumab will be placed in the treatment pathway.  ***Q6.*** *Would tucatinib with trastuzumab be a candidate for managed access?*  We do not consider tucatinib in combination with trastuzumab to be a candidate for managed access.  ***Q7.*** *Do you consider that the use of tucatinib with trastuzumab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?*  Clinical expert opinion has indicated that the response rate seen for the tucatinib with trastuzumab combination in the MOUNTAINEER study will have a potential substantial effect on quality of life which is unlikely to be included in the QALY calculation.  ***Q8.*** *Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.*  Objective response rate was a primary outcome measure of the MOUNTAINEER study.  ***Q9.*** *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:*  ***a).*** *Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which tucatinib with trastuzumab will be licensed.*  No equity or equality issues have been identified following the availability and use of tucatinib in combination with trastuzumab in the proposed indication.  ***b).*** *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*  No equity or equality issues have been identified following the availability and use of tucatinib in combination with trastuzumab in the proposed indication.  **c*).*** *Could have any adverse impact on people with a particular disability or disabilities.*  No equity or equality issues have been identified following the availability and use of tucatinib in combination with trastuzumab in the proposed indication.  *Q10. Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.*  Not applicable as no equity or equality issues have been identified following the availability and use of tucatinib in combination with trastuzumab in the proposed indication. | Thank you for your comment. No further action is needed. |
| Bower cancer UK | Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. - Trial data. | Thank you for your comment. No further action needed. |
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| Additional comments on the draft scope |  |  |  |
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**The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope**

* Servier
* Roche