NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Trifluridine–tipiracil for treating metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma after 2 or more therapies

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using trifluridine–tipiracil in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

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Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using trifluridine–tipiracil in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 24 January 2020

Second appraisal committee meeting: To be confirmed

Details of membership of the appraisal committee are given in section 5.

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1 Recommendations

1.1 Trifluridine–tipiracil is not recommended, within its marketing authorisation, for treating metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma in adults who have had 2 or more systemic treatment regimens.

1.2 This recommendation is not intended to affect treatment with trifluridine–tipiracil that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Current treatment for metastatic gastric cancer and gastro-oesophageal junction cancer, for most people who have had 2 treatments, is best supportive care.

The clinical evidence suggests that people having trifluridine–tipiracil live longer compared with best supportive care. But the evidence also suggests that it is unlikely to extend how long people live by at least 3 months, particularly in the people who are most relevant to the NHS (the subgroup of people in Europe who have not had ramucirumab). This means trifluridine–tipiracil does not meet NICE's criterion to be considered a life-extending treatment at the end of life.

The most plausible cost-effectiveness estimate is much higher than what NICE normally considers an acceptable use of NHS resources. Therefore, trifluridine–tipiracil cannot be recommended for routine use in the NHS.

Further data collection is unlikely to change the cost-effectiveness estimates by much. Therefore, trifluridine–tipiracil cannot be recommended for use within the Cancer Drugs Fund.

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2 Information about trifluridine–tipiracil

Marketing authorisation indication

2.1 Trifluridine–tipiracil (Lonsurf, Servier) is indicated as 'monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least 2 prior systemic treatment regimens for advanced disease'.

Dosage in the marketing authorisation

2.2 The dosage is based on the patient's body surface area. The recommended starting dose of trifluridine–tipiracil in adults is 35 mg/m^2. It is taken orally, twice daily on days 1 to 5 and days 8 to 12 of each 28-day cycle, for as long as benefit is observed or until unacceptable toxicity occurs. The dosage must not exceed 80 mg per dose.

Price

2.3 The list price of trifluridine–tipiracil is £500 per pack of 20 tablets containing 15 mg of trifluridine and 6.14 mg of tipiracil, and £666.67 per pack of 20 tablets containing 20 mg of trifluridine and 8.19 mg of tipiracil (excluding VAT; BNF online, accessed December 2019).

The company has an existing commercial arrangement with the NHS. This makes trifluridine–tipiracil available to the NHS with a discount, which would have applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Servier, a review of this submission by the evidence review group (ERG), and the technical

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report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that no issues were resolved during the technical engagement stage. It discussed the following issues that were outstanding after the technical engagement stage:

- comparator
- generalisability of the TAGS trial
- extrapolation of overall survival
- end of life
- utility values.

Unless otherwise indicated, gastric cancer refers to both gastric cancer and gastro-oesophageal junction cancer.

Treatment pathway and comparator

There is an unmet need for third-line treatment options for gastric cancer

3.1 The initial symptoms of gastric cancer are vague and similar to other stomach conditions, but for advanced disease may include lack of appetite, weight loss, fluid in the abdomen and blood in the stool. The clinical experts estimated that life expectancy after 2 previous treatments is between 2 and 4 months in current practice. They explained that there is no standard therapy for previously treated metastatic gastric cancer but in clinical practice in the NHS in England, treatment is usually in line with the European Society for Medical Oncology (ESMO) guideline for gastric cancer. The clinical experts advised that paclitaxel is generally used after 1 treatment, and irinotecan may be used after 2 treatments but for most people it is not appropriate because of the risk of side effects. They estimated that third-line chemotherapy is used in about 10% of people, with most people having best supportive care alone. The committee was aware that the ESMO guideline had recently been updated to recommend trifluridine–tipiracil as a third-line treatment option for people with an

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Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1. The committee noted that there was no patient expert submission for this appraisal. But the clinical experts explained that maintaining health-related quality of life is very important to this population and an oral treatment such as trifluridine–tipiracil would help because it does not need many hospital visits, allowing people to spend more time at home. The committee concluded that there is an unmet need for third-line treatment options for gastric cancer.

