NICE National Institute for Health and Care Excellence

NICE guidance

Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement

Technology appraisal guidance
Published: 11 September 2024

www.nice.org.uk/guidance/ta1005

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 Recommendation

1.1 Futibatinib is recommended, within its marketing authorisation, as an option for treating locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that has progressed after at least 1 line of systemic treatment in adults. Futibatinib is only recommended if the company provides it according to the commercial arrangement.

Why the committee made this recommendation

Usual treatment for locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or rearrangement that has progressed after systemic treatment is pemigatinib. Futibatinib would be an alternative option to pemigatinib.

There are no clinical trials directly comparing futibatinib with pemigatinib. An indirect comparison of futibatinib and pemigatinib suggests that they may have similar effectiveness, but this is uncertain.

A cost comparison suggests that futibatinib has similar costs to pemigatinib. So, futibatinib is recommended.

2 Information about futibatinib

Marketing authorisation indication

2.1 Futibatinib (Lytgobi, Taiho) is indicated for 'the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for futibatinib.

Price

2.3 The list price of futibatinib is £2,386.33 per pack containing 35, 28 or 21 4-mg tablets (excluding VAT, company submission).

2.4 The company has a commercial arrangement. This makes futibatinib available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Taiho, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Cholangiocarcinoma and futibatinib

3.1 Cholangiocarcinoma is a rare cancer of the bile tract. It is classified as intrahepatic or extrahepatic based on the location of the primary tumour. Fibroblast growth factor receptor 2 (FGFR2) fusions or rearrangements occur in up to 15% of intrahepatic tumours. A patient expert explained that cholangiocarcinoma is often diagnosed late. This means that curative surgery is often not possible and there are very few treatment options available. They explained that the lack of specialised care leads to delays in getting an accurate diagnosis. People diagnosed with advanced cholangiocarcinoma are aware of the poor prognosis and there is a substantial mental health burden. Another patient expert added that treatment options for cholangiocarcinoma have improved recently with durvalumab becoming available as a first-line treatment (see NICE's technology appraisal guidance on durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer) and pemigatinib becoming available as a second-line treatment (see NICE's technology appraisal guidance on pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [TA722]). The patient expert hoped that futibatinib would offer another treatment option if resistance developed to pemigatinib. Patient experts added that unlike the chemotherapy regimens offered historically or earlier in the treatment pathway, futibatinib is an oral treatment. This avoids the need to go into hospital for chemotherapy, which is a considerable quality-of-life advantage for people with the condition and their families. Patient experts added that side effects are often reduced with oral medicines because smaller doses can be taken over longer periods. They added that with targeted treatments, toxicity is mild and treatments are generally well tolerated.

Clinical management

Treatment pathway and comparators

3.2 The committee considered the treatment pathway for advanced or metastatic cholangiocarcinoma in the UK. For people who cannot have surgery, first-line treatment is typically gemcitabine plus cisplatin with or without durvalumab. Second-line treatment was historically with modified folinic acid, fluorouracil and oxaliplatin (mFOLFOX). More recently, the British Society of Gastroenterology's cholangiocarcinoma guidelines (2023) and the European Society for Medical Oncology guideline on biliary tract cancer (2022) have highlighted the importance of molecular profiling and using treatment options based on targetable gene alterations. TA722 recommends pemigatinib as a second-line treatment for locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or rearrangement. Because pemigatinib is the only targeted treatment for cholangiocarcinoma with FGFR2 fusions or rearrangements, the company considered pemigatinib to be the only relevant comparator to futibatinib. The EAG suggested that mFOLFOX should also be considered as a comparator because it may still be used in this population. The clinical expert explained that it would not be appropriate for people with an FGFR2 alteration to have mFOLFOX chemotherapy when a targeted option such as pemigatinib is available. The expert added that, although there is no data directly comparing mFOLFOX and pemigatinib, there has been a clear improvement in outcomes and quality of life with pemigatinib. The committee recalled the patient expert's view that futibatinib may offer another treatment option if resistance develops to pemigatinib (see section 3.1). But it noted that the company had positioned futibatinib as an alternative to pemigatinib, rather than after pemigatinib, so it could not evaluate futibatinib in this positioning. The committee considered the clinical expert's view that all people with a known FGFR2 alteration would have pemigatinib. It concluded that pemigatinib was the only relevant comparator.

