NICE National Institute for Health and Care Excellence

NICE guidance

Trifluridine–tipiracil for previously treated metastatic colorectal cancer

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 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

1 Recommendations

1.1 Trifluridine–tipiracil is recommended, within its marketing authorisation, as an option for treating metastatic colorectal cancer, that is:

- in adults who have had previous treatment with available therapies including fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, anti-vascular endothelial growth factor (VEGF) agents and anti-epidermal growth factor receptor (EGFR) agents, or when these therapies are not suitable **and**
- only when the company provides trifluridine–tipiracil with the discount agreed in the patient access scheme.

2 Information on trifluridine–tipiracil

Description of the technology

2.1 Trifluridine–tipiracil (Lonsurf, Servier Laboratories) combines 2 drugs: a nucleoside analogue (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil). Trifluridine is taken into the DNA of tumour cells and inhibits tumour growth. Tipiracil slows the breakdown of trifluridine to prolong this action.

Marketing authorisation

2.2 Trifluridine–tipiracil has a marketing authorisation for the 'treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF [anti-vascular endothelial growth factor] agents, and anti-EGFR [anti-epidermal growth factor receptor] agents.'

Adverse reactions

2.3 The most frequently seen adverse drug reactions are neutropenia, nausea, fatigue, anaemia and leukopenia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

Recommended dose and schedule

2.4 The recommended starting dose of trifluridine–tipiracil in adults is 35 mg/m^2/dose administered orally twice daily on days 1 to 5 and days 8 to 12 of each 28-day cycle for as long as there is a benefit or until there is unacceptable toxicity. Each dose must not exceed 80 mg.

Price

2.5 The list price of a 20-tablet pack of 15 mg trifluridine–tipiracil is £500, and that of 20 mg trifluridine–tipiracil is £667. Each dose is also available in 60-tablet packs at pro rata prices.

2.6 The average cost per patient per cycle of treatment is estimated at £2,032 based on the list price.

2.7 The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of trifluridine–tipiracil, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee considered evidence submitted by Servier Laboratories and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of trifluridine–tipiracil, having considered evidence on the nature of metastatic colorectal cancer and the value placed on the benefits of trifluridine–tipiracil by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Patients' perspective

4.1 The patient experts stated that, after multiple lines of treatment, metastatic colorectal cancer is more likely to be resistant to other drugs. Therefore, another treatment option, especially one that is taken orally and offers some survival benefit, gives people hope. The committee recognised that patients value options in treatment, and that trifluridine–tipiracil would be welcomed by patients and their families.

Position in the treatment pathway

4.2 The committee noted that NICE's previous guideline on colorectal cancer (CG131) recommended FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) or XELOX (capecitabine plus oxaliplatin) as first-line treatments, and single-agent irinotecan or FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatments (single-agent irinotecan is recommended only after FOLFOX). The committee was aware that there is no positive NICE guidance on third- or subsequent-line treatments.

4.3 The committee noted that trifluridine–tipiracil has a marketing authorisation for 'adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF [anti-vascular endothelial growth factor] agents, and anti-EGFR [anti-epidermal growth factor receptor] agents'. It understood that the company proposed that trifluridine–tipiracil would be used as a third- or subsequent-line treatment. The

clinical experts agreed that this was the point at which they would mainly offer trifluridine–tipiracil. The committee discussed the meaning of 'not considered candidates for available therapies', noting that there was no evidence from clinical trials for this population. It heard from the clinical experts that this refers to people who, in clinical practice, would not be considered fit enough to have the therapies recommended by NICE first and second line. However, the committee understood that this is a very small group. The clinical experts noted that trifluridine–tipiracil was available in some centres in the UK as part of a 'named patient programme'. In this, over 95% of people had had 2 or more therapies before having trifluridine–tipiracil. The committee agreed that, in clinical practice, trifluridine–tipiracil would mainly be used in people who have previously had 2 or more therapies when there are no further treatment options.