The most appropriate comparator is best supportive care

3.2 The company submitted cost-effectiveness analyses comparing trifluridine–tipiracil and best supportive care against placebo and best supportive care. It advised that there is lack of evidence to support the use of third-line chemotherapy and that its expert advice suggested this is usually restricted to clinical trials. The committee recalled that third-line chemotherapy is appropriate but it is used in only a small proportion of people in current practice, with most people having best supportive care alone (see section 3.1). It noted that there were no cost-effectiveness analyses comparing trifluridine–tipiracil with third-line chemotherapy. The clinical experts explained that although there is no clear definition of best supportive care, it usually includes treatments to control symptoms such as pain. The committee concluded that the most appropriate comparator is best supportive care.

Clinical evidence

The TAGS trial's subgroup of people in Europe who have not had ramucirumab is the most relevant population for decision making

3.3 The clinical evidence for trifluridine–tipiracil came from TAGS, a phase III randomised controlled trial. It compared trifluridine–tipiracil and best supportive care against placebo and best supportive care in 507 adults with metastatic gastric cancer (including 29% with gastro-oesophageal junction cancer) who had had at least 2 treatments for advanced disease.

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The committee was aware of several issues that may impact the generalisability of the full intention-to-treat analysis from TAGS to the NHS in England:

- Of the full intention-to-treat population, 33% had had ramucirumab but this treatment is not available in the NHS in England (see NICE's technology appraisal guidance on ramucirumab for treating advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy). The clinical experts explained that the subgroup of people who had not had ramucirumab is more likely to represent the population in the NHS in England. But they advised that having ramucirumab is not likely to affect the relative treatment effect of trifluridine–tipiracil.
- Of the full intention-to-treat population, 14% were from Japan. Census data in England and Wales suggest about 1.5% of people are categorised as 'other Asian', which is likely to include people from Japan. The ERG explained that in TAGS, patients from Japan had a longer median overall survival compared with people from other parts of the world (see table 1). It suggested that possible reasons for this are biological factors and differences in the treatment pathway.
- There were 63% of the full intention-to-treat population who had 3 or more previous treatments. The clinical experts expected this to be less than 5% in clinical practice in England.
- All patients had an ECOG performance score of 0 or 1. The commissioning expert from NHS England advised that, if it were recommended, trifluridine–tipiracil would only be offered to people with an ECOG score of 0 or 1 in line with the trial data.

The company preferred to use data from a TAGS subgroup of people from Europe who had not had ramucirumab, because this is more generalisable to the treatment pathway and population in the NHS in England. The company highlighted that its preferred subgroup included fewer people from Japan and fewer people who had 3 or more previous

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treatments than the full intention-to-treat population (exact data is confidential and cannot be reported here). The committee recognised that the company's preferred subgroup may be more representative of the population in the NHS in England. However, it noted that this subgroup still included a higher proportion of people from Japan than would be expected in England, and that data from patients from Japan may be less generalisable to NHS practice. The committee understood that trifluridine–tipiracil improved overall survival compared with placebo and best supportive care in the full intention-to-treat population and all subgroup analyses (see table 1). The committee concluded that the TAGS subgroup of people from Europe who had not had ramucirumab was the most relevant to the NHS in England.

Table 1 Overall-survival results from TAGS

	Median overall survival (months, 95% confidence interval)		
TAGS population	**Trifluridine–tipiracil**	**Best supportive care**	**Hazard ratio (95% confidence interval)**
Intention-to-treat (n=507)	5.7 (4.8 to 6.2)	3.6 (3.1 to 4.1)	0.69 (0.56 to 0.85)
No previous ramucirumab (n=338)	6.0 (5.1 to 6.9)	3.3 (2.8 to 3.9)	0.66 (0.51 to 0.85)
Japan subgroup (n=73)	6.3	5.9	0.77 (0.46 to 1.30)
Europe and US subgroup (n=434)	5.4	3.3	0.68 (0.54 to 0.85)
Europe subgroup, post-hoc analyses (n=408)	Not reported	Not reported	0.67 (0.53 to 0.86)
No previous ramucirumab, Europe subgroup, post-hoc analyses (n=312)	Confidential and cannot be reported here		Not reported

Economic model

The company's economic model is suitable for decision making

3.4 The company included a partitioned survival cost-effectiveness model in its evidence submission. The model comprised 3 health states

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representing progression-free disease, progressed disease and death. Health-state occupancy over time was informed by survival curves from TAGS data. The ERG advised that the model was generally clear and appropriate. The committee concluded that the company's model was suitable for decision making.

