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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.
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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. 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 is not recommended for routine use in the NHS.

Further data collection is unlikely to change the cost-effectiveness estimate because the trial follow up is almost finished. Therefore, trifluridine–tipiracil is not recommended for use within the Cancer Drugs Fund.
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 schedule is available in the summary of product characteristics.

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 November 2020).

2.4 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 considered evidence submitted by Servier, a review of this submission by the evidence review group (ERG), and the technical 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, they 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 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 people with metastatic gastric cancer. They advised that an oral treatment such as trifluridine–tipiracil would be preferred 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 with placebo and best supportive care. It advised that there is a 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 is used in only a small proportion of people in current practice, with most people having best supportive care alone (see section 3.1). 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 third-line, European subgroup data from TAGS is acceptable for decision making

3.3 The clinical evidence for trifluridine–tipiracil came from TAGS, a phase 3 randomised controlled trial. It compared trifluridine–tipiracil and best supportive care with 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, and who had an ECOG performance score of 0 or 1. 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 previous 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 the TAGS trial, patients from Japan had a longer median overall survival (6.3 months for trifluridine–tipiracil and 5.9 months for best supportive care) compared with people from other parts of the world (median overall survival 5.4 months for trifluridine–tipiracil and 3.3 months for best supportive care). 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 had 3 or more previous treatments. The clinical experts expected this to be less than 5% in clinical practice in England.

In its original submission, the company used data from a subgroup of people from TAGS who had not had ramucirumab. The company highlighted that this subgroup included fewer people from Japan and fewer people who had 3 or more previous treatments than the full intention-to-treat population (the exact data are confidential and cannot be reported here). The committee noted that this subgroup still included a higher proportion of people from Japan than would be expected in England, which may make it less generalisable to NHS practice. In response to consultation, the company provided analyses using TAGS subgroup data from people who had had exactly 2 previous treatments (the third-line subgroup). The company stated that this subgroup represented most people who would have trifluridine–tipiracil in clinical practice. One analysis included data for people from all trial locations, while the other restricted the data to only include people who lived in Europe. The committee agreed that the data restricted to people who lived in Europe were likely to be generalisable to NHS practice. These data still provide a large enough sample size for robust analysis. It concluded that the third-line, European subgroup data from TAGS was acceptable for decision making.

The committee's requested propensity score analysis to correct for imbalanced characteristics in TAGS is suitable for decision making

3.4 The ERG advised that the committee's preferred third-line, European subgroup (see section 3.3) had imbalances in patient characteristics between the 2 arms of the TAGS trial. Some of these could favour survival after treatment with
trifluridine–tipiracil and some could favour survival after treatment with placebo (the exact numbers are confidential and cannot be reported here). The company accepted that any subgroup analysis may be at risk of imbalances in characteristics, but it felt there were no imbalances in verified prognostic factors in this analysis. After the second meeting, the committee requested additional analyses to adjust the third-line data for imbalances in:

- peritoneal metastases
- ECOG performance status
- intestinal or non-intestinal histology
- previous treatment with irinotecan and
- region (not included in the Europe-only analysis).

The ERG found the company's propensity score-based analyses reasonable, but noted that some uncertainty remained. This was because it was not clear whether all relevant characteristics had been included in the model. The committee understood that trifluridine–tipiracil improved overall survival compared with placebo and best supportive care in all unadjusted analyses. The company's adjusted analyses showed similar overall survival results (the exact data are confidential and cannot be reported here). The company explained that this was because of the small sample size and the 5 selected characteristics having opposing effects. The committee agreed that the company's rationale was acceptable, but there was still some uncertainty about whether all relevant factors were included in the analysis. However, the committee concluded that the adjusted analysis was acceptable, and took the uncertainty into account in its decision making.