Clinical effectiveness

FOENIX-CCA2

3.3 The clinical evidence for futibatinib came from FOENIX-CCA2. This was a phase 2, single-arm, open-label study in adults with locally advanced, metastatic or unresectable intrahepatic cholangiocarcinoma with FGFR2 fusions or rearrangements. People in FOENIX-CCA2 had to have had at least 1 previous systemic gemcitabine and platinum-based chemotherapy. The company presented data from the final data cut-off with a median follow up of 25 months. The objective response rate was 41.7% (95% confidence interval [CI] 32.1% to 51.9%). The median progression-free survival was 8.94 months (95% CI 6.74 to 11.00) and the median overall survival was 20.0 months (95% CI 16.40 to 24.60). The committee noted that, because FOENIX-CCA2 was a single-arm study, it did not provide evidence of the relative effectiveness of futibatinib compared with pemigatinib. It also noted the short follow up and high level of censoring in the overall survival data presented for futibatinib.

Comparison with pemigatinib

3.4 The clinical evidence for pemigatinib came from FIGHT-202. Similarly to FOENIX-CCA2, this was a phase 2, single-arm, open-label study in adults with advanced, metastatic or unresectable cholangiocarcinoma with FGFR2 fusions or rearrangements. People in FIGHT-202 had to have disease progression after at least 1 previous treatment. The company used data from cohort A of FIGHT-202, for people with an FGFR2 fusion or rearrangement. The median follow up in the final data cut-off for FIGHT-202 was 42.9 months. The median progression-free survival was 7.0 months (95% CI 6.1 to 10.5) and the median overall survival was 17.5 months (95% CI 14.4 to 22.9). Because the clinical evidence for futibatinib and pemigatinib came from 2 different trials, the company did an unanchored matching-adjusted indirect comparison (MAIC) to compare results from FOENIX-CCA2 and FIGHT-202. The futibatinib population in FOENIX-CCA2 was adjusted (reweighted) to align more closely to the pemigatinib population in FIGHT-202. The company included 7 confounding factors in the base-case MAIC. These included age, gender, Eastern Cooperative Oncology Group performance

status, previous treatment lines, previous surgery, baseline hypoalbuminaemia, and tumour protein 53 alteration status. The company stated that the small reduction in the effective sample size after matching showed good overlap in baseline characteristics between the 2 trials. MAIC (adjusted) hazard ratios for futibatinib compared with pemigatinib were 0.95 (95% CI 0.72 to 1.21) for overall survival and 1.07 (95% CI 0.86 to 1.30) for progression-free survival. The company added that results of the MAIC were similar to the naive (unadjusted) comparison and concluded that futibatinib and pemigatinib had very similar efficacy profiles. The EAG added that an assumption of equal effectiveness between the 2 treatments would not be unreasonable, but cautioned that results were from an unanchored indirect comparison, which is not a robust method of comparison. The clinical expert explained that there is no reason why pemigatinib would be more effective than futibatinib because both treatments are biologically similar. They added that, if anything, they would expect slightly greater efficacy for futibatinib. This is because, in their experience, futibatinib does not generate as many resistance mutations because it binds irreversibly to FGFR. But they added that further data collection would be unlikely to demonstrate any differences between the 2 treatments. The committee considered the results of the company's MAIC. It noted the high uncertainty in both the unadjusted and adjusted comparisons as demonstrated by the wide confidence intervals. The committee concluded that there was no clear evidence of a difference in efficacy between pemigatinib and futibatinib.