Overall-survival extrapolation

The model should use overall-survival curves that are fitted independently to each trial arm

3.5 The company extrapolated overall survival in both treatment arms using an accelerated failure time model, which included a dependent variable to capture the effect of treatment. In its base-case analysis the company used a lognormal curve that was applied for the entire duration of the model. This approach assumes that the relative treatment effect is constant over time. The ERG explained that the Kaplan-Meier data from the intention-to-treat population and the committee's preferred population (the Europe subgroup who had not had ramucirumab) showed that the treatment curves crossed or almost converged. This indicates that the treatment effect was not constant over time. Because of this, the ERG preferred separate curves fitted independently to each treatment arm. It noted that this had little difference in statistical fit compared with the dependent models. The company maintained its preference for the dependent model in its base-case analysis but accepted that other approaches may also be valid. The committee concluded that the model should use survival curves fitted independently to each trial arm to extrapolate overall survival.

A full lognormal survival curve is the most plausible

3.6 The company used a lognormal curve to extrapolate overall survival for the entire duration of the model in its base-case analysis. The clinical experts predicted that 20% to 25% of people survive to 6 months in current practice, which reduces to 10% to 15% at 1 year. The committee

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noted exploratory analyses that modelled overall survival using the relatively mature Kaplan-Meier data for the first 12 or 18 months of the model, then applied a parametric curve to extrapolate beyond each timepoint. The ERG advised that using the Kaplan-Meier data was problematic because the timepoint when the observed data was replaced by the parametric curve was arbitrary. It was also necessary to use the available parametric curves, based on the full duration of trial data rather than the end portion alone, to extrapolate beyond each timepoint. The ERG explained that its preferred method for extrapolating the overall survival was a parametric model used for the entire time horizon. The committee concluded that a full lognormal curve was most plausible, and should be considered for decision making.

Utility values

The company's utility values mapped from TAGS EORTC QLQ-30 data are acceptable for decision-making

3.7 The company's base-case utility values were 0.764 for the progression-free health state and 0.652 for progressed disease. These values came from TAGS data on EORTC QLQ-C30. This is a disease-specific measure, mapped onto the generic EQ-5D-3L scale using an algorithm from a small Greek study that included people with non-metastatic gastric cancer. The committee was aware that at the clarification stage, the company did not provide cost-effectiveness results using alternative mapping studies from Versteegh et al. (2012) or Longworth et al. (2014). The company clarified that this was because neither study was in gastric cancer and 1 study did not use the UK value set. The committee noted that the company's preferred utility values were higher than those used in NICE's technology appraisal guidance on ramucirumab for treating advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy, particularly for progressed disease (0.652 compared with 0.587). The utility values in that appraisal were based on EQ-5D data from a trial (RAINBOW) and included people with

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metastatic disease after 1 previous treatment. The company did not consider those utility values appropriate because they did not account for correlation between utility scores for the same patient over time. The committee noted that the preferred utility values in the ramucirumab appraisal included data from multiple timepoints for the progression-free health state but not for progressed disease. The clinical experts advised that, in their opinion, the most appropriate data source would be the population from the TAGS trial who had at least 2 previous treatments and no previous ramucirumab and had good performance status. The committee concluded that the company's mapped utility values from TAGS were acceptable for decision making.

End of life

Trifluridine–tipiracil is not considered to be a life-extending treatment at the end of life

3.8 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The committee recalled the poor prognosis for people with gastric cancer who have had previous treatments (see section 3.1). The committee noted that using its preferred assumptions (see section 3.9) the mean survival in the best supportive care arm of the model was 6.5 months. Therefore it concluded that the short life expectancy criterion was met. The committee understood that the mean survival gain in the company's base case was 2.7 months, equivalent to a 44% increase compared with best supportive care. However, it noted that in its preferred analysis (see section 3.9) the overall survival gain from the model was only 1.7 months. This is equivalent to a 26% increase compared with best supportive care. The committee referred to the NICE methods guide and considered whether the extension-to-life criterion could be met with an overall survival gain of less than 3 months, given the mature survival data and the poor prognosis for people with metastatic gastric cancer. It was aware of 1 previous technology appraisal that

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applied the extension-to-life criterion despite an overall survival gain of 2.4 months, because the disease has a poor prognosis and the survival data were robust (see NICE's technology appraisal guidance on paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer). The clinical experts explained that an overall-survival benefit of 2 months is clinically meaningful, particularly if this could be achieved while maintaining good quality of life, because it would allow patients to benefit from a longer time free of worsening symptoms. The committee agreed that, in line with the NICE methods guide, the criterion requiring a 3-month survival gain should only be relaxed in exceptional circumstances, rather than routinely. The mean modelled survival gain for trifluridine–tipiracil using the committee's preferred analysis (1.7 months) was lower than the gain in the paclitaxel appraisal, and considerably lower than 3 months. Based on the evidence presented, the committee was not convinced that trifluridine–tipiracil provided an adequate survival benefit. It concluded that trifluridine–tipiracil did not meet the extension-to-life criterion, and therefore could not be considered a life-extending treatment at the end of life.