**Economic model**

**The company's economic model is suitable for decision making**

3.5 The company included a partitioned survival cost-effectiveness model in its evidence submission. The model comprised 3 health states representing progression-free disease, progressed disease and death. Health-state occupancy over time was informed by survival functions 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.
Adverse events

Neutropenia may impact health-related quality of life

3.6 In TAGS, the most common side effects included nausea, anaemia, decreased appetite, vomiting, diarrhoea, fatigue, neutropenia, asthenia and thrombocytopenia. Anaemia was considerably more common in the trifluridine–tipiracil group than the placebo group (45% compared with 19%). Neutropenia was also more common (53% compared with 4%). The company included adverse events such as neutropenia in the model to capture their effect on health-related quality of life. The committee noted that in the summary of product characteristics for trifluridine–tipiracil, neutropenia was 1 of the most common side effects that led to treatment being stopped, delayed or interrupted. It concluded that neutropenia may affect health-related quality of life.

Overall survival extrapolation

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

3.7 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. This approach assumes that the relative treatment effect is constant over time. In its base-case analysis, the company used a log-normal function that was applied for the entire duration of the model. The ERG explained that the Kaplan–Meier estimates from the intention-to-treat population, new analyses at consultation and analyses in the committee’s preferred population (the third-line, European subgroup) all showed that trifluridine–tipiracil survival either crossed or almost converged with best supportive care survival. This indicates that the treatment effect was not constant over time. The committee heard that because of this, the ERG preferred separate functions that were fitted independently to each treatment arm. 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 functions fitted independently to each trial arm to extrapolate overall survival.
A full log-normal survival function is the most plausible

3.8 The company used a log-normal function 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 noted exploratory analyses that modelled overall survival using the relatively mature Kaplan–Meier estimates for the first 12 or 18 months of the model, then applied a parametric function to extrapolate beyond each timepoint. The ERG advised that using the Kaplan–Meier estimates was problematic because the timepoint when the observed data was replaced by the parametric function was arbitrary. Also, the available parametric functions had been estimated using the full duration of trial data rather than the end portion. The committee noted that the ERG's preferred method for extrapolating the overall survival was a parametric model used for the entire time horizon. It concluded that a full log-normal function was most plausible, and should be considered for decision making.

Trifluridine–tipiracil treatment duration

The company's generalised gamma function is acceptable, but the Kaplan–Meier analysis is also plausible

3.9 The company's revised base-case analysis, using the committee's preferred approach (see section 3.4), used a generalised gamma function to model treatment duration, fitted to the adjusted TAGS third-line European subgroup. The committee noted that the Kaplan–Meier estimates showed that no patients were having trifluridine–tipiracil at 1 year. At the third meeting, the company confirmed that there were no other data on treatment duration for this population with metastatic gastric cancer. It also clarified that in the full TAGS population, the maximum time on trifluridine–tipiracil was around 1.2 years, indicating that very few people would be expected to remain on treatment for a long time. The ERG explained that it preferred to use an extrapolated function, rather than the Kaplan–Meier estimates, to better reflect uncertainty in the data. This is because in clinical practice, there may be a small number of people who do stay on treatment for a long time, but this was not reflected in the Kaplan–Meier estimates. The ERG advised that the generalised gamma function was reasonable, but other parametric functions could not be ruled out based on their statistical fit to the data, including some that predicted more people having...
long-term treatment. The committee agreed that people are unlikely to remain on treatment with trifluridine–tipiracil for very long, and so functions with long tails were not appropriate. It agreed that the generalised gamma function was acceptable for decision making, but noted that using the Kaplan–Meier estimates may also be plausible.

Utility values

The company’s utility values mapped from TAGS EORTC QLQ-C30 data are acceptable for decision making

3.10 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), as requested by the ERG. The company clarified that this was because neither study was in gastric cancer and Versteegh et al. (2012) 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, 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 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, no previous treatment with ramucirumab and had good performance status. The committee concluded that the company’s mapped utility values from TAGS were acceptable for decision making.
Carer quality-of-life improvement should not be captured in the model

3.11 At consultation, the company highlighted a Turkish study of 72 patients with gastric cancer and 72 caregivers. This reported improvement in the carers' quality of life after a nursing care intervention. The company noted that the benefit for carers and families from delaying disease progression with trifluridine–tipiracil was not captured in its model. However, the committee concluded that there was no evidence that the quality-of-life gain would be significant and so carer quality-of-life improvement should not be considered in the model.