Clinical effectiveness

4.4 The committee considered the 2 clinical trials presented by the company; Yoshino et al. (2012), and RECOURSE. Both trials were double-blind randomised controlled trials comparing trifluridine–tipiracil with placebo in adults with metastatic colorectal cancer who had had 2 or more regimens of standard chemotherapy, and in whom fluoropyrimidine, irinotecan and oxaliplatin had stopped working or were unsuitable. The primary endpoint was overall survival in both trials. The committee agreed that both trials were relevant to the decision problem and suitable for assessing the clinical effectiveness of trifluridine–tipiracil.

Generalisability of trial results

4.5 The committee was aware that both trials provided evidence for people who had previously had 2 or more therapies, but not for those in whom available therapies were not suitable. The committee recalled that only a few people would not be considered fit enough to have the therapies recommended by NICE first and second line (see section 4.3). Furthermore, it heard from the clinical experts that trifluridine–tipiracil was unlikely to replace those therapies. The committee agreed that the evidence could be generalised to people in whom available therapies are not suitable.

4.6 The committee was aware that in RECOURSE, but not in Yoshino et al. (2012), patients must have had bevacizumab before enrolling in the trial; patients with KRAS wild-type tumours also must have had cetuximab or panitumumab. The committee noted that none of these therapies were recommended by NICE, or funded by the Cancer Drugs Fund, for previously treated metastatic colorectal cancer. Therefore, people in England are unlikely to have had bevacizumab, cetuximab or panitumumab before trifluridine–tipiracil. The company considered that there was no biological reason for the effect of trifluridine–tipiracil to differ in people who do or do not have biological therapies. The committee noted that 22% of patients in Yoshino et al. did not have bevacizumab. In this group, the hazard ratio for overall survival was 0.37 (95% confidence interval [CI] 0.16 to 0.86) compared with 0.63 (95% CI 0.42 to 0.95) in those who did have bevacizumab; there was no statistically significant interaction between the 2 groups. However, the committee considered these results were inconclusive because it was unclear whether previous treatments had differed between the 2 groups in a way that affected survival outcomes. The committee heard from the clinical experts that effectiveness would be expected to diminish with each additional line of treatment. In addition, the clinical experts questioned whether bevacizumab increases survival; therefore, the long-term benefit of previous bevacizumab treatment was unclear. The committee concluded that trifluridine–tipiracil would be similarly effective in people who have or have not had bevacizumab, and that the results of the trials were generalisable to NHS patients in England who have not had bevacizumab.

Meta-analysis of trials

4.7 The committee considered the company's meta-analysis of Yoshino et al. (2012) and RECOURSE, noting that the company 'naively' pooled the efficacy data from the 2 trials. The committee heard from the ERG that the trials had similar designs, and that patients in both trials had similar disease characteristics at baseline. Also, the pooled results mirrored the individual trials. During the committee meeting, the company confirmed that the results were almost the same whether the meta-analysis was or was not stratified (adjusted) by trial. The committee noted the ERG's comments in the meeting that the naive pooling of data was unlikely to be biased. Given the similarity between the 2 trials and the consistency between the results, the committee concluded that the company's

original meta-analysis provided valid results.

Results

4.8 The committee discussed the results of the trials, noting that the survival data were 'mature'; that is most patients had died by the end of the follow-up period (Yoshino et al.; 72.8%; RECOURSE: 89.0%). Compared with placebo, trifluridine–tipiracil increased median overall survival by 2.4 months in Yoshino et al. (2012) and by 2.0 months in RECOURSE. The company's meta-analysis of Yoshino et al. and RECOURSE showed that trifluridine–tipiracil led to a statistically significant increase in overall survival (hazard ratio [HR] 0.67, 95% CI 0.58 to 0.78) and progression-free survival (HR 0.46, 95% CI 0.40 to 0.53). The committee heard from the clinical and patient experts that, for an end-of-line treatment, even small extensions to life are important. Also, people at this stage of the disease would be unlikely to tolerate treatments with severe adverse effects. According to the experts, trifluridine–tipiracil offers the advantage of being an oral treatment with minimal adverse effects. The committee concluded that the survival benefit of trifluridine–tipiracil, although relatively small, was clinically meaningful.