Cost-effectiveness estimate

The most plausible incremental cost-effectiveness ratio (ICER) is substantially higher than £30,000 per quality-adjusted life year (QALY) gained

3.9 The company's base-case ICER for trifluridine–tipiracil compared with best supportive care was £45,164 per QALY gained, including the commercial discount for trifluridine–tipiracil. The committee noted that the company's cost-effectiveness estimates for its probabilistic sensitivity analysis showed a wide range of incremental QALYs (and ICERs). The company's cost-effectiveness acceptability curve suggested that the probability of trifluridine–tipiracil being cost effective at a threshold of £50,000 per QALY gained was 64%. However, this did not include all of the committee's preferred assumptions, which were:

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- using data from the TAGS European subgroup of people who had not had ramucirumab (see section 3.3)
- fitting curves independently to each trial arm to model overall survival (see section 3.5)
- using a lognormal curve for overall survival (see section 3.6)
- using the company's utility values mapped from TAGS (see section 3.7).

The committee understood that after taking into account all of its preferred assumptions, the most plausible ICER was £68,061 per QALY gained. It understood that using data for the full intention-to-treat population rather than the European subgroup and using survival curves with a dependent variable for the treatment effect reduced the ICER. However, it noted that the resulting ICERs were still much higher than £30,000 per QALY gained. The committee also understood that using utility values from ramucirumab and using the observed survival data to model the first 12 or 18 months of survival increased the ICER.

Trifluridine–tipiracil could not be recommended for routine use in the NHS

3.10 The committee concluded that all ICERs, including the most plausible ICER based on its preferred assumptions, were substantially higher than £30,000 per QALY gained. Therefore, trifluridine–tipiracil could not be recommended for routine use in the NHS.

Cancer Drugs Fund

Trifluridine–tipiracil does not meet the criteria to be considered for inclusion in the Cancer Drugs Fund

3.11 Having concluded that trifluridine–tipiracil could not be recommended for routine use, the committee then considered whether it could be recommended for treating gastric cancer within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund

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agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum).

- The company had not expressed an interest in the treatment being considered for funding through the Cancer Drugs Fund.
- The most plausible ICER, including all the committee's preferred assumptions, was £68,061 per QALY gained. The committee considered that this was substantially higher than £30,000 per QALY gained, therefore there was no plausible potential to satisfy the criteria for routine use.
- The key uncertainty relates to the extrapolation of overall survival. However the overall-survival data from TAGS are relatively mature, therefore further data collection is unlikely to change the cost-effectiveness results.

The committee concluded that trifluridine–tipiracil does not meet the criteria to be considered for inclusion in the Cancer Drugs Fund.

Innovation

Trifluridine–tipiracil is not innovative and all benefits are captured in the model

3.12 The committee recalled the poor prognosis for people with metastatic gastric cancer and that there is an unmet need for third-line treatment options (see section 3.1). The committee understood that the company considered trifluridine–tipiracil to be innovative because it provides an alternative oral treatment option that increases overall survival. It also noted that the utility values in the company's analysis did not include the health-related quality of life of carers of people with gastric cancer. The committee recalled that trifluridine–tipiracil was clinically effective compared with best supportive care (see section 3.3), but noted that it had not seen evidence of additional benefits that were not captured in the model. It concluded that trifluridine–tipiracil is not innovative, and all relevant benefits had been captured in the cost-effectiveness estimates.

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Equalities considerations

There are no equalities issues relevant to the recommendation

3.13 The committee understood that no equalities issues were raised during scoping and technical engagement. It also noted that no potential equality issues were identified in the company submission. The committee concluded there were no equalities issues relevant to the recommendation.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Selby
Chair, appraisal committee
December 2019

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

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The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Abitha Senthinathan
Technical lead

Jamie Elvidge
Technical adviser

Louise Jafferally
Project manager

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