

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal document

**Pemigatinib for treating relapsed or refractory
advanced cholangiocarcinoma with FGFR2
fusion or rearrangement**

1 Recommendations

- 1.1 Pemigatinib 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 systemic therapy in adults. It is recommended only if the company provides pemigatinib according to the commercial arrangement (see [section 2](#)).

Why the committee made these recommendations

Current treatment for advanced cholangiocarcinoma with an FGFR2 fusion or rearrangement that has progressed after systemic therapy is symptom control, with or without modified folinic acid, 5-fluorouracil and oxaliplatin (mFOLFOX) chemotherapy.

Clinical evidence from 1 study suggests that pemigatinib may be more effective than current treatments. This is uncertain because the study did not directly compare pemigatinib with symptom control or mFOLFOX. But the cancer is rare. This means the number of people who could take part in a study is small, making it difficult to collect robust comparative data. So, the uncertainty is considered acceptable.

Pemigatinib meets NICE's criteria for a life-extending treatment at the end of life. The cost-effectiveness estimates are uncertain but are likely to be within the range that NICE considers a cost-effective use of NHS resources. So, pemigatinib is recommended.

2 Information about pemigatinib

Marketing authorisation indication

- 2.1 Pemigatinib (Pemaryze, Incyte Corporation) has a conditional marketing authorisation for ‘the treatment of adults 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](#).

Price

- 2.3 The list price of pemigatinib is £7,159.04 for a pack of 14 x 13.5 mg tablets (company submission), which is an annual cost of £124,430. The company has a commercial arrangement (simple discount patient access scheme). This makes pemigatinib 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 [appraisal committee](#) considered evidence submitted by Incyte Corporation, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

Treatment pathway and comparator

There is an unmet need for a disease-modifying treatment for advanced cholangiocarcinoma with an FGFR2 fusion or rearrangement after systemic therapy

3.1 Cholangiocarcinoma is a rare cancer that develops from the epithelial lining of the bile ducts. It is classified as intrahepatic or extrahepatic based on the location of the primary tumour. Fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement may lead to the tumours forming. The clinical experts advised that the aim of treatment for advanced cholangiocarcinoma with FGFR2 fusion or rearrangement that is refractory to chemotherapy is to improve symptoms, delay tumour progression and extend survival. There are no licensed, targeted or disease-modifying therapies currently available in the NHS to treat this condition. The clinical and patient experts highlighted that treatment for the condition has not improved in over a decade. Therefore, current treatment is further chemotherapy containing modified folinic acid, 5-fluorouracil and oxaliplatin, plus active symptom control (mFOLFOX+ASC). If further chemotherapy is not suitable, ASC alone is offered. The patient and clinical experts emphasised the aggressive nature of this cancer and its poor prognosis. The patient experts described the difficulty of being diagnosed with a cancer for which there are very few treatment options and of being told of the poor prognosis often while feeling well. They also highlighted difficulty accessing experts in this condition. There is a lack of effective treatment options. Also, chemotherapy may or may not extend life at the expense of debilitating side-effects, which may have a significant effect on quality of life. The committee concluded that there is an urgent unmet need for people with advanced cholangiocarcinoma with FGFR2 fusion or rearrangement after systemic therapy. It agreed that people with this condition would welcome a disease-modifying treatment option like pemigatinib.

mFOLFOX+ASC and ASC alone are the most appropriate comparators

3.2 The company submission compared pemigatinib with mFOLFOX+ASC and ASC alone in people with advanced cholangiocarcinoma with FGFR2 fusion or rearrangement after systemic therapy. The ERG noted uncertainty in clinical guidelines and an absence of real-world prescribing data. It highlighted that clinical advice to the company suggested that capecitabine with oxaliplatin may be preferred to mFOLFOX for some people. It advised that it is likely that other chemotherapy agents are also given in routine NHS practice. The clinical experts advised that the relevant comparators currently used in routine clinical practice include mFOLFOX+ASC and ASC alone. The committee concluded that these are the most appropriate comparators for this appraisal.