End of life

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

3.12 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 3.13), 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 revised base-case analysis (third line, all regions) was 2.9 months, equivalent to a 44% increase compared with best supportive care. It noted that in its preferred analysis (see section 3.4), the overall survival gain from the model was 2.7 months, equivalent to a 41% 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 applied the extension-to-life criterion despite an overall survival gain of 2.4 months (40%), 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 committee considered that the evidence base for each
appraisal is different and that it was not bound by how the NICE methods guide was interpreted for a separate appraisal. It also noted that there were other technology appraisals when the end of life criteria were not accepted because of a life extension of less than 3 months, even though the short life expectancy criterion was met (see NICE’s technology appraisal guidance on cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel, azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts and necitumumab for untreated advanced or metastatic squamous non-small-cell lung 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. However, 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. It noted that adverse events, such as grade 3 or 4 neutropenia, were common side effects from treatment with trifluridine–tipiracil (see section 3.6). These could have a negative effect on the quality of life of a person with metastatic gastric cancer. 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 estimates

The most plausible ICER is substantially higher than £30,000 per QALY gained

3.13 The company’s revised base-case incremental cost-effectiveness ratio (ICER) for trifluridine–tipiracil compared with best supportive care for the third-line, all regions subgroup, was £45,662 per quality-adjusted life year (QALY) gained, including the commercial discount for trifluridine–tipiracil. The company’s revised base case included data from people in all regions of the TAGS trial, whereas the committee preferred to consider adjusted analyses on the European subgroup (see sections 3.3 and 3.4). It also considered the Kaplan–Meier estimates for treatment duration to be plausible (see section 3.9). The committee noted that in its preferred analyses, the most plausible ICER was £49,771 per QALY gained. This analysis used the generalised gamma function to
model trifluridine–tipiracil treatment duration (see section 3.9). The ICER remained much higher than £30,000 per QALY gained when using the Kaplan–Meier estimates to model treatment duration for trifluridine–tipiracil. The committee concluded that cost-effectiveness results from all plausible scenario analyses were much higher than £30,000 per QALY gained.

**Trifluridine–tipiracil is not recommended for routine use in the NHS**

3.14 Trifluridine–tipiracil was not considered a life-extending treatment at the end of life (section 3.12). Therefore, the relevant decision-making threshold was £20,000 to £30,000 per QALY gained. 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**

3.15 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 agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The most plausible ICER, including all the committee's preferred assumptions, was substantially higher than £30,000 per QALY gained. The key uncertainty related to the expected life extension with trifluridine–tipiracil. Overall survival data from the committee's preferred TAGS subgroup (see section 3.3) were very mature, and the company advised that no further data collection is planned in that population. Therefore, there was no scenario with plausible potential to satisfy the criteria for routine use, and there is unlikely to be additional evidence that would affect this conclusion. The committee concluded that trifluridine–tipiracil did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund.
Innovation

All relevant benefits are captured in the model

3.16 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 company considered trifluridine–tipiracil to be innovative because it provides an alternative oral treatment option that increases overall survival. The committee recalled that trifluridine–tipiracil was clinically effective compared with best supportive care (see section 3.3), but it had not seen evidence of additional benefits that were not captured in the model. It concluded that all relevant benefits had been captured in the cost-effectiveness estimates.

Equalities considerations

There are no equalities issues relevant to the recommendation

3.17 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 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.

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 and Emma Douch
Technical leads

Jamie Elvidge and Sally Doss
Technical advisers

Louise Jafferally
Project manager

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Accreditation

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