NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations [ID3740]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations [ID3740]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

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3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
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4. **Comments on the Appraisal Consultation Document from experts:**
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations [ID3740]

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the appraisal committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the appraisal committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the appraisal committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the appraisal committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the appraisal committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee (company)	Incyte Biosciences UK Ltd	The company is disappointed with the appraisal committee's preliminary decision that pemigatinib is not recommended, within its marketing authorisation, for treating locally advanced or metastatic cholangiocarcinoma (CCA) with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that has progressed after systemic therapy in adults. As discussed during the appraisal meeting there are limited efficacious treatment options currently available for patients who have progressed following first-line treatment. Second line chemotherapy (mFOLFOX) provides marginal benefit for both progression-free survival and overall survival. This emphasises the urgent unmet need for access to targeted treatments such as pemigatinib to avoid a poor prognosis in those patients with an FGFR2 fusion/rearrangement. As a potent and selective FGFR1, 2, and 3 inhibitor, pemigatinib is also being investigated in previously untreated CCA patients with FGFR2 fusions/rearrangements whose disease is either unresectable or metastatic. FIGHT-302, a phase III trial, will provide comparative efficacy and safety versus standard of care and continues Incyte's commitment to driving research in an area of cancer that has underserved for over a decade. In addition to the comments below, the Company is pleased to be able to provide further supporting data to the appraisal process, which can be found in the Appendices to this response. Appendix 1 – Additional clinical validation Appendix 2 – Additional overall survival data Appendix 3 – ABC-06 and MAIC-adjusted FIGHT-202 independent survival extrapolations Appendix 4 – Updated cost-effectiveness results including an updated PAS	Thank you for your comment. The FAD recommends pemigatinib for treating locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or rearrangement that has progressed after systemic therapy in adults. Please see FAD section 1.1, section 3.9, section 3.10 and section 3.14 for a summary of these considerations.
2	Consultee (company)	Incyte Biosciences UK Ltd	The clinical plausibility of the survival extrapolations is unclear In section 3.9 of the ACD, the committee "noted a lack of clinical validation for the comparator arm but acknowledged that a recent updated publication of ABC-06 may be informative. The committee concluded that the justification for the preferred parametric curve and the clinical expectations of survival were unclear, so the cost-effectiveness estimates for pemigatinib were uncertain."	Thank you for your comment. The appraisal committee considered the additional clinical estimates of the

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In response to this comment, the company has sought additional validation from a clinical expert to provide clarity on the expectations of survival for cholangiocarcinoma patients previously treated with chemotherapy or active symptom control, and to identify any further suitable published literature that could serve as external validation of survival extrapolations. The validation interview conducted is summarised in Appendix 1.

Clinical validation suggested that for patients receiving active symptom control (ASC) alone, it would be unlikely for patients to survive beyond 3 years and therefore 5 years. For patients treated with mFOLFOX+ASC, clinical validation suggested overall survival at 3 years would be approximately 3%, while at 5 years this may be slightly higher than the 0.1% predicted in the original company base case.

Although there is no additional follow-up from ABC-06, the updated publication does provide additional detail on patient outcomes by tumour site.2 Here, results suggest that the prognosis of patients with intrahepatic CCA(iCCA) is no better than eextrahepatic CCA (eCCA), and potentially worse, with lower median progression free survival (PFS), OS and 6 month overall survival (OS) rate (Figure 1). As an FGFR2-selected population is likely to have a higher proportion of patients with intrahepatic disease3, should FGFR2 have no prognostic value, this suggests that the outcomes from ABC-06 may be over-estimating the outcomes for the indication in this appraisal.

Figure 1: ABC-06 patient outcomes by tumour site[2]
<table>
<tr><th></th><th>All patients</th><th>iCCA</th><th>eCCA</th></tr>
<tr><td>n (ASC-alone)</td><td>81</td><td>38</td><td>19</td></tr>
<tr><td>n (ASC+FOLFOX)</td><td>81</td><td>34</td><td>26</td></tr>
<tr><td>Overall survival</td><td></td><td></td><td></td></tr>
<tr><td>Adjusted* HR (95% CI) OS</td><td>0.69 (0.50-0.97)</td><td>0.64 (0.38-1.06)</td><td>0.84 (0.45-1.57)</td></tr>
<tr><td>Median OS months (ASC-alone); months (95% CI)</td><td>5.3 (95% CI 4.1-5.8)</td><td>5.2 (3.7-5.8)</td><td>5.4 (3.9-6.4)</td></tr>
<tr><td>Median OS months (ASC+FOLFOX); months (95% CI)</td><td>6.2 (95% CI 5.4-7.6)</td><td>5.7 (4.1-7.4)</td><td>6.2 (4.0-7.9)</td></tr>
<tr><td>6m OS rate (ASC-alone) (%)</td><td>35.5%</td><td>30.8%</td><td>36.8%</td></tr>
<tr><td>6m OS rate (ASC+FOLFOX) (%)</td><td>50.6%</td><td>44.1%</td><td>53.9%</td></tr>
<tr><td>12m OS rate (ASC-alone) (%)</td><td>11.4%</td><td>11.2%</td><td>10.5%</td></tr>
<tr><td>12m OS rate (ASC+FOLFOX) (%)</td><td>25.9%</td><td>26.5%</td><td>15.4%</td></tr>
<tr><td>Progression-free survival</td><td></td><td></td><td></td></tr>
<tr><td>Median PFS (ASC+FOLFOX); months (95% CI)</td><td>4.0 months (3.2-5.0)</td><td>3.3 months (2.5-5.2)</td><td>4.0 months (2.9-5.9)</td></tr>
</table>

Aside from ABC-06, the ClarIDHy phase III randomized trial has been identified as a potential source of validation for survival estimates in a similar patient population. ClarIDHy studies the efficacy of ivosidenib versus placebo in previously treated cholangiocarcinoma patients with an isocitrate dehydrogenase 1
</td><td>plausibility of the survival extrapolations, noting the importance of the company's clinical experts estimates in the decision to choose the log-logistic for extrapolating overall survival. Please see FAD section 3.10 for a summary of these considerations.</td></tr>
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(IDH1) mutation. This was considered a suitable trial for comparison because of the high proportion of patients with intrahepatic disease (95%).[4] Similarly to FIGHT-202, this study is for a molecularly selected population, and although recent publications suggest that IDH1 has no significant prognostic value, like FGFR2, the case is still unclear.[5, 6] The ClarIDHy trial included 61 patients treated with placebo who were permitted to crossover to active treatment with ivosidenib at disease progression. Median OS for patients treated with placebo was 7.5 months, while analysis that adjusted for crossover using the RPSFT method predicted a median OS of 5.1 months. It is clear that the ClarIDHy placebo arm, when adjusted for crossover, is consistent with outcomes from ABC-06 (Error! Reference source not found. and Figure 2).

Table 1: ClarIDHy patient outcomes vs. ABC-06 vs. FIGHT-202
<table>
<tr><th>Months</th><th>Zhu Placebo</th><th>Zhu Placebo RPSFT</th><th>ABC-06 mFOLFOX</th><th>ABC-06 ASC alone</th><th>FIGHT-202 pemigatinib</th></tr>
<tr><td>6</td><td>57%</td><td>48%</td><td>52%</td><td>36%</td><td>89%</td></tr>
<tr><td>12</td><td>36%</td><td>17%</td><td>28%</td><td>12%</td><td>67%</td></tr>
<tr><td>18</td><td>26%</td><td>11%</td><td>10%</td><td>9%</td><td>49%</td></tr>
<tr><td>24</td><td>16%</td><td>#N/A</td><td>8%</td><td>3%</td><td>39%</td></tr>
<tr><td>30</td><td>11%</td><td>#N/A</td><td>#N/A</td><td>3%</td><td>35%</td></tr>
<tr><td>36</td><td>#N/A</td><td>#N/A</td><td>#N/A</td><td>#N/A</td><td>28%</td></tr>
</table>

Even when compared with outcomes from other studies identified in the company systematic literature review (SLR) and considered for inclusion within the matching adjusted indirect comparison (MAIC) (see company responses to ERG clarification questions A18 and A19), ABC-06 survival outcomes are broadly consistent between studies while still allowing for heterogeneity in patient population (Appendix 2). Due to the severity of the disease, most studies only report data up to 2 years, with only 2 studies reporting up to 3 years (with only 1 and 4 patients at risk) and no studies reporting survival at 5 years. Although patient characteristics do vary between studies, these support an overall survival extrapolation that predicts a minority of chemotherapy patients alive at 3 years, and almost no patients at 5 years.