Clinical-effectiveness evidence

The clinical evidence for pemigatinib is from a single-arm non-randomised study

3.3 The clinical evidence for pemigatinib came from FIGHT-202. This was a phase 2, single-arm, non-randomised, open label study in people with advanced or surgically unresectable cholangiocarcinoma that had not responded to previous therapy. Only cohort A of FIGHT-202, which included people with FGFR2 fusion or rearrangement, was relevant to this appraisal. The clinical evidence from the latest data cut is considered confidential by the company so cannot be reported here. In an earlier data cut (March 2019), the median progression-free survival was 6.9 months and the median overall survival was 21.1 months. The committee noted that, because FIGHT-202 was a single-arm study, it did not provide evidence of the relative effectiveness of pemigatinib compared with current treatment options. But it acknowledged that doing studies for advanced chemorefractory cholangiocarcinoma is difficult because of the rarity of this cancer. It concluded that, in the absence of direct evidence, indirect comparisons were needed to assess the relative effectiveness of pemigatinib compared with the comparators.

The population in cohort A of FIGHT-202 is appropriate for decision making

3.4 The ERG highlighted that cohort A of FIGHT-202 was a subset of the population in the marketing authorisation. It highlighted that 98% of people in cohort A had intrahepatic disease. However, the marketing authorisation and the NICE scope include people with non-intrahepatic disease. The company stated that there is no biological reason that pemigatinib would not provide benefit to people with non-intrahepatic cholangiocarcinoma with FGFR2 fusion or rearrangement. The clinical experts advised that about 40% of people with advanced cholangiocarcinoma have intrahepatic disease. However, they explained that, in advanced cancer, it is difficult to differentiate intrahepatic disease from other subtypes. They advised that FGFR2 fusion or rearrangement can be present in non-intrahepatic disease but it is uncommon. To be eligible for pemigatinib, people will be identified by the presence of an FGFR2 fusion or rearrangement and not by the disease subtype. The committee concluded that the population in cohort A of FIGHT-202 was appropriate for decision making.

Comparative evidence

The comparative evidence from ABC-06 is appropriate for decision making but has limitations

3.5 No studies directly compared pemigatinib with treatments currently used in the NHS. The main comparative evidence was from ABC-06. This was a phase 3, randomised, open label study of mFOLFOX+ASC or ASC alone for people with locally advanced or metastatic biliary tract cancers previously treated with gemcitabine plus cisplatin chemotherapy. The committee noted that ABC-06 was done in a different population to FIGHT-202 and did not report FGFR2 mutation status in either treatment group. It understood that FGFR2 mutation status appears to be an important prognostic indicator, and that not knowing the FGFR2 mutation

status in the ABC-06 population was a significant limitation. However, at the second committee meeting, the company described new evidence suggesting that the FGFR2 mutation is not a significant predictor of overall survival. So, the committee considered that the prognostic value of FGFR2 mutation status is uncertain. The clinical experts explained that, because of the rarity of this cancer it is difficult to do comparative studies in the relevant sub-population. The committee acknowledged that because of the rarity of the cancer, the data on the comparators from ABC-06 were the best available evidence. Despite the limitations, it concluded that the comparative efficacy and safety data from ABC-06 were the most appropriate evidence for decision making.