Adverse events

4.9 The committee noted that, in clinical trials, trifluridine–tipiracil was associated with a higher incidence of adverse events than placebo (Yoshino et al.; 96.5% compared with 70.2%; RECOURSE: 85.7% compared with 54.7%). It heard that patients considered the safety profile of trifluridine–tipiracil to be acceptable. The clinical experts also stated that trifluridine–tipiracil was well tolerated by people who took part in the named patient programme, and caused less fatigue than regorafenib (whose NICE technology appraisal was terminated), which may also be used at the same stage in the treatment pathway as trifluridine–tipiracil. The committee concluded that trifluridine–tipiracil had an acceptable burden of adverse events.

Cost effectiveness

Survival modelling

4.10 To model overall survival and progression-free survival, the company fitted independent models for each treatment group (trifluridine–tipiracil or placebo); in this method, the treatment effects do not need to meet the proportional hazards assumption. The ERG, however, preferred a single model with a covariate (predictor) for the treatment group because it noted that the log-cumulative hazard plots for overall survival and for progression-free survival indicated that the proportional hazards assumption would hold. The committee was aware that the pooled data for overall survival and progression-free survival were very mature (86% and 89% respectively). This meant that the choice of the model was unlikely to influence the results greatly; when the ERG chose a different model, this had a negligible impact on the incremental cost-effectiveness ratio (ICER). Moreover, the committee did not consider the log-cumulative hazard plots for progression-free survival to strongly indicate that the proportional hazards assumption would hold. Because of this, the committee concluded that modelling each treatment group independently was reasonable and more appropriate than including the treatment group as a predictor in the model.

Body surface area

4.11 The committee was aware that the dose of trifluridine–tipiracil, and hence its cost, is based on body surface area. To model the dose that people would receive, the company estimated the distribution of body surface area from patients in RECOURSE. It grouped patients based on their body surface area, then fitted the log-normal distribution to these data. The ERG considered that using the actual (observed) data on body surface area from RECOURSE was more reasonable. The committee noted that the average body surface area in RECOURSE was 1.78 m^2, which was lower than the average body surface area among the UK general population. The committee did not consider that a value from the general population was a relevant comparison because people with advanced colorectal cancer would likely be smaller than the general population, as confirmed by the clinical experts. The committee recognised that the

modelling of body surface area should minimally influence the cost of treatment because trifluridine–tipiracil is taken orally and patients are grouped into dosing groups. This means that patients with slightly different body surface areas may be in the same dosing group and have the same dose. The committee did not consider there was a need to use parametric methods (notably, a reason to extrapolate) to estimate body surface area, preferring to use the data from the trial for decision making.

Health-related quality of life

4.12 The committee noted that neither the clinical trials (Yoshino et al. [2012] and RECOURSE) nor the named patient programme provided data on health-related quality of life. To estimate health-related quality of life in the model, the company averaged utility values from the CORRECT trial, which evaluated regorafenib for previously treated metastatic colorectal cancer, and the evidence submission for NICE's previous technology appraisal guidance on cetuximab for the first-line treatment of metastatic colorectal cancer (TA176). The committee understood that the company considered these 2 sources reflected utility values at both ends of the range. The ERG was concerned about using the submission for NICE's technology appraisal guidance on cetuximab to source utility values because the pre-progression utility value from that submission was derived using the Health Utilities Index Mark 3 instrument, which was not in line with the NICE reference case, and it was not ultimately used in the model for that appraisal. Furthermore, the post-progression utility value was derived from people with KRAS wild-type metastatic colorectal cancer that was refractory to chemotherapy, and the ERG could not verify its original source. Because of this, the ERG preferred using CORRECT only to source utility values. The committee heard from the clinical experts that the population in CORRECT reasonably reflected people who would have trifluridine–tipiracil. The committee concluded that, to apply utility values, using the average value from 2 sources is methodologically worse than using data collected from clinical trials, or than using CORRECT alone.