For pemigatinib OS extrapolations, further clinical validation of the most recent datacut (April 2020) from FIGHT-202 suggested that parametric models provided reliable estimates of overall survival for patients treated with pemigatinib at 3 years given the observed follow-up data, and that considering the evidence at the maximum follow-up of 3 years from FIGHT-202, predicted survival at 5 years would be between 10-13% (Appendix 1)

Figure 2: ClarIDHy overall survival vs. ABC-06 vs. FIGHT-202
</td><td></td></tr>
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			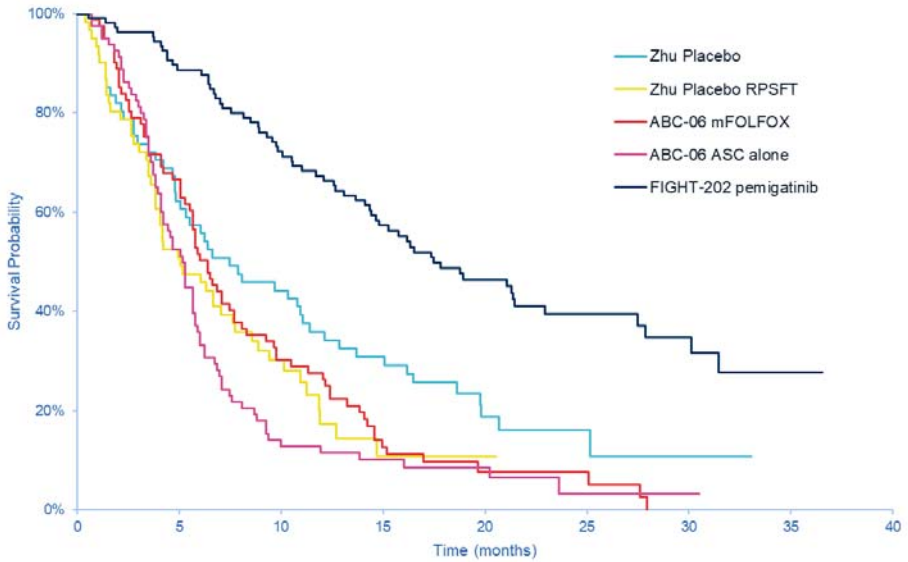 **Key:** ASC, active symptom control; RPSFT, rank-preserving structural failure time.	
3	Consultee (company)	Incyte Biosciences UK Ltd	**Fitting independent models to each group is more appropriate** In Section 3.10 of the ACD, "the committee considered that it was not appropriate to apply the hazard ratio to the treatment arm to generate parametric curves for comparator survival…as it requires the assumption of proportional hazards." Pg. 11 The company have chosen a pragmatic approach that aims to best reflect the available published estimates of overall survival for both pemigatinib and the relevant comparators while also remaining clinically plausible. While assessment of the proportional hazards assumption is to some extent subjective, based on assessment of the log-cumulative hazard plots, the Company argue that the proportional hazards assumption does hold and therefore application of a hazard ratio to generate parametric curves for comparator survival is appropriate. This rationale was originally presented in Section B.3.3 and Appendix L of the company submission, and has been presented again for OS using the FIGHT-202 April 2020 cut in Figure 3. In the original company submission, as an alternative option for modelling survival, independent survival models were made available within the economic model provided by the company, and tested as scenario analyses (Table 61, Section B3.8.3). At technical engagement stage, when updating the model and inputs using the FIGHT-202 April 2020 data, only the unadjusted FIGHT-202 extrapolation and the	Thank you for your comment. The appraisal committee agreed that the proportional hazards assumption may be reasonable. Please see FAD section 3.9 for a summary of these considerations.

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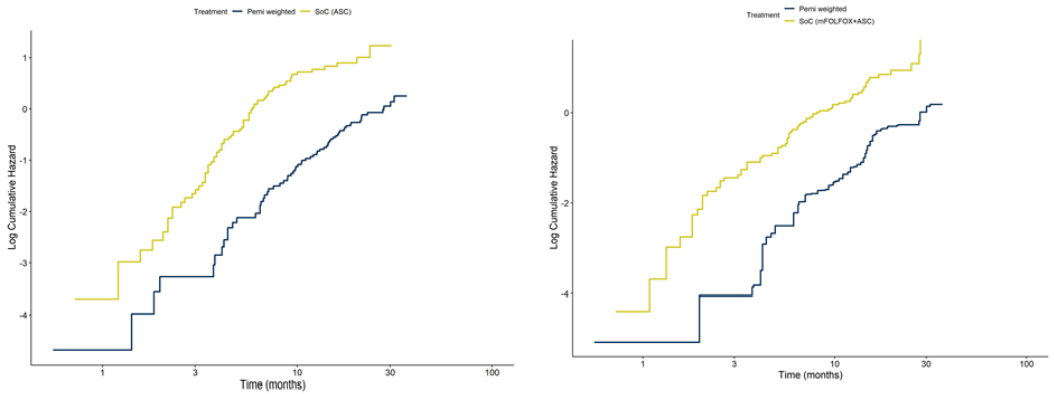
			MAIC HRs were updated, as the independent models had not been considered in either the ERG base case or scenario analyses. Although these options are not thought to provide any more robust or clinically plausible outcomes than the company base case, these options have now been updated in the cost-effectiveness model with April 2020 data, and are presented as scenarios in Appendix 4. The rationale for the curves chosen in these scenarios is presented below. **Figure 3: Log-cumulative hazard plots for MAIC adjusted pemigatinib overall survival versus ASC and mFOLFOX+ASC (April 2020 data cut)** 	
4	Consultee (company)	Incyte Biosciences UK Ltd	**<u>Company base case</u>** The current company base case assumptions for survival modelling are justified in the company technical engagement response and appendices. In these documents, published evidence for a decreasing probability of death over time for cholangiocarcinoma patients was presented, alongside the smoothed hazards from FIGHT-202.[7] Updated AIC/BIC statistics from FIGHT-202 April 2020 extrapolations were presented, and log-logistic was preferred due to a better AIC/BIC than other extrapolations (>5 points over generalised gamma BIC). The log-logistic curve was considered to be clinically plausible regarding long-term survival (10-13% at 5 years), although other extrapolations (such as generalised gamma) also meet these criteria, and are tested in scenario analysis within the appendix to this response (Appendix 2). As the Weibull extrapolation only predicted 5-year survival at 5%, and models increasing hazards over time, it was considered inappropriate.	Thank you for your comment. The appraisal 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

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			Applying the MAIC HR predicts long-term survival in line with clinical expectation and other published evidence for similar populations of chemotherapy- and ASC-treated patients (Appendix 2). Using the MAIC HR and leaving the FIGHT-202 data unadjusted also allows modelling of survival in the exact population of the appraisal's indication (i.e. that of FIGHT-202) without any adjustment of patient characteristics. The application of the MAIC HR to the log-logistic extrapolation of FIGHT-202 data was criticised at the ACM, due to the accelerated failure time (AFT) assumption of the log-logistic (and generalised gamma) survival models. Although the non-AFT survival models from FIGHT-202 OS data all show hazards that do not decrease, an additional scenario has been presented in Appendix 4 using the exponential function for OS (and PFS) extrapolation of FIGHT-202 data – this scenario shows similar cost-effectiveness results to the company base case, and should alleviate the committee's technical concerns regarding application of the MAIC HR to an AFT model. **Independent model scenario** In order to address the committee's consideration that fitting independent survival models would be more appropriate, a scenario has been explored whereby FIGHT-202 data and ABC-06 data are extrapolated independently of each other. For the pemigatinib OS extrapolation, three options for extrapolation are considered: 1. Extrapolation using unadjusted FIGHT-202 trial data (as per the company base case) 2. Extrapolation using FIGHT-202 trial data that has been adjusted using a MAIC and the patient characteristics from the ASC arm of ABC-06 3. Extrapolation using FIGHT-202 trial data that has been adjusted using a MAIC and the patient characteristics from the mFOLFOX+ASC arm of ABC-06 Irrespective of which arm is used for the MAIC, the log-logistic arm remains a good candidate for the base case choice for OS extrapolation of FIGHT-202 data, for the same reasons as described above (see Appendix for AIC/BIC statistics and curve extrapolations). However, generalised gamma is also explored in scenario analysis. For PFS, log-normal remained a good visual and statistical fit when using the MAIC-adjusted FIGHT-202 data, and in order to keep consistency with the unadjusted extrapolations and the comparator arm (see below), log-normal remained as the base case for MAIC-adjusted extrapolations of FIGHT-202 PFS data. TOT remained unchanged from the company base case, as TOT was not adjusted in the MAIC. For the comparator arms, NICE TSD 14 suggests that when modelling treatment arms independently, the same extrapolation function should be used across treatment arms. The OS smoothed hazard plots for both arms of ABC-06 show increasing hazards initially, before plateauing. After this, the smoothed hazard for ASC decreases, whereas that for mFOLFOX+ASC increases, although these changes in shape are likely driven by small patient numbers (Figure 4 and Figure 5). As the log-logistic extrapolation	appraisal committee agreed that the log-logistic is statistically a better fitting model than the generalised gamma model. The appraisal committee noted that the log-logistic and generalised gamma are appropriate for extrapolating overall survival, but slightly preferred the log-logistic curve. Please see FAD section 3.9 and section 3.10 for a summary of these considerations.

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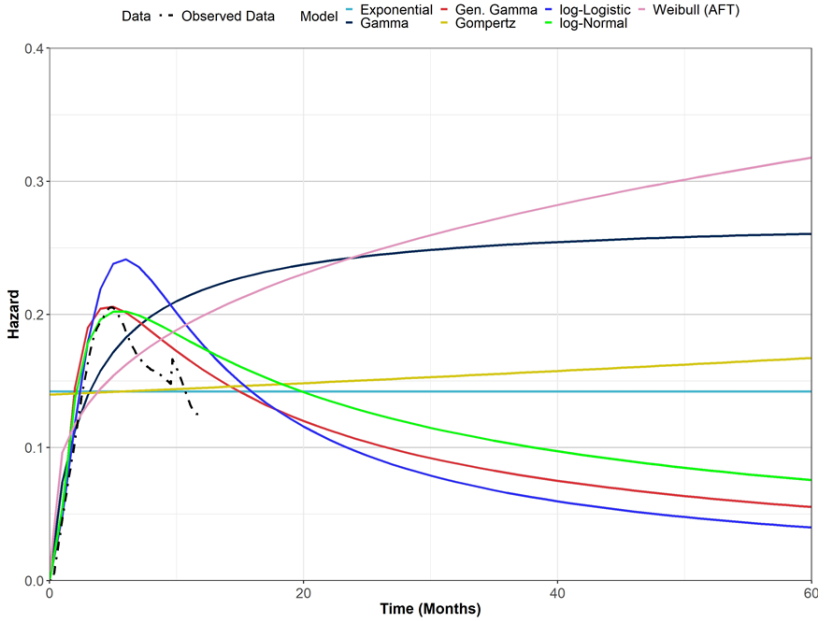
			is also a strong statistical fit for both arms of ABC-06, and the published evidence showing decreasing probability of death over time would also apply to the comparator arm, this was selected as the base case for OS in both comparator arms.[7] These provide long term survival as expected from clinicians (Table 3 and Table 4 in Appendix). However, as generalised gamma was also a good statistical fit, providing estimates aligned with clinical expectation, these extrapolations were tested in scenario analysis. For PFS, the log-normal extrapolation was a good visual fit and had the best statistical fit to the mFOLFOX+ASC ABC-06 data. As such, this was chosen as the base case PFS extrapolation for this scenario. Although other models did provide similar statistical fit, the choice of PFS extrapolation is not a big driver of model results. **Figure 4: ABC-06 ASC, Overall survival smoothed hazard plots**  **Figure 5: ABC-06 mFOLFOX, Overall survival smoothed hazard plots**	