Pemigatinib is likely to be more effective than the comparators

3.6 In the absence of direct comparative evidence, the estimate of the relative treatment effect of pemigatinib compared with mFOLFOX+ASC and ASC alone was based on an unanchored matching adjusted indirect comparison of patient-level data from FIGHT-202 and data from ABC-06. The weightings were derived using a propensity score logistic regression model adjusted for selected prognostic factors. The weighted hazard ratios for overall survival and progression-free survival are considered confidential by the company and exact results cannot be reported here. In general, the results were more favourable for pemigatinib. The hazard ratio for overall survival was lower for pemigatinib compared with mFOLFOX+ASC and ASC alone. The hazard ratio for progression-free survival was also lower for pemigatinib compared with mFOLFOX+ASC. Progression-free survival data were not available for the ASC-alone arm from ABC-06. So, the company assumed that the progression-free survival hazard ratio for pemigatinib compared with ASC alone was the same as the progression-free survival hazard ratio for pemigatinib compared with mFOLFOX+ASC. The ERG advised that the estimate of comparative treatment effect was highly uncertain and likely to be biased because the matching adjusted indirect comparison was done between mismatched study populations (see section 3.5). The committee noted the

lack of direct comparative evidence (see section 3.3) and the limitations of using a matching adjusted indirect comparison to compare the efficacy of pemigatinib with the comparators. However, it recognised the rarity of the cancer and limitations in the available evidence for the comparators. It concluded that the matching adjusted indirect comparison suggests pemigatinib was more effective than the comparators, but that this was uncertain.

Comparative safety evidence is likely to have little effect on the cost-effectiveness estimates

3.7 The company did not do a matching adjusted indirect comparison for the safety of pemigatinib compared with the comparators. Instead, it used unadjusted adverse-event rates for pemigatinib from FIGHT-202 and for mFOLFOX+ASC and ASC alone from ABC-06. The ERG advised that no conclusions could be drawn about the safety of pemigatinib, relative to mFOLFOX+ASC and ASC alone, in the specified population without comparative safety evidence. It noted that there was little value in doing a matching adjusted indirect comparison with poor quality evidence. During technical engagement, the company provided additional analyses that varied the modelled adverse events rates for the comparator to extreme values. These showed that the cost-effectiveness estimates were not sensitive to comparative safety data. The committee concluded that there was a lack of comparative safety evidence for pemigatinib and its comparators, but that this was unlikely to have much effect on the cost-effectiveness estimates.

Economic model

The company's economic model is appropriate for decision making

3.8 The company's partitioned survival model used parametric survival models to predict outcomes including time-on-treatment, progression-free survival and overall survival. The model included people in both the progression-free and post-progression health states, either on or off

treatment. It used a life-time horizon with a cycle length of 1 week. An annual discount rate of 3.5% was applied to costs and outcomes. The committee concluded the company's economic model was appropriate for decision making.

Survival analysis

Independently fitted models are appropriate

3.9 In the company's base-case analysis, long-term survival with pemigatinib was estimated by fitting parametric survival models to unadjusted overall-survival data from cohort A of FIGHT-202. Long-term survival for the comparators was estimated by applying the inverse of the relative treatment effect from the matching adjusted indirect comparison (see section 3.6). The company preferred the log-logistic model to extrapolate overall survival from FIGHT-202 and the log-logistic model to extrapolate overall survival from both arms of ABC-06 for its base-case. The committee considered that applying the hazard ratio to the treatment arm to generate parametric curves for comparator survival may be inappropriate. It noted that applying the hazard ratios from the indirect comparison requires the assumption of proportional hazards. The committee also noted that the company's selected log-logistic parametric curves were not proportional-hazards models. In response to the appraisal consultation document, the company provided log-cumulative hazard plots for overall survival with pemigatinib derived from the matched adjusted indirect comparison. These suggested that the proportional hazards assumption was reasonable. The company also provided new scenarios in which FIGHT-202 and ABC-06 data were extrapolated independently using the April 2020 data cut, but it did not agree that independent models provide more robust or clinically plausible outcomes. However, the committee concluded that it was more appropriate to fit independent curves to each arm instead of applying the assumption of proportional hazards to non-proportional hazard models.

