NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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www.nice.org.uk/guidance/ta852

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 is 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.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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.

Contents

This guidance replaces TA669.

1 Recommendations

1.1 Trifluridine–tipiracil is recommended, within its marketing authorisation, as an option for treating metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma in adults who have had 2 or more treatment regimens. It is only recommended if the company provides trifluridine–tipiracil according to the commercial arrangement.

Why the committee made these recommendations

This evaluation uses new cost-effectiveness estimates to update trifluridine–tipiracil for treating metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma after 2 or more therapies (NICE technology appraisal guidance TA669). No new clinical evidence was reviewed.

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

The clinical evidence suggests that people having trifluridine–tipiracil live longer compared with best supportive care. When taking into account the severity of the condition and its effect on quality and length of life, the most likely cost-effectiveness estimate is within the range that NICE normally considers an acceptable use of NHS resources. So, trifluridine–tipiracil is recommended.

2 Information about trifluridine–tipiracil

Marketing authorisation indication

2.1 Trifluridine–tipiracil (Lonsurf, Servier) is indicated for '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 for trifluridine–tipiracil.

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 October 2022).

2.4 The company has a commercial arrangement. This makes trifluridine–tipiracil available to the NHS with a discount. 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 evaluation committee considered evidence submitted by Servier, a review of this submission by the external assessment group (EAG) and responses from stakeholders for the original appraisal. New cost-effectiveness estimates were submitted by Servier and considered for this update of NICE's technology appraisal guidance on trifluridine–tipiracil for treating metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma after 2 or more therapies (TA669). See the committee papers for full details of the evidence.

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

Clinical management

Treatment options

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 treatment 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.

Comparators

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 effectiveness

Clinical trial evidence and generalisability

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 EAG explained that in TAGS, 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.

Propensity score analysis

3.4 The EAG 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 EAG 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

Company's modelling approach

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 EAG 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

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 one 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

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 EAG 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 EAG 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.

Full log-normal survival function

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 EAG 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 EAG'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

Generalised gamma and Kaplan–Meier analysis

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 EAG 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 EAG 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

Source of utility values

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 EAG. 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

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.

Severity modifier

Highest QALY weighting

3.12 For this update, the company provided evidence that metastatic gastric cancer after 2 or more treatments is a severe condition. The severity modifier allows the committee to give more weight to health benefits in the most severe conditions. The company provided absolute and proportional quality-adjusted life year (QALY) shortfall estimates in line with NICE's health technology evaluations manual. Absolute QALY shortfall is the future health that is lost by people living with a condition, including quality and length of life, compared with the expected future health of people without the condition over their remaining lifetime. Proportional QALY shortfall represents the proportion of future health that is lost by people living with the condition, including quality and length of life. The company provided evidence for the committee's preferred population, the third-line European subgroup from the TAGS trial (see section 3.3). This population had a mean age of 62 and was 33.3% female. People with these characteristics without metastatic gastric cancer after 2 or more treatments would be expected to gain 11.69 QALYs. The company's model estimated that people with metastatic gastric cancer after 2 or more treatments who have best supportive care would be expected to gain 0.37 QALYs. The company used these estimates to calculate an absolute QALY shortfall of 11.3 and a proportional QALY shortfall of 0.97. The committee considered the advice about severity as a decision modifier, which allows it to apply a greater weight to the QALYs for technologies indicated for conditions with a high degree of severity. It noted that if either the absolute or the proportional QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply. The company stated that although the absolute QALY shortfall was less than 12, which would imply no QALY weight, the proportional QALY shortfall of 0.97 implies the highest QALY weight of 1.7. The EAG confirmed that the company's analyses had been implemented correctly and supported the use of the 1.7 QALY weight. The committee noted that uncertainty around inputs had not been fully explored. But it recognised that uncertainty had been explored in the original appraisal and that the new analyses were based on its preferred assumptions. So, the committee concluded that the

highest severity weight of 1.7 applied to the QALYs was appropriate.

Cost-effectiveness estimates

Company cost-effectiveness estimates

3.13 The company's updated incremental cost-effectiveness ratio (ICER) for trifluridine–tipiracil compared with best supportive care for the third-line European subgroup was £29,347 per QALY gained, including the confidential commercial discount for trifluridine–tipiracil and a 1.7 QALY severity weight (see section 3.12). The committee noted that this analysis was based on its preferred assumptions, including the third-line European subgroup and the generalised gamma function for extrapolating trifluridine–tipiracil treatment duration. The committee concluded that the most plausible cost-effectiveness result was less than £30,000 per QALY gained.

Recommended for routine use

3.14 The committee considered that the acceptable decision-making threshold was £20,000 to £30,000 per QALY gained. The committee concluded that the most plausible ICER based on its preferred assumptions, was less than £30,000 per QALY gained. Therefore, trifluridine–tipiracil is recommended for routine use in the NHS.

Other factors

Innovation

3.15 The committee recalled the poor prognosis for people with metastatic gastric cancer and that there is an unmet need for treatment options after 2 or more treatments (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.

Equality issues

3.16 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 that no equalities issues were identified relevant to the recommendation.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma after 2 or more treatments and the doctor responsible for their care thinks that trifluridine–tipiracil is the right treatment, it should be available for use, in line with NICE's

recommendations.

5 Evaluation committee members and NICE project team

Evaluation 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 evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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

Chair

Stephen O'Brien
Chair, Technology appraisal evaluation committee C

NICE project team

Each evaluation 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.

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