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			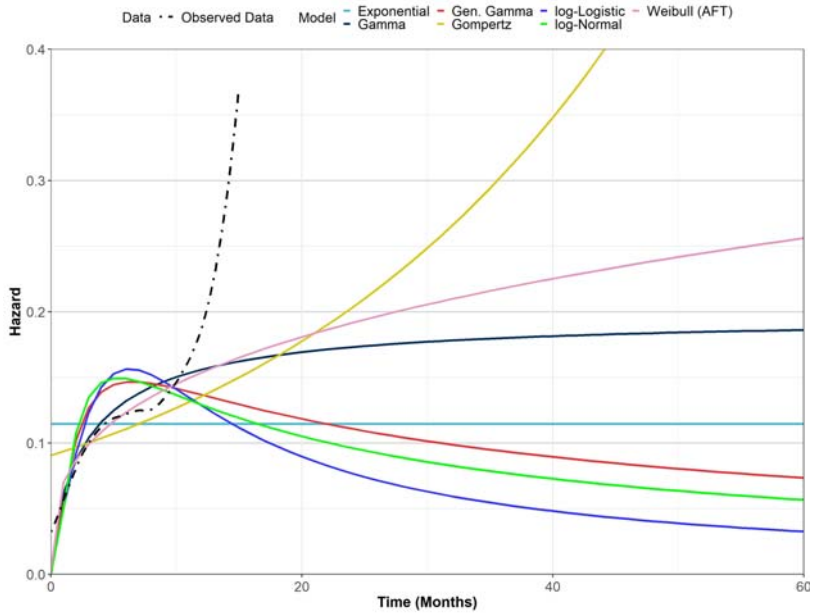 Results of cost-effectiveness analysis using unadjusted FIGHT-202 extrapolations, and extrapolations from FIGHT-202 adjusted using the ASC and the ASC+mFOLFOX arms are shown in Appendix 4. These results show that it is the choice of overall survival extrapolation that is the primary driver of model results, rather than the method of overall survival extrapolation. ICERs between analyses using HRs or using independent survival models with the same underlying extrapolation function all provide similar results. However, although the ICERs are similar, all scenarios using independent survival models predict a small number of ASC patients alive at 3 and 5 years. This is contrary to clinical expectation, which suggests that these extrapolations may overestimate ASC survival. For the ASC+mFOLFOX arm, the company base case model does slightly underpredict 3- and 5-year survival compared to clinical expectation (0.4% versus 3% at 3 years, and 0.0% versus 0.1% at 5 years). On the other hand, the independent survival models may overpredict long-term ASC+mFOLFOX survival compared to clinical opinion (1.2% versus 0.1% at 5 years), and this is also at the expense of changing the modelled patient population by adjusting the FIGHT-202 clinical trial data to match the ABC-06 patient characteristics. These scenarios provide useful evidence showing that the different methods of estimating comparator survival and relative efficacy all provide very similar cost-effectiveness results, and it is the underlying survival function that is the biggest driver of cost-effectiveness model results. The company believe log-logistic is the most appropriate extrapolation function for OS, as this shows a good visual and statistical	

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			fit, demonstrates decreasing hazards over time, and provides long-term estimates in line with clinical opinion, irrespective of any MAIC adjustment. Although generalised gamma does also meet a number of these same criteria, MAIC adjustment of FIGHT-202 data do provide long-term survival estimates slightly below that expected from clinical validation (Appendix 4, 8.4-9.9% versus 10-13%).	
5	Consultee (company)	Incyte Biosciences UK Ltd	In Section 3.12 of the ACD, the committee suggest that "The prevalence of FGFR2 fusion or rearrangement is about 10% across all types of cholangiocarcinoma and adding FGFR2 as a target would incur an additional cost of £34." Although it is unclear where the committee estimate of FGFR2 prevalence has been sourced from, the stated cost has been included in the updated company base case cost-effectiveness analysis using the reported FGFR2+ prevalence in the UK from FIGHT-202, which was validated by clinical experts.[1] The results of this updated company base case are presented in Appendix 4.	Thank you for your comment. The appraisal committee concluded that it is appropriate to include the genetic testing costs in the cost-effectiveness analysis. Please see FAD section 3.11 for a summary of these considerations.
6	Consultee (company)	Incyte Biosciences UK Ltd	**Costs of optical coherence tomography should be included in the cost-effectiveness analysis** In Section 3.13 of the ACD the "committee concluded that the costs of optical coherence tomography should be included in the economic analysis." This was based on the suggestion of the CDF clinical lead and an expectation of what guidance would be issued in the licensed indication. The licensed indication for pemigatinib now includes guidance that an optical tomography scan should be considered: - at pemigatinib treatment initiation; - followed by every 2 months for the first 6 months of treatment; - then every 3 months while on treatment - and urgently at any time for visual symptoms.[8] Clinical expert opinion was that these observations would typically be done as part of a standard clinical exam and that it was not clear what additional benefit there was from increased monitoring when these events would be picked up routinely.[9] However, to accommodate the Committee's request and present analysis consistent with the monitoring suggested in the pemigatinib license, updated company base case results include the cost of OCT monitoring, sourced from the NHS reference costs.[10] The frequency of visual symptoms used in the model was taken from FIGHT-202 Cohort A using the prevalence of "blurred vision".	Thank you for your comment. The appraisal committee concluded that it is appropriate to include the costs of optical coherence tomography in the cost-effectiveness analysis. Please see FAD section 3.12 for a summary of these considerations.
7	Consultee	AMMF – The Cholangiocarcinoma Charity	AMMF – the Cholangiocarcinoma Charity, advocates for all those with cholangiocarcinoma. As such, we would like to express huge disappointment and dissatisfaction at the decision made by the NICE committee in not recommending Pemigatinib.	Thank you for your comment. The FAD recommends pemigatinib for

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				treating locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or rearrangement that has progressed after systemic therapy in adults. Please see FAD section 1.1.
8	Consultee	AMMF – The Cholangiocarcinoma Charity	To illustrate the effectiveness of pemigatinib, on 14.04.2021 AMMF received the following in an email from one of our consultant oncologist contacts, "One of my patients came for a second opinion. In brief he has an intrahepatic cholangiocarcinoma, received cisplatin and gemcitabine (first-line) and oxaliplatin-capecitabine (second line). His cancer was impossible to biopsy for molecular profiling. In the end we had an available trial slot for liquid biopsy (ctDNA) and found an FGFR fusion. We had to apply to Incyte for pemigatinib and the whole time he was deteriorating. Finally, he started treatment in February and within a week started feeling better – his scan has shown a remarkable improvement after 3 cycles. He walked 150 Km last week! I suggested that he should share his story and have signposted him to AMMF …"	Thank you for your comment. The appraisal committee noted the benefits of pemigatinib for people with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations. Please see FAD section 3.6 for a summary of these considerations.
9	Consultee	AMMF – The Cholangiocarcinoma Charity	Pemigatinib is a treatment that is very much needed by those who are eligible within the cholangiocarcinoma community. It is hard to imagine patients with more unmet needs than those with cholangiocarcinoma. Frequently diagnosed at a late stage, for those cholangiocarcinoma patients who are inoperable this is indeed a death sentence – their survival time will be very limited. There is pitifully little in the treatment armoury for these inoperable patients: a first line chemotherapy combination that hasn't changed in over a decade and which may or may not gain them a few extra months of life, and clinical trials for some.	Thank you for your comment. The appraisal committee noted the benefits of pemigatinib for people with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations and that there is an unmet need for disease-modifying treatment. The appraisal committee agreed that pemigatinib is considered to be a life-extending

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				treatment at the end of life. Please see FAD section 3.1, section 3.6 and section 3.13 for a summary of these considerations.
10	Consultee	AMMF – The Cholangiocarcinoma Charity	Until recently there was no standard 2nd line treatment at all for those for whom the first line treatment failed, or those who had relapsed. Since the ABC-06 study, a further chemotherapy combination is now offered. However, once again this may or may not work for the patient and they will not know this until they have endured several cycles of treatment and various difficult, stressful side effects.	Thank you for your comment. The appraisal committee noted the benefits of pemigatinib for people with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations. However, the appraisal committee acknowledged the lack of comparative safety data for pemigatinib and its comparators. Please see FAD section 3.6 and section 3.7 for a summary of these considerations.
11	Consultee	AMMF – The Cholangiocarcinoma Charity	However, we now know that if a patient is found to have the FGFR2 alteration, then the therapy pemigatinib will be helpful for them. Plus, this treatment has very manageable toxicities and so offers significant overall benefit for these patients.	Thank you for your comment. The appraisal committee noted the benefits of pemigatinib for people with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations. However, the appraisal committee acknowledged the lack of comparative

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				safety data for pemigatinib and its comparators. Please see FAD section 3.6 and section 3.7 for a summary of these considerations.
12	Consultee	AMMF – The Cholangiocarcinoma Charity	NICE committee's decision means that for cholangiocarcinoma patients with an FGFR2 alteration, who may have received very little effective treatment since their diagnosis, this therapy which would extend their life is to be denied to them. This decision will seem incomprehensible and unjustifiable, even more so if it is perceived to be on grounds of cost. Because there is so little in the way of treatments available to CCA patients, overall they probably cost the NHS considerably less than treating patients with other cancers, added to which it is such an aggressive cancer, most inoperable patients will survive a very short time anyway – again less cost on the NHS.	Thank you for your comment. The appraisal committee noted the benefits of pemigatinib for people with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations. The appraisal committee must consider the costs associated with treatments in its decision making and evaluate whether the most plausible cost-effectiveness estimates are within the range that NICE normally considers an acceptable use of NHS resources. Based on the evidence presented and the revised commercial arrangements the committee concluded that pemigatinib is likely to be within the range that NICE considers a cost-effective use of NHS