The log-logistic parametric curve is the most plausible

3.10 At the first appraisal committee meeting, the committee stated that there was a lack of clear justification for the selected parametric curve. It agreed that it would like to have seen clearer clinical expectations of survival in the treatment and comparator arms over time. In response to the appraisal consultation document, the company's clinical experts suggested a probability of overall survival at 5 years of about 0.1% for people having mFOLFOX+ASC and of close to 0% for those having ASC alone. The company's clinical experts struggled to choose the most plausible curve for the pemigatinib survival extrapolation. After appraisal consultation, the clinical experts predicted survival at 5 years of between 10% and 13% for people who have pemigatinib, based on evidence from the maximum follow-up of 3 years from FIGHT-202. The committee noted that a recent publication of data from ABC-06 may be informative. The company submitted this after consultation but it did not include additional follow-up data. The company also provided external data from ClarIDHy, a phase 3 randomised study, to validate the estimated survival for the comparator groups. When adjusted for crossover, the ClarIDHy placebo arm was consistent with outcomes from ABC-06. The committee noted that ClarIDHy was for a different molecular population, the iDH1 mutation, and that similarities between the iDH1 and FGFR2 mutation populations did not necessarily equate to similar survival characteristics in people with FGFR2 mutations. The company preferred the log-logistic curve to extrapolate overall survival with pemigatinib because the company's clinical experts agreed that a declining hazard function over time was plausible, it was a good visual and statistical fit, and it was clinically plausible. The company also explored the generalised gamma curve in scenario analysis, which the committee agreed also predicted a declining hazard function and was clinically plausible. The committee noted that the generalised gamma curve predicted a lower 5-year survival compared with the log-logistic curve for the extrapolated FIGHT-202 data and both arms of ABC-06. It considered that the log-logistic model was a

statistically better fit than the generalised gamma model. Also, the 5-year survival predicted by the log-logistic curve was within the clinical expert's estimated range. The committee considered that both the log-logistic and generalised gamma curves could be reasonable, but concluded that it would base its decision making on the log-logistic curve.

Additional costs

NHS England's genetic testing costs are included in the cost-effectiveness analysis

3.11 At the first appraisal committee meeting, the clinical experts advised that FGFR2 testing is not done as part of routine clinical practice in the UK. The committee noted that the 2020/21 National Genomic Test Directory does not include FGFR2 mutation testing for people with cholangiocarcinoma. The Cancer Drugs Fund clinical lead advised that there is already a multitarget panel test for people with cholangiocarcinoma to assess eligibility for other treatments. The prevalence of FGFR2 fusion or rearrangement is about 10% across all types of cholangiocarcinoma. So, adding FGFR2 as a target would incur an additional cost of £34, which would be applicable if pemigatinib is recommended for routine use in NHS practice. This gives a preferred cost of £340 for each additional person identified who is FGFR2-positive. The committee concluded that NHS England's genetic testing costs and the prevalence of FGFR2 fusion or rearrangement should have been included in the cost-effectiveness analysis. After consultation, the company included the costs of FGFR2 genetic testing in its base-case analysis.

Costs of optical coherence tomography are included in the cost-effectiveness analysis

3.12 Pemigatinib treatment can sometimes cause retinal pigment epithelial detachment. At the first appraisal committee meeting, the Cancer Drugs Fund clinical lead advised that ophthalmological examination using optical coherence tomography would be needed before and after starting

treatment with pemigatinib in the NHS. The company confirmed that this is detailed in the summary of product characteristics. The committee concluded that the costs of optical coherence tomography should be included in the economic analysis. After consultation, the company included the cost of optical coherence tomography in its analysis.