Cost-effectiveness results

4.13 The committee considered the cost-effectiveness results including the patient

access scheme discount. It noted that the deterministic ICER from the company's base case revised in response to a request for clarification from the ERG was £42,674 per quality-adjusted life year (QALY) gained for trifluridine–tipiracil compared with best supportive care. The ERG estimated a probabilistic ICER of £52,695 per QALY gained based on clinical data from RECOURSE only, but also presented an ICER based on the pooled dataset, which was £49,392 per QALY gained. The committee was aware that the ERG's ICER of £49,392 per QALY gained used the utility values from CORRECT (see section 4.12), and the data on body surface area seen in RECOURSE (see section 4.11), both of which it preferred. This ICER, however, did not reflect the use of independent models for each treatment group to model survival, but the committee recalled that this modification individually had a negligible impact on the ICER (see section 4.10). Therefore, the committee concluded that the ERG's ICER of £49,392 per QALY gained most closely mirrored its preferred analysis.

End-of-life considerations

4.14 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods.

4.15 The committee discussed whether trifluridine–tipiracil is indicated for patients with a short life expectancy, normally less than 24 months. It agreed that the best estimate of expected survival using current standard of care was observed in the control group of the trials. In RECOURSE, the median overall survival in the placebo group was 5.2 months. The mean overall survival estimated by the company's model for people who had placebo was 7.9 months using the pooled dataset including patients from Yoshino et al. (2012) and RECOURSE. The committee concluded that trifluridine–tipiracil for third- or subsequent-line treatment of metastatic colorectal cancer meets the criterion for short life expectancy.

4.16 The committee considered the survival benefit of trifluridine–tipiracil in the context of the end-of-life criteria:

- It noted that the ERG's modified base case, using pooled data from Yoshino

et al. (2012) and RECOURSE, estimated that trifluridine–tipiracil would extend mean overall survival by 3.2 months compared with best supportive care; this estimate was based on extrapolating survival beyond the follow-up period and up to the end of the time horizon. The committee recognised that the modelled estimate of 3.2 months was based on mature data in the trials, suggesting that this estimate was fairly robust.

- The ERG highlighted the difference in restricted mean overall survival of 2.4 months, which was based on the conservative and unrealistic assumption that all remaining patients died just after the trial ended.

- The committee recognised that people in clinical practice may derive a greater survival advantage than patients in the trials because they will not have had all the therapies that the trial patients would have had, although it was aware that there were no conclusive data on this (see section 4.5).

The committee considered that it should view the survival benefit with trifluridine–tipiracil in the context of the life expectancy of this population. It agreed that potentially adding an average of 3.2 months to a particularly short life expectancy of 7.9 months would represent a clinically meaningful benefit. The committee appreciated that trifluridine–tipiracil represents a well-tolerated treatment that would help extend life by even a relatively short time, while maintaining a reasonably good quality of life at a late stage in the treatment pathway when there are no further options left. The committee concluded that trifluridine–tipiracil, as a third- or subsequent-line treatment for metastatic colorectal cancer, met the criterion for extending life.

4.17 Having concluded that trifluridine–tipiracil meets the end-of-life criteria for the third-line treatment of metastatic colorectal cancer, and that the most plausible ICER was £49,392 per QALY gained, the committee concluded that it could recommend trifluridine–tipiracil as a cost-effective use of NHS resources for adults who have had previous treatment with available therapies including fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, anti-vascular endothelial growth factor (VEGF) agents and anti-epidermal growth factor receptor (EGFR) agents, or when these therapies are not suitable, and only when the company provides trifluridine–tipiracil with the discount agreed in the patient access scheme.

Pharmaceutical Price Regulation Scheme 2014

4.18 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014 and, in particular, the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

5 Implementation

5.1 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 appraisal within 3 months of its date of publication.

5.2 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.

5.3 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.

5.4 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 colorectal cancer and the healthcare professional responsible for their care thinks that trifluridine–tipiracil is the right treatment, it should be available for use, in line with NICE's recommendations.

6 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 B.

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.

Ahmed Elsada
Technical Lead

Raisa Sidhu
Technical Adviser

Jeremy Powell
Project Manager

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