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				resources. Please see FAD section 3.6, section 3.13 and section 3.14 for a summary of these considerations.
13	Consultee	AMMF – The Cholangiocarcinoma Charity	The use of targeted therapies in cholangiocarcinoma represents the single most valuable advance in the management of this cancer in the last decade. Pemigatinib has shown proven efficacy for those with an FGFR2 alteration, manageable toxicities, and offers significant overall benefit for eligible patients. Therefore, AMMF asks the committee, on behalf of all cholangiocarcinoma patients, to reconsider their decision.	Thank you for your comment. The appraisal committee noted the benefits of pemigatinib for people with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations. However, the appraisal committee acknowledged the lack of comparative safety data for pemigatinib and its comparators. Please see FAD section 3.6, section 3.7 and section 3.13 for a summary of these considerations.
14	Clinical and patient experts and NHS commissioning experts	Patient Expert	I am genuinely concerned and deeply saddened by the recent decision made by the NICE committee in not recommending Pemigatinib.	Thank you for your comment. The FAD recommends pemigatinib for treating locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or rearrangement that has progressed after systemic therapy in adults. Please see

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				FAD section 1.1.
15	Clinical and patient experts and NHS commissioning experts	Patient Expert	As a patient that has directly been impacted by cholangiocarcinoma, this decision has a huge impact on not only my own future but that of other cholangiocarcinoma patients too. Currently the only potential curative treatment available here in the UK for patients diagnosed with cholangiocarcinoma is a liver resection. Due to the aggressive nature of this type of cancer and the fact it is exceedingly difficult to diagnose early enough for treatment, most patients die before being able to receive any form of treatment plan.	Thank you for your comment. The FAD recommends pemigatinib for treating locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or rearrangement that has progressed after systemic therapy in adults. Please see FAD section 1.1.
16	Clinical and patient experts and NHS commissioning experts	Patient Expert	The chemotherapy used for this cancer has not changed in a number of years and has been proven to have little to no success. Also patients that have been lucky enough to have had a liver resection, still have an extremely high chance of recurrence going forward too.	Thank you for your comment. The appraisal committee noted the benefits of pemigatinib for people with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations. The committee also acknowledged that chemotherapy and active symptom control are the only current available treatments. Please see FAD section 3.1 and section 3.2 for a summary of these considerations.
17	Clinical and patient experts and NHS commissioning experts	Patient Expert	Pemigatinib, would allow patients that have the FGFR2 mutation the chance of extra valuable time with their families. This treatment has proven to have very manageable toxicities too, allowing patients to continue with their normal activities and quality of life. Through molecular profiling and then administration of this more targeted therapy, it would be the first step in the right direction for cholangiocarcinoma patients, who are normally resigned to a terminal diagnosis from the outset.	Thank you for your comment. The appraisal committee noted the benefits of pemigatinib for people

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				with relapsed or refractory advanced cholangiocarcinoma with FGFR2. Please see FAD section 3.1 for a summary of these considerations.
18	Clinical and patient experts and NHS commissioning experts	Patient Expert	With the increasing incidence of this cancer across all age groups, and mortality that parallels that incidence, it is critical new treatments like this are given the chance to be used. All cancer patients regardless of whether their cancer is a rarer cancer, or one of the more well- known cancers, should be offered the right to a treatment that has proven success in prolonging life, regardless of cost. The small minority of patients that would be eligible for this treatment, should not be discriminated against, because there isn't a bigger pool of data to substantiate the effectiveness of this drug due to the low survival rates. Other highly respected health authorities have already approved this treatment due to its success. The cost should be put into perspective of saving/extending lives of those people eligible for this treatment.	Thank you for your comment. The appraisal committee acknowledged the rarity of relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations. The committee also noted the company had identified all of the available data to validate the survival estimates, given the rarity of the cancer. Please see FAD section 3.14 for a summary of these considerations.
19	Clinical and patient experts and NHS commissioning experts	Patient Expert	This therapy has recently been approved in both the USA and Europe, offering cholangiocarcinoma patients there, the opportunity for this first targeted treatment, specifically aimed at cholangiocarcinoma patients and giving them valuable extra time with their families. With the success of this treatment in these other countries, it is unjust to expect those patients with this mutation here in the UK, to have to travel to other countries to seek this treatment. It could be easily available to them here too, so I really hope the committee will reconsider its decision and give those diagnosed with cholangiocarcinoma a chance of life!	Thank you for your comment. The FAD recommends pemigatinib for treating locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement that has progressed after systemic therapy in adults. Please see FAD section 1.1.

References

1. A. Hollebecque, I.M. Silverman, S. Owens, et al. Comprehensive Genomic Profiling and Clinical Outcomes in Patients With Fibroblast Growth Factor Receptor Rearrangement-Positive Cholangiocarcinoma Treated With Pemigatinib in the FIGHT-202 Trial. Annals of Oncology. Barcelona, Spain. 2019. (suppl_5): v253-v324.
2. Lamarca A, Palmer DH, Wasan HS, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *The Lancet Oncology*. 2021.
3. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2020; 21(5):671-84.
4. Zhu AX, Macarulla T, Javle MM, et al. Final results from ClarIDHy, a global, phase III, randomized, double-blind study of ivosidenib (IVO) versus placebo (PBO) in patients (pts) with previously treated cholangiocarcinoma (CCA) and an isocitrate dehydrogenase 1 (IDH1) mutation. *Journal of Clinical Oncology*. 2021; 39(3_suppl):266-.
5. Boscoe AN, Rolland C and Kelley RK. Frequency and prognostic significance of isocitrate dehydrogenase 1 mutations in cholangiocarcinoma: a systematic literature review. *J Gastrointest Oncol*. 2019; 10(4):751-65.
6. Lee K, Song YS, Shin Y, et al. Intrahepatic cholangiocarcinomas with IDH1/2 mutation-associated hypermethylation at selective genes and their clinicopathological features. *Scientific Reports*. 2020; 10(1):15820.
7. McNamara MG, Lopes A, Wasan H, et al. Landmark survival analysis and impact of anatomic site of origin in prospective clinical trials of biliary tract cancer. *J Hepatol*. 2020; 73(5):1109-17.
8. Incyte Corporation. Pemigatinib (Pemazyre). *Summary of Product Characteristics (SPC)*. 2021.
9. Incyte Corporation. Scottish Clinical Validation: Dr McNamara. 2021.
10. NHS Improvement. National schedule of reference costs. 2018. (Updated: 17 December 2018) Available at: https://improvement.nhs.uk/resources/reference-costs/. Accessed: 6 November 2019.

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Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations [ID3740]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Incyte Biosciences UK Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No disclosures**
Name of commentator person completing form:	[redacted]

Comment number	Comments

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1.	The company is disappointed with the Appraisal Committee's preliminary decision that pemigatinib is not recommended, within its marketing authorisation, for treating locally advanced or metastatic cholangiocarcinoma (CCA) with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that has progressed after systemic therapy in adults. As discussed during the appraisal meeting there are limited efficacious treatment options currently available for patients who have progressed following first-line treatment. Second line chemotherapy (mFOLFOX) provides marginal benefit for both progression-free survival and overall survival. This emphasises the urgent unmet need for access to targeted treatments such as pemigatinib to avoid a poor prognosis in those patients with an FGFR2 fusion/rearrangement. As a potent and selective FGFR1, 2, and 3 inhibitor, pemigatinib is also being investigated in previously untreated CCA patients with FGFR2 fusions/rearrangements whose disease is either unresectable or metastatic. FIGHT-302, a phase III trial, will provide comparative efficacy and safety versus standard of care and continues Incyte's commitment to driving research in an area of cancer that has underserved for over a decade. In addition to the comments below, the Company is pleased to be able to provide further supporting data to the appraisal process, which can be found in the Appendices to this response. Appendix 1 – Additional clinical validation Appendix 2 – Additional overall survival data Appendix 3 – ABC-06 and MAIC-adjusted FIGHT-202 independent survival extrapolations Appendix 4 – Updated cost-effectiveness results including an updated PAS
2. Clinical plausibility of survival extrapolations	**The clinical plausibility of the survival extrapolations is unclear** In section 3.9 of the ACD, the committee *"noted a lack of clinical validation for the comparator arm but acknowledged that a recent updated publication of ABC-06 may be informative. The committee concluded that the justification for the preferred parametric curve and the clinical expectations of survival were unclear, so the cost-effectiveness estimates for pemigatinib were uncertain."* In response to this comment, the company has sought additional validation from a clinical expert to provide clarity on the expectations of survival for cholangiocarcinoma patients previously treated with chemotherapy or active symptom control, and to identify any further suitable published literature that could serve as external validation of survival extrapolations. The validation interview conducted is summarised in Appendix 1. Clinical validation suggested that for patients receiving active symptom control (ASC) alone, it would be unlikely for patients to survive beyond 3 years and therefore 5 years. For patients treated with mFOLFOX+ASC, clinical validation suggested overall survival at 3 years would be approximately 3%, while at 5 years this may be slightly higher than the 0.1% predicted in the original company base case. Although there is no additional follow-up from ABC-06, the updated publication does provide additional detail on patient outcomes by tumour site.[2] Here, results suggest that the prognosis of patients with intrahepatic CCA(iCCA) is no better than eextrahepatic CCA (eCCA), and potentially worse, with lower median progression free survival (PFS), OS and 6 month overall survival (OS) rate (Figure 1). As an FGFR2-selected population is likely to have a higher proportion of patients

with intrahepatic disease[3], should FGFR2 have no prognostic value, this suggests that the outcomes from ABC-06 may be over-estimating the outcomes for the indication in this appraisal.