Economic model

Company's modelling approach

3.5 The company developed a partitioned survival model with 3 health states: progression-free, progressed, and death. At clarification stage, the company added functionality to the model to allow for independent modelling of time on treatment as requested by the EAG. The model cycle length was 21 days and a lifetime time horizon was used. After the clarification stage, the EAG identified and corrected several errors in the model, which mainly related to the probabilistic sensitivity analysis. The committee concluded that the revised economic model was appropriate for decision making.

Proportional hazards assumption

3.6 The company modelled overall and progression-free survival for futibatinib by fitting parametric survival models to unadjusted data from FOENIX-CCA2. The company used the hazard ratios derived from the MAIC (see section 3.4) to model overall and progression-free survival for pemigatinib based on overall and progression-free survival for futibatinib. This assumed that the 2 treatments had proportional hazards. The EAG did not agree with the proportional hazards assumption. This was because the log cumulative hazards plots crossed and hazard function plots for each treatment showed a different pattern. It also noted that the Kaplan–Meier estimates of overall survival for pemigatinib and futibatinib crossed at around 24 months. Because of this, the EAG preferred to model overall and progression-free survival independently for the 2 treatment arms. For futibatinib, the EAG preferred to use the effectiveness estimates from the MAIC. These had been adjusted to match the pemigatinib trial population. For pemigatinib, the EAG preferred to use unadjusted data. The committee agreed with the EAG that the proportional hazards assumption was violated. The committee's further considerations around survival extrapolations are discussed in section 3.7.

Overall and progression-free survival extrapolations

3.7 The company preferred log-normal models for both overall and progression-free survival for futibatinib. Predicted 5-year overall survival was around 11% and 5-year progression-free survival was around 1%. With the MAIC hazard ratios applied, survival estimates were similar for pemigatinib. The EAG preferred independent Weibull models for overall survival and log-normal models for progression-free survival. Predicted 5-year overall survival was around 1.5% for futibatinib and 8.4% for pemigatinib. Predicted progression-free survival was around 1.0% for futibatinib and 1.7% for pemigatinib. The committee noted that the company's and EAG's extrapolations of progression-free survival were similar between treatment arms. But there was a large difference between treatments in terms of overall survival estimates in the EAG's base case, with futibatinib expected to have much lower overall survival than pemigatinib at 5 years. It recalled the clinical expert's opinion that the 2 treatments are likely to have similar efficacy (see section 3.4). It also heard from the clinical expert that a small

number of people may have surgery after treatment. Based on this, the committee considered that the EAG's Weibull extrapolation of overall survival for futibatinib may be too pessimistic. The EAG noted that they would expect 5-year survival to be between 3% and 10% based on input from the EAG's clinical adviser. The EAG added that none of the extrapolations predicted survival within this range, so the Weibull model was selected as a conservative option. Less-conservative options such as the log-logistic and log-normal models were tested as scenario analyses. The committee considered the clinical expert's view that, if anything, survival may be expected to be slightly better for futibatinib than pemigatinib. But it noted that this was not shown in the data from either the unadjusted or adjusted comparisons of overall survival. As discussed in section 3.4, the committee concluded that there was no clear evidence of a difference in efficacy between pemigatinib and futibatinib.

Time-on-treatment extrapolations

3.8 The company assumed that time on treatment was equal to progression-free survival for both pemigatinib and futibatinib. It noted that for both treatments, median progression-free survival and median time on treatment were similar. Respective median progression-free survival and median time on treatment were 8.9 months and 9.1 months for futibatinib and 6.9 months and 7.2 months for pemigatinib. The EAG preferred to use the time-on-treatment data for futibatinib from the FOENIX-CCA2 trial. In the absence of publicly available time-on-treatment data for pemigatinib, the EAG preferred to use the inverse of the MAIC hazard ratio for progression-free survival. The resulting hazard ratio of 0.93 was applied to the futibatinib time-on-treatment extrapolation to estimate time on treatment for pemigatinib. The committee noted that the EAG's approach was more favourable to futibatinib than the company's approach. This is because it resulted in a shorter mean duration of treatment and lower total treatment costs for futibatinib compared with pemigatinib. The committee considered that because it had previously concluded that there was no clear evidence of a difference in efficacy between treatments (see section 3.4 and section 3.7), there would be no rationale for assuming different rates of discontinuation. So, the committee concluded that time on treatment should be the same for futibatinib and pemigatinib.