End of life criteria

Pemigatinib is considered to be a life-extending treatment at the end of life

3.13 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](#). For the short life-expectancy criterion, the company's base-case model estimated a mean undiscounted life expectancy of 8.0 months for mFOLFOX+ASC and 7.3 months for ASC alone. For the life-extension criterion, the company's base-case model estimated an undiscounted mean incremental life expectancy with pemigatinib of 25.6 months compared with mFOLFOX+ASC and 26.4 months compared with ASC alone. The ERG advised that these estimates were highly uncertain given the uncertainty in the results from the matching adjusted indirect comparison and the approach used to estimate health outcomes in the company's economic model. The clinical experts confirmed that people with relapsed or refractory cholangiocarcinoma with FGFR2 fusion or rearrangement have a life expectancy of between 4.7 and 10 months with current treatment. The committee was satisfied that pemigatinib meets the short life-expectancy criterion with current care. It acknowledged that the extension-to-life criterion with pemigatinib was less certain because of limitations in the survival analysis (see sections 3.9 and 3.10). However, it considered that the risk of the extension-to-life criterion not being met was relatively small, given that the estimates were substantially greater than 3 months. The committee concluded that pemigatinib could be considered a life-extending treatment at the end of life.

Cost-effectiveness estimates

The most plausible incremental cost-effectiveness ratios are below £50,000 per quality-adjusted life year gained

3.14 [NICE's guide to the methods of technology appraisal](#) highlights that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the incremental cost-effectiveness ratios (ICERs). It states that the committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted the high level of uncertainty, specifically about the matching adjusted indirect comparison (see section 3.6). But it acknowledged that the company had identified all the available data to validate the survival estimates, given the rarity of the cancer. For a life-extending treatment at the end of life, the upper limit of the range usually considered to represent a cost-effective use of NHS resources is £50,000 per quality-adjusted life year (QALY) gained. The committee noted that the company's new base-case ICERs for pemigatinib, including an updated patient access scheme, were £42,076 per QALY gained compared with mFOLFOX+ASC, and £45,029 per QALY gained compared with ASC alone. The committee's preferred assumptions for decision making at the second appraisal committee meeting were to use:

- independently fitted models (see section 3.9)
- the log-logistic curve to extrapolate long-term overall survival with pemigatinib (see section 3.10).

Using these preferred assumptions, the ICER was between £45,051 and £45,808 per QALY gained compared with mFOLFOX+ASC, and between £44,354 and £45,010 per QALY gained compared with ASC alone. The ICER value depended on whether the FIGHT-202 data were adjusted for the mFOLFOX+ASC or ASC-alone data from ABC-06.

Other scenarios, including using the generalised gamma curve to

extrapolate long-term survival with pemigatinib, resulted in higher ICERs. The committee considered the uncertainty in the clinical evidence but noted the rarity of the cancer being appraised. It concluded the cost-effectiveness estimates for pemigatinib suggest it is an acceptable use of NHS resources for a life-extending treatment at the end of life. So pemigatinib was recommended for routine use in the NHS.

Innovation

Pemigatinib is an innovative treatment for advanced cholangiocarcinoma with an FGFR2 fusion or rearrangement

3.15 The company considered pemigatinib to be innovative because there are no other licensed or targeted disease-modifying treatment options for advanced cholangiocarcinoma with an FGFR2 fusion or rearrangement. The patient and clinical experts emphasised the importance of improving debilitating symptoms and health-related quality of life, and of extending life, and the potential benefit from pemigatinib in achieving this. The committee noted the potential benefits of pemigatinib for people with advanced cholangiocarcinoma with an FGFR2 fusion or rearrangement. But it concluded that it had not been presented with evidence of any additional benefits that had not been captured in the QALY calculations.

Equalities considerations

There are no equalities issues relevant to the recommendation

3.16 No equalities issues were raised during scoping and technical engagement. No potential equality issues were identified in the company submission. The committee concluded that there were no equalities issues 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 appraisal within 3 months of its date of publication. Because pemigatinib has been available through the early access to medicines scheme, NHS England and commissioning groups have agreed to provide funding to implement this guidance 30 days after 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 fast track appraisal), at which point funding will switch to routine commissioning budgets. The [NHS England and NHS Improvement 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 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 appraisal document.

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 relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement and the doctor responsible for their care thinks that pemigatinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien

Chair, appraisal committee

June 2021

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 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.

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ISBN: [to be added at publication]