Figure 1: ABC-06 patient outcomes by tumour site[2]

	All patients	iCCA	eCCA
n (ASC-alone)	81	38	19
n (ASC+FOLFOX)	81	34	26
Overall survival			
Adjusted* HR (95% CI) OS	0.69 (0.50-0.97)	0.64 (0.38-1.06)	0.84 (0.45-1.57)
Median OS months (ASC-alone); months (95% CI)	5.3 (95% CI 4.1-5.8)	5.2 (3.7-5.8)	5.4 (3.9-6.4)
Median OS months (ASC+FOLFOX); months (95% CI)	6.2 (95% CI 5.4-7.6)	5.7 (4.1-7.4)	6.2 (4.0-7.9)
6m OS rate (ASC-alone) (%)	35.5%	30.8%	36.8%
6m OS rate (ASC+FOLFOX) (%)	50.6%	44.1%	53.9%
12m OS rate (ASC-alone) (%)	11.4%	11.2%	10.5%
12m OS rate (ASC+FOLFOX) (%)	25.9%	26.5%	15.4%
Progression-free survival			
Median PFS (ASC+FOLFOX); months (95% CI)	4.0 months (3.2-5.0)	3.3 months (2.5-5.2)	4.0 months (2.9-5.9)

Aside from ABC-06, the ClarIDHy phase III randomized trial has been identified as a potential source of validation for survival estimates in a similar patient population. ClarIDHy studies the efficacy of ivosidenib versus placebo in previously treated cholangiocarcinoma patients with an isocitrate dehydrogenase 1 (IDH1) mutation. This was considered a suitable trial for comparison because of the high proportion of patients with intrahepatic disease (95%).[4] Similarly to FIGHT-202, this study is for a molecularly selected population, and although recent publications suggest that IDH1 has no significant prognostic value, like FGFR2, the case is still unclear.[5, 6] The ClarIDHy trial included 61 patients treated with placebo who were permitted to crossover to active treatment with ivosidenib at disease progression. Median OS for patients treated with placebo was 7.5 months, while analysis that adjusted for crossover using the RPSFT method predicted a median OS of 5.1 months. It is clear that the ClarIDHy placebo arm, when adjusted for crossover, is consistent with outcomes from ABC-06 (Table 1 and Figure 2).

Table 1: ClarIDHy patient outcomes vs. ABC-06 vs. FIGHT-202

Months	**Zhu Placebo**	**Zhu Placebo RPSFT**	**ABC-06 mFOLFOX**	**ABC-06 ASC alone**	**FIGHT-202 pemigatinib**
6	57%	48%	52%	36%	89%
12	36%	17%	28%	12%	67%
18	26%	11%	10%	9%	49%
24	16%	#N/A	8%	3%	39%
30	11%	#N/A	#N/A	3%	35%
36	**#N/A**	**#N/A**	**#N/A**	**#N/A**	28%

Even when compared with outcomes from other studies identified in the company systematic literature review (SLR) and considered for inclusion within the matching adjusted indirect comparison (MAIC) (see company responses to ERG clarification questions A18 and A19), ABC-06 survival outcomes are broadly consistent between studies while still allowing for heterogeneity in patient population (Appendix 2). Due to the severity of the disease, most studies only report data up to 2 years, with only 2 studies reporting up to 3 years (with only 1 and 4 patients at risk) and no studies reporting survival at 5 years. Although patient characteristics do vary between studies, these support an overall survival extrapolation that predicts a minority of chemotherapy patients alive at 3 years, and almost no patients at 5 years.

For pemigatinib OS extrapolations, further clinical validation of the most recent datacut (April 2020) from FIGHT-202 suggested that parametric models provided reliable estimates of overall

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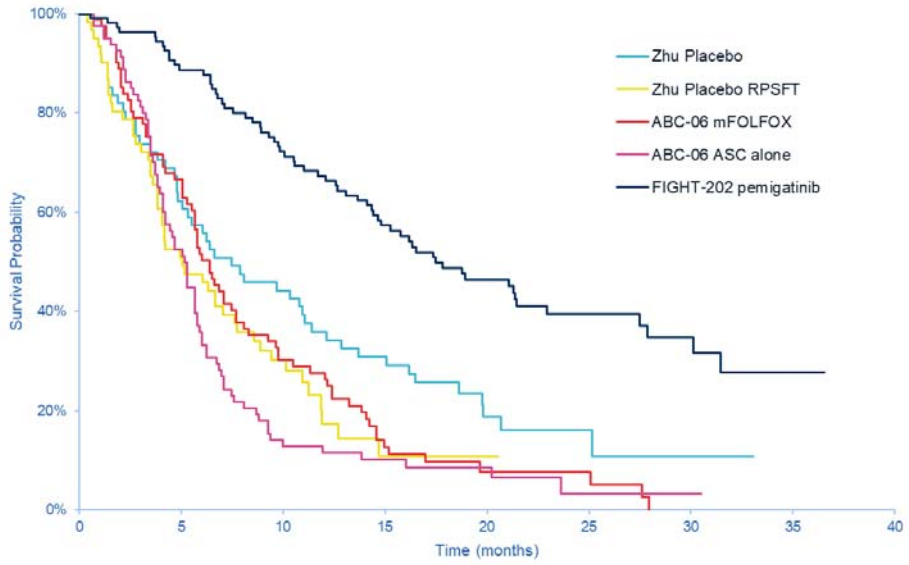
	survival for patients treated with pemigatinib at 3 years given the observed follow-up data, and that considering the evidence at the maximum follow-up of 3 years from FIGHT-202, predicted survival at 5 years would be between 10-13% (Appendix 1) **Figure 2: ClarIDHy overall survival vs. ABC-06 vs. FIGHT-202**  **Key:** ASC, active symptom control; RPSFT, rank-preserving structural failure time.
3. Fitting independent models to each group is more appropriate	**Fitting independent models to each group is more appropriate** In Section 3.10 of the ACD, "the committee considered that it was not appropriate to apply the hazard ratio to the treatment arm to generate parametric curves for comparator survival…as it requires the assumption of proportional hazards." Pg. 11 The company have chosen a pragmatic approach that aims to best reflect the available published estimates of overall survival for both pemigatinib and the relevant comparators while also remaining clinically plausible. While assessment of the proportional hazards assumption is to some extent subjective, based on assessment of the log-cumulative hazard plots, the Company argue that the proportional hazards assumption does hold and therefore application of a hazard ratio to generate parametric curves for comparator survival is appropriate. This rationale was originally presented in Section B.3.3 and Appendix L of the company submission, and has been presented again for OS using the FIGHT-202 April 2020 cut in Figure 3. In the original company submission, as an alternative option for modelling survival, independent survival models were made available within the economic model provided by the company, and tested as scenario analyses (Table 61, Section B3.8.3). At technical engagement stage, when updating the model and inputs using the FIGHT-202 April 2020 data, only the unadjusted FIGHT-202 extrapolation and the MAIC HRs were updated, as the independent models had not been considered in either the ERG base case or scenario analyses. Although these options are not thought to provide any more robust or clinically plausible outcomes than the company base case, these options have now been updated in the cost-effectiveness model with April 2020 data, and are presented as scenarios in Appendix 4. The rationale for the curves chosen in these scenarios is presented below.

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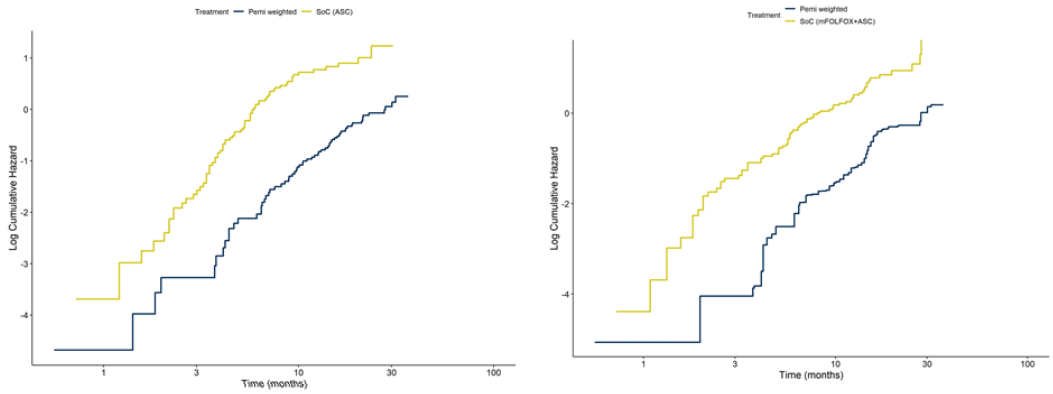
	Figure 3: Log-cumulative hazard plots for MAIC adjusted pemigatinib overall survival versus ASC and mFOLFOX+ASC (April 2020 data cut) 
4. Long-term survival estimates are highly uncertain in both groups and further analyses are needed	**Company base case** The current company base case assumptions for survival modelling are justified in the company technical engagement response and appendices. In these documents, published evidence for a decreasing probability of death over time for cholangiocarcinoma patients was presented, alongside the smoothed hazards from FIGHT-202.[7] Updated AIC/BIC statistics from FIGHT-202 April 2020 extrapolations were presented, and log-logistic was preferred due to a better AIC/BIC than other extrapolations (>5 points over generalised gamma BIC). The log-logistic curve was considered to be clinically plausible regarding long-term survival (10-13% at 5 years), although other extrapolations (such as generalised gamma) also meet these criteria, and are tested in scenario analysis within the appendix to this response (Appendix 2). As the Weibull extrapolation only predicted 5-year survival at 5%, and models increasing hazards over time, it was considered inappropriate. Applying the MAIC HR predicts long-term survival in line with clinical expectation and other published evidence for similar populations of chemotherapy- and ASC-treated patients (Appendix 2). Using the MAIC HR and leaving the FIGHT-202 data unadjusted also allows modelling of survival in the exact population of the appraisal's indication (i.e. that of FIGHT-202) without any adjustment of patient characteristics. The application of the MAIC HR to the log-logistic extrapolation of FIGHT-202 data was criticised at the ACM, due to the accelerated failure time (AFT) assumption of the log-logistic (and generalised gamma) survival models. Although the non-AFT survival models from FIGHT-202 OS data all show hazards that do not decrease, an additional scenario has been presented in Appendix 4 using the exponential function for OS (and PFS) extrapolation of FIGHT-202 data – this scenario shows similar cost-effectiveness results to the company base case, and should alleviate the committee's technical concerns regarding application of the MAIC HR to an AFT model. **Independent model scenario** In order to address the committee's consideration that fitting independent survival models would be more appropriate, a scenario has been explored whereby FIGHT-202 data and ABC-06 data are extrapolated independently of each other. For the pemigatinib OS extrapolation, three options for extrapolation are considered: 1. Extrapolation using unadjusted FIGHT-202 trial data (as per the company base case)