Severity

3.9 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to quality-adjusted life years (QALYs; a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company calculated absolute and proportional QALY shortfall estimates in line with NICE's manual on health technology evaluations. The estimates of proportional and absolute shortfall are considered confidential by the company so cannot be reported here. The company's resulting QALY weight of 1.2 was validated by the EAG. The committee concluded that the severity weight of 1.2 applied to the QALYs was appropriate. The committee added that if a condition is severe, QALY losses as well as QALY gains should be weighted for severity.

Acceptable ICER

3.10 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained (when a technology is both more costly and more effective), judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted that no similar guidance exists on an appropriate threshold when a technology is less costly and less effective. It added that there may be discontinuity in what is accepted as cost effective in these circumstances.

Cost-effectiveness estimates

3.11 Because pemigatinib has a confidential discount, all ICERs are confidential and cannot be reported here. Differences between the company's and EAG's base case included:

- The approach for modelling overall and progression-free survival:
  - The company preferred to use log-normal models for both overall and progression-free survival for futibatinib, with hazard ratios applied to estimate survival for pemigatinib.
  - The EAG preferred to model both treatment arms independently using Weibull models for overall survival and log-normal models for progression-free survival (see section 3.7).
- The approach for modelling time on treatment:
  - The company preferred to assume that time on treatment was equal to progression-free survival for both arms.
  - The EAG preferred to use time-on-treatment data for futibatinib from FOENIX-CCA2 with a hazard ratio applied to estimate time on treatment for pemigatinib (see section 3.8).

    In the company's base case, futibatinib was slightly less costly and slightly more effective than futibatinib. In the EAG's base case, futibatinib was less costly but also less effective. This was because the EAG's survival extrapolations resulted in decreased QALYs for futibatinib compared with pemigatinib. The committee noted that in the company's base case futibatinib was more effective and in the EAG's base case futibatinib was less effective. This demonstrated the high level of uncertainty resulting from the small incremental QALYs. Using the committee's preference of assuming no difference between treatments, the committee took costs into consideration in its decision making. The committee noted that the cost for futibatinib is similar to that of pemigatinib. So, the committee concluded that futibatinib could be considered a cost-effective use of NHS resources.

Conclusion

Recommendation

3.12 The committee concluded that there was no clear evidence of a difference in efficacy between futibatinib and pemigatinib. But, the 2 treatments were not compared in the same trial, so it is unclear whether futibatinib is better or worse than pemigatinib. The committee considered all estimates of cost effectiveness for futibatinib compared with pemigatinib, as well as the acquisition costs for both treatments with the confidential discounts for each treatment applied. The committee concluded that the cost for futibatinib was similar to that of pemigatinib. It agreed that the cost-effectiveness estimates for futibatinib were within the range that NICE considers an acceptable use of NHS resources. So, the committee recommended futibatinib as an alternative option to pemigatinib for previously treated locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or rearrangement.

Other factors

Equality

3.13 The committee did not identify any equality issues.

Uncaptured benefits

3.14 The committee considered whether there were any additional benefits of futibatinib not captured in the economic modelling. It concluded that there were no benefits not captured in the model.

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 integrated care boards, 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 or commercial availability of the product.

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 previously treated, advanced cholangiocarcinoma with FGFR2 fusion or rearrangement and the healthcare professional responsible for their care thinks that futibatinib 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 being 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 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 evaluation), a technical adviser and a project manager.

Anna Willis
Technical lead

Caron Jones
Technical adviser

Kate Moore
Project manager

ISBN: 978-1-4731-6125-2