2. Extrapolation using FIGHT-202 trial data that has been adjusted using a MAIC and the patient characteristics from the ASC arm of ABC-06
3. Extrapolation using FIGHT-202 trial data that has been adjusted using a MAIC and the patient characteristics from the mFOLFOX+ASC arm of ABC-06

Irrespective of which arm is used for the MAIC, the log-logistic arm remains a good candidate for the base case choice for OS extrapolation of FIGHT-202 data, for the same reasons as described above (see Appendix for AIC/BIC statistics and curve extrapolations). However, generalised gamma is also explored in scenario analysis. For PFS, log-normal remained a good visual and statistical fit when using the MAIC-adjusted FIGHT-202 data, and in order to keep consistency with the unadjusted extrapolations and the comparator arm (see below), log-normal remained as the base case for MAIC-adjusted extrapolations of FIGHT-202 PFS data. TOT remained unchanged from the company base case, as TOT was not adjusted in the MAIC.

For the comparator arms, NICE TSD 14 suggests that when modelling treatment arms independently, the same extrapolation function should be used across treatment arms. The OS smoothed hazard plots for both arms of ABC-06 show increasing hazards initially, before plateauing. After this, the smoothed hazard for ASC decreases, whereas that for mFOLFOX+ASC increases, although these changes in shape are likely driven by small patient numbers (Figure 4 and Figure 5). As the log-logistic extrapolation is also a strong statistical fit for both arms of ABC-06, and the published evidence showing decreasing probability of death over time would also apply to the comparator arm, this was selected as the base case for OS in both comparator arms.[7] These provide long term survival as expected from clinicians (Table 3 and Table 4 in Appendix). However, as generalised gamma was also a good statistical fit, providing estimates aligned with clinical expectation, these extrapolations were tested in scenario analysis. For PFS, the log-normal extrapolation was a good visual fit and had the best statistical fit to the mFOLFOX+ASC ABC-06 data. As such, this was chosen as the base case PFS extrapolation for this scenario. Although other models did provide similar statistical fit, the choice of PFS extrapolation is not a big driver of model results.

Figure 4: ABC-06 ASC, Overall survival smoothed hazard plots

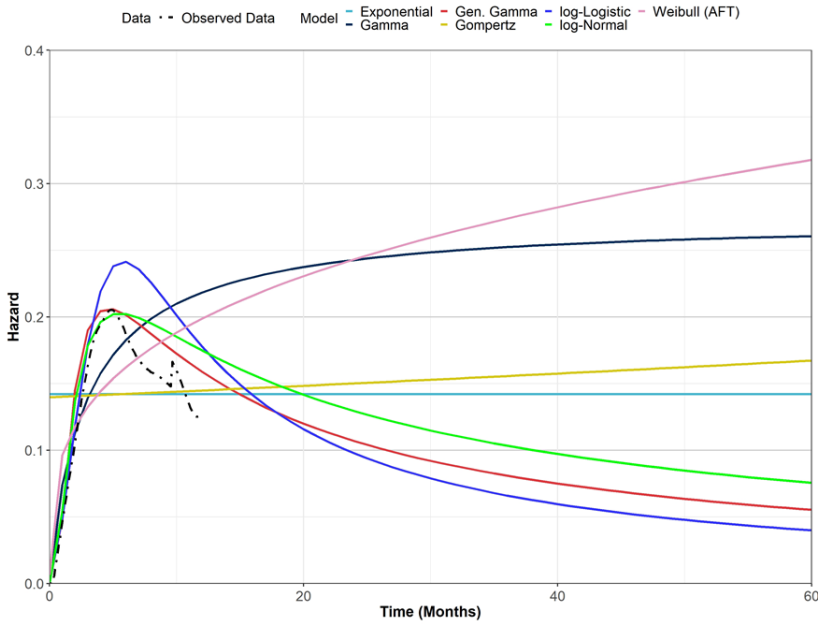


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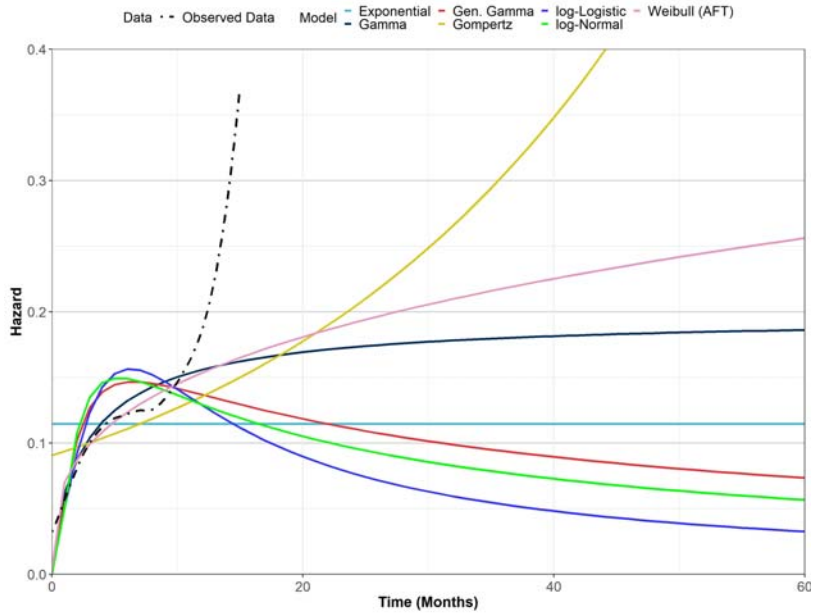
	Figure 5: ABC-06 mFOLFOX, Overall survival smoothed hazard plots  Results of cost-effectiveness analysis using unadjusted FIGHT-202 extrapolations, and extrapolations from FIGHT-202 adjusted using the ASC and the ASC+mFOLFOX arms are shown in Appendix 4. These results show that it is the choice of overall survival extrapolation that is the primary driver of model results, rather than the method of overall survival extrapolation. ICERs between analyses using HRs or using independent survival models with the same underlying extrapolation function all provide similar results. However, although the ICERs are similar, all scenarios using independent survival models predict a small number of ASC patients alive at 3 and 5 years. This is contrary to clinical expectation, which suggests that these extrapolations may overestimate ASC survival. For the ASC+mFOLFOX arm, the company base case model does slightly underpredict 3- and 5-year survival compared to clinical expectation (0.4% versus 3% at 3 years, and 0.0% versus 0.1% at 5 years). On the other hand, the independent survival models may overpredict long-term ASC+mFOLFOX survival compared to clinical opinion (1.2% versus 0.1% at 5 years), and this is also at the expense of changing the modelled patient population by adjusting the FIGHT-202 clinical trial data to match the ABC-06 patient characteristics. These scenarios provide useful evidence showing that the different methods of estimating comparator survival and relative efficacy all provide very similar cost-effectiveness results, and it is the underlying survival function that is the biggest driver of cost-effectiveness model results. The company believe log-logistic is the most appropriate extrapolation function for OS, as this shows a good visual and statistical fit, demonstrates decreasing hazards over time, and provides long-term estimates in line with clinical opinion, irrespective of any MAIC adjustment. Although generalised gamma does also meet a number of these same criteria, MAIC adjustment of FIGHT-202 data do provide long-term survival estimates slightly below that expected from clinical validation (Appendix 4, 8.4-9.9% versus 10-13%).
5. FGFR genetic testing	In Section 3.12 of the ACD, the committee suggest that “The prevalence of FGFR2 fusion or rearrangement is about 10% across all types of cholangiocarcinoma and adding FGFR2 as a target would incur an additional cost of £34.“

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	Although it is unclear where the committee estimate of FGFR2 prevalence has been sourced from, the stated cost has been included in the updated company base case cost-effectiveness analysis using the reported FGFR2+ prevalence in the UK from FIGHT-202, which was validated by clinical experts.[1] The results of this updated company base case are presented in Appendix 4.
6. Optical coherence tomography test costs	**Costs of optical coherence tomography should be included in the cost-effectiveness analysis** In Section 3.13 of the ACD the "committee concluded that the costs of optical coherence tomography should be included in the economic analysis." This was based on the suggestion of the CDF clinical lead and an expectation of what guidance would be issued in the licensed indication. The licensed indication for pemigatinib now includes guidance that an optical tomography scan should be considered: - at pemigatinib treatment initiation; - followed by every 2 months for the first 6 months of treatment; - then every 3 months while on treatment - and urgently at any time for visual symptoms.[8] Clinical expert opinion was that these observations would typically be done as part of a standard clinical exam and that it was not clear what additional benefit there was from increased monitoring when these events would be picked up routinely.[9] However, to accommodate the Committee's request and present analysis consistent with the monitoring suggested in the pemigatinib license, updated company base case results include the cost of OCT monitoring, sourced from the NHS reference costs.[10] The frequency of visual symptoms used in the model was taken from FIGHT-202 Cohort A using the prevalence of "blurred vision".

Insert extra rows as needed

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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

References

1. A. Hollebecque, I.M. Silverman, S. Owens, et al. Comprehensive Genomic Profiling and Clinical Outcomes in Patients With Fibroblast Growth Factor Receptor Rearrangement-Positive Cholangiocarcinoma Treated With Pemigatinib in the FIGHT-202 Trial. Annals of Oncology. Barcelona, Spain. 2019. (suppl_5): v253-v324.
2. Lamarca A, Palmer DH, Wasan HS, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *The Lancet Oncology*. 2021.
3. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2020; 21(5):671-84.
4. Zhu AX, Macarulla T, Javle MM, et al. Final results from ClarIDHy, a global, phase III, randomized, double-blind study of ivosidenib (IVO) versus placebo (PBO) in patients (pts) with previously treated cholangiocarcinoma (CCA) and an isocitrate dehydrogenase 1 (IDH1) mutation. *Journal of Clinical Oncology*. 2021; 39(3_suppl):266-.
5. Boscoe AN, Rolland C and Kelley RK. Frequency and prognostic significance of isocitrate dehydrogenase 1 mutations in cholangiocarcinoma: a systematic literature review. *J Gastrointest Oncol*. 2019; 10(4):751-65.
6. Lee K, Song YS, Shin Y, et al. Intrahepatic cholangiocarcinomas with IDH1/2 mutation-associated hypermethylation at selective genes and their clinicopathological features. *Scientific Reports*. 2020; 10(1):15820.
7. McNamara MG, Lopes A, Wasan H, et al. Landmark survival analysis and impact of anatomic site of origin in prospective clinical trials of biliary tract cancer. *J Hepatol*. 2020; 73(5):1109-17.
8. Incyte Corporation. Pemigatinib (Pemazyre). *Summary of Product Characteristics (SPC)*. 2021.
9. Incyte Corporation. Scottish Clinical Validation: Dr McNamara. 2021.
10. NHS Improvement. National schedule of reference costs. 2018. (Updated: 17 December 2018) Available at: https://improvement.nhs.uk/resources/reference-costs/. Accessed: 6 November 2019.

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Incyte Biosciences UK Ltd – ID3740 Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations

ACD response Appendices

Appendix 1 – Additional clinical validation

Incyte is currently planning for reimbursement submissions for pemigatinib as treatment for adult patients with advanced/metastatic or surgically unresectable cholangiocarcinoma (CCA) including fibroblast growth factor receptor 2 (*FGFR2)* fusion/rearrangements who failed previous therapy. An appraisal by the National Institute for Health and Care Excellence (NICE) is currently ongoing and submission to the Scottish Medicines Consortium (SMC) is planned.

The aim of this clinical validation meeting was primarily to seek further validation and clarification on specific requests made by NICE in their appraisal consultation document (ACD). These specific requests included:

1. Additional clarification on the clinical expectation of overall survival (OS) in both groups (pemigatinib and active symptom control/mFOLFOX) at 3 and 5 years
2. Any relevant external data to estimate expected survival for the comparator group(s)
3. The clinical expectation and likely cost associated with optical coherence tomography (OCT) required in combination with pemigatinib treatment

While the meeting focussed on requests made by NICE, where appropriate clinical opinion was sought which could also support submissions to the SMC. The clinical validation meeting took place on Friday 7 May 2021 at 15:00 – 16:00 GMT via WebEx. In attendance were the following:

Expert: Dr Mairéad McNamara (MMN)

Incyte: Shevani Naidoo (SN), Michael Thompson (MT) and Rachel Greig (RG)

BresMed: Karl Patterson (KP), Grant McCarthy (GM)

The following slides were presented during the meeting:

Pemigatinib Clinical Validation-7May21.p

Clinical Validation

SN began by briefly summarising the objectives of the clinical validation call while also providing context for where pemigatinib is currently at in the appraisal process for both NICE and the SMC. Key points were that pemigatinib has recently received regulatory approval, but also received an initial negative decision from NICE following the first appraisal committee meeting. As part of their initial decision NICE have requested additional analyses and clarification on a few key points which will be the focus of this meeting. SN handed over to KP to present the sections covering extrapolations of OS for pemigatinib, active symptom control (ASC) and mFOLFOX + ASC.

Clinical expectation of OS

KP started by presenting data for the ABC-06 comparator active symptom control (ASC) including the six options available to extrapolate OS.[1] MMN was asked what overall survival would be expected at 3 and 5 years for ASC?

- MMN suggested that it would be unlikely for patients to survive beyond 3 years, suggesting estimates would be close to 0%.
- It followed that at 5 years MMN confirmed that you would not expect anyone to still be alive. When asked, MMN did suggest that the prognosis of patients with iCCA may be slightly better but would not be very different from the estimates given.

KP asked if there any other data sources that may be informative to validate these extrapolations?

- MMN suggested two studies (Lowery et al. 2019 and Walter et al.) provided estimates based on retrospective database analysis.[2]

KP then moved on to present the same overall survival extrapolations for mFOLFOX + ASC. MM was asked what overall survival would be expected at 3 and 5 years for mFOLFOX + ASC?

- MMN suggested that 3 year survival would be approximately 3%. At 5 years, while the probability of survival would be very low it was more likely to be slightly higher than the 0.1% predicted by the models presented.
- MMN suggested that given the prognosis of patients with iCCA, they are also more likely to go on to receive 2L treatment. Overall, around 25% of patients with CCA will receive 2L active therapy.

KP provided a summary of the hazard plots for pemigatinib OS and how they should be interpreted with each figure showing how the probability of death changes over time based on the observed FIGHT-202 trial data and how well the available models are able to match those trends. The extrapolated survival models were then presented for pemigatinib and MMN was asked what overall survival would be expected at 3 and 5 years for patients treated with pemigatinib?

- MMN began by saying she had not previously seen data from this latest data cut (April 2020) from FIGHT-202 and the data looked very good.[3]
- MMN suggested that while the estimates of 3-year survival from the extrapolated models seemed very good, these were acceptable given the observed follow-up data from FIGHT-202.
- For predicted survival at 5 years, MM suggested estimates between 10-13% would be appropriate.

OCT scanning for patients treated with pemigatinib

KP handed over to MT who introduced the topic of optical tomography scans as a requested form of patient monitoring stated in the summary of product characteristics and based on rare retinal symptoms observed in the FIGHT-202 study.[4] MT first asked what visual symptoms would be identified as needing urgent further investigation?

- MMN suggested that any defects in the visual field would warrant further investigation, including central scotoma. Floaters wouldn't be considered a defect as much due to the fact floaters are fairly common in healthy people's vision. Patients may also present with zig zag lines in their vision or visual migraines which may need to be investigated further.
- MMN suggested that all these observations (central nerve examination) would typically be done as standard as part of the clinical exam, if indicated clinically, and that it wasn't clear what benefit there was to this form of increased monitoring when a standard clinical exam would pick up these events routinely and further referral and investigations would then be instituted.

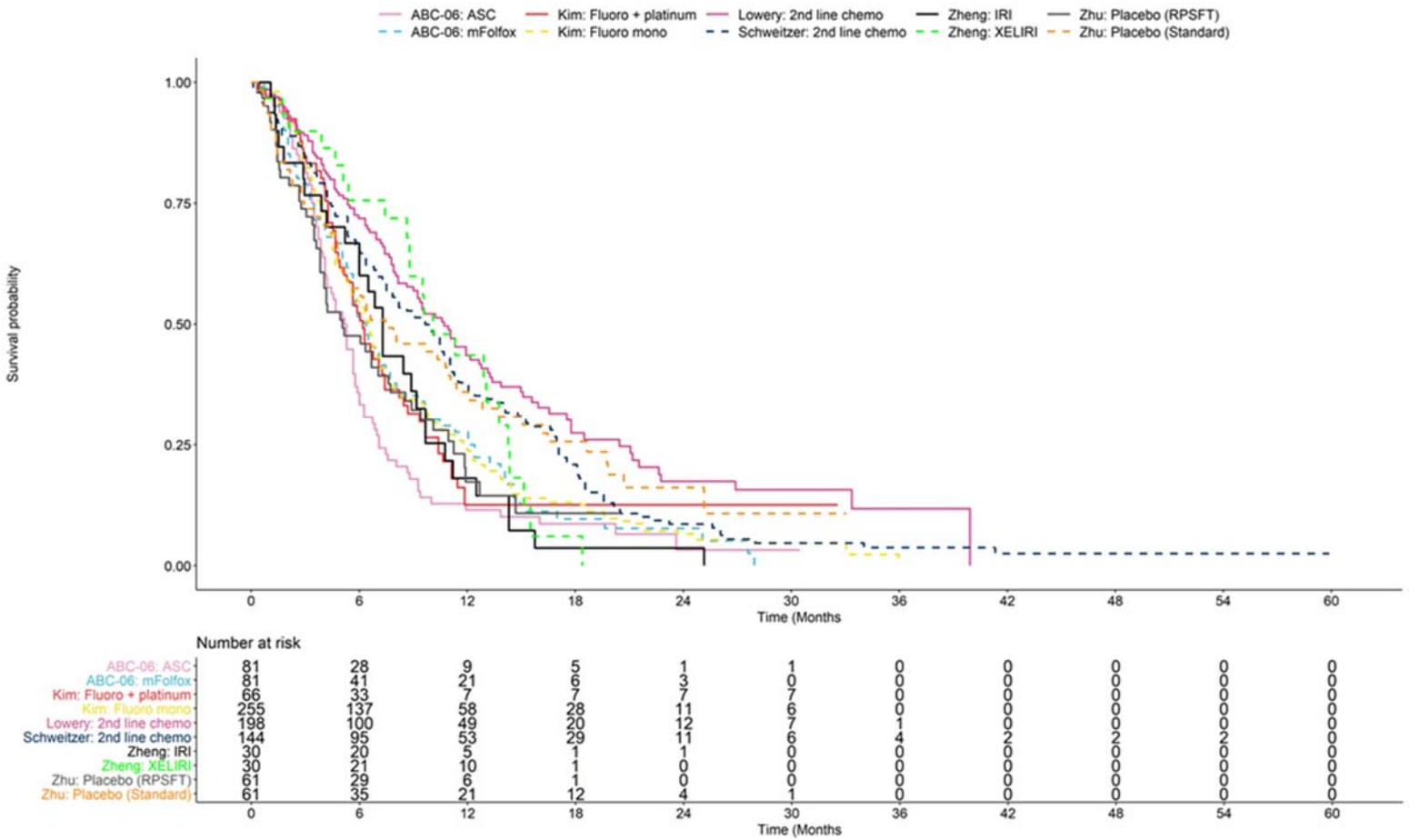
Appendix 2 – Additional overall survival data

Table 1: Patient characteristics at baseline for studies considered for indirect treatment comparison

Study name	N	Treatment	Study design	UK patients	Treatment line	FGFR2+ (%)	Age Median (range)	Men (%)	Intrahepatic CCA (%)	ECOG PS 0–1 (%)
Abou-Alfa et al 2020[5]	107	Pemigatinib	SAT	N	Second line or later	(100)	56 (26–77)	39	98	95
Kim 2017[6]	255	Fluoropyrimidine alone	Retrospective study	N - Korea	Second line	NR	60 (27 - 82)	57.3	43.9	91.3
Kim 2017[6]	66	Fluoropyrimidine plus platinum								
Lamarca et al 2019[7]	81	ASC* + mFOLFOX *Active Symptom Control	RCT	Y	Second line	NR	65 (26-847)	53	42	100
Lamarca et al 2019[7]	81	ASC* *Active Symptom Control				NR	65 (26-81)	46	47	100
Lowery et al 2019[2]	198	Chemotherapy (gemcitabine-based, 5-FU-based, intrahepatic FUDR or other)	Retrospective study	N - USA	Second-line	NR	62 (21-91)	43.4	61.1	NR
Schweitzer et al 2019	144	Chemotherapy (gemcitabine-based, 5-FU-based or other)	Retrospective study	N – Germany	Second-line	NR	59.6 (NR)	56.9	56.3	83.6
Zheng 2018[8]	60	Irinotecan plus capecitabine	RCT	N - China	Second line	NR	54 (26-70)	53.3	20 (66.7%)	100
Zheng 2018[8]	60	Irinotecan				NR	55 (40-68)	63.3	21 (70.0%)	100
Zhu 2021[9]	61	Placebo	RCT	Y	Second or third line	NR	63 (40-83)	39	95.1	98.3

Key: ASC, active symptom control; CCA, cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; FGFR2, fibroblast growth factor receptor 2; FOLFIRINOX, Oxaliplatin + leucovorin + irinotecan + fluorouracil bolus; FOLFOX, folinic acid, fluorouracil and oxaliplatin; FP, fluoropyrimidines; FU, fluorouracil; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; NR, not reported; PS, performance status; RCT, randomised controlled

Figure 1: Reported overall survival outcomes for studies considered in the MAIC analyses



Key: ASC, active symptom control; mFOLFOX, modified folinic acid, fluorouracil, and oxaliplatin; IRI, irinotecan; XELIRI, Irinotecan and capecitabine, RPSFT, rank preserving failure time

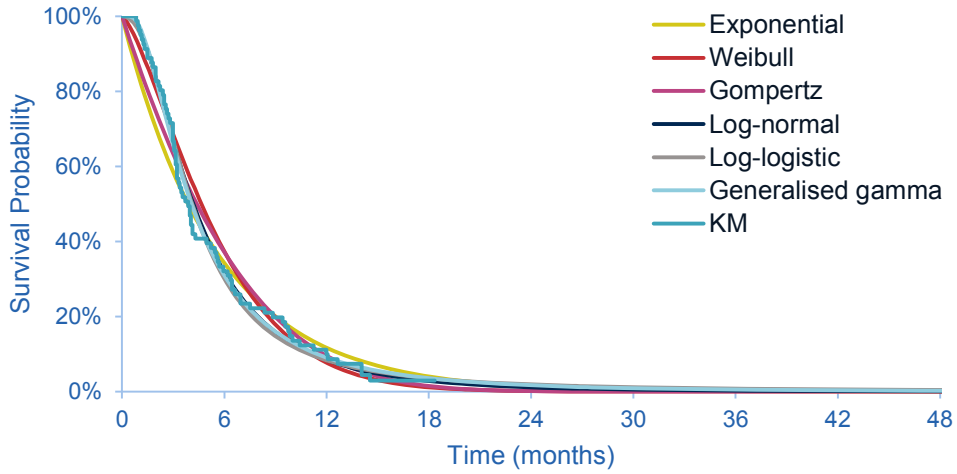
Notes: Although both Schweitzer et al. and Lowery et al. show patient survival at 3 years, both of these studies are retrospective, include no UK patients, are for second-line only, and include patients treated with a range of chemotherapies, some falling under the category of 'other'. Lowery et al. also does not report ECOG score. As such, these estimates may not be as reflective of the UK population as ABC-06 or Zhu et al.

Appendix 3 – ABC-06 and MAIC-adjusted FIGHT-202 independent survival extrapolations

ABC-06 parametric survival model extrapolations

mFOLFOX+ASC

Figure 2: ABC-06 mFOLFOX+ASC PFS KM data and fitted PSM models

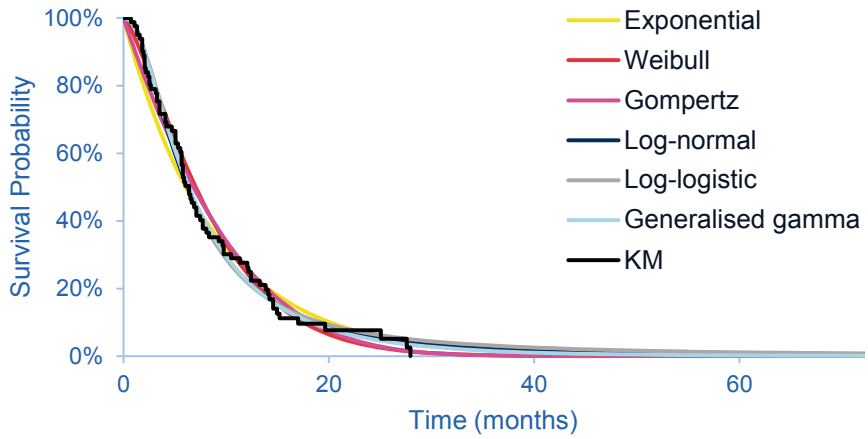


Key: mFOLFOX+ASC, modified **folinic acid, fluorouracil, and oxaliplatin**; PFS, progression-free survial; KM, Kaplan-Meier, PSM, parametric survival model

Table 2: ABC-06 mFOLFOX+ASC PFS – AIC and BIC

Model	AIC	BIC
Exponential	426.60	428.99
Generalised Gamma	406.41	413.59
Gompertz	425.29	430.08
Log-logistic	407.06	411.84
Log-normal	**404.87**	**409.65**
Weibull	416.72	421.51
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; mFOLFOX+ASC, modified folinic acid, fluorouracil, and oxaliplatin; PFS, progression-free survial; KM, Kaplan-Meier, PSM, parametric survival model		

Figure 3: ABC-06 mFOLFOX+ASC OS KM data and fitted PSM models



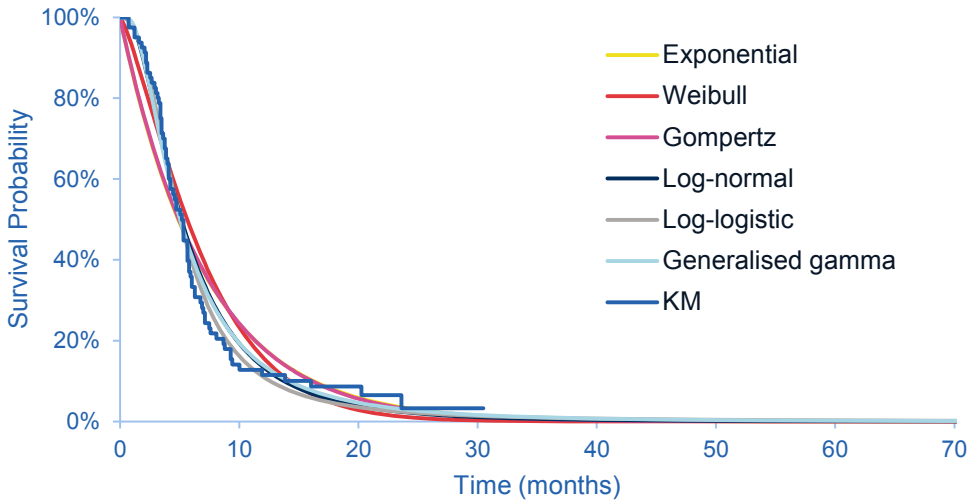
Key: mFOLFOX+ASC, modified **folinic acid, fluorouracil, and oxaliplatin**; PFS, progression-free survial; KM, Kaplan-Meier, PSM, parametric survival model

Table 3: ABC-06 mFOLFOX+ASC OS – AIC and BIC

Model	**AIC**	**BIC**
Exponential	477.08	479.48
Generalised Gamma	467.94	475.12
Gompertz	475.96	480.75
Log-logistic	468.91	473.70
Log-normal	**466.22**	**471.01**
Weibull	470.81	475.60
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; mFOLFOX+ASC, modified folinic acid, fluorouracil, and oxaliplatin; PFS, progression-free survial; KM, Kaplan-Meier, PSM, parametric survival model		

ASC

Figure 4: ABC-06 ASC OS KM data and fitted PSM models



Key: mFOLFOX+ASC, modified folinic acid, fluorouracil, and oxaliplatin; PFS, progression-free survial; KM, Kaplan-Meier, PSM, parametric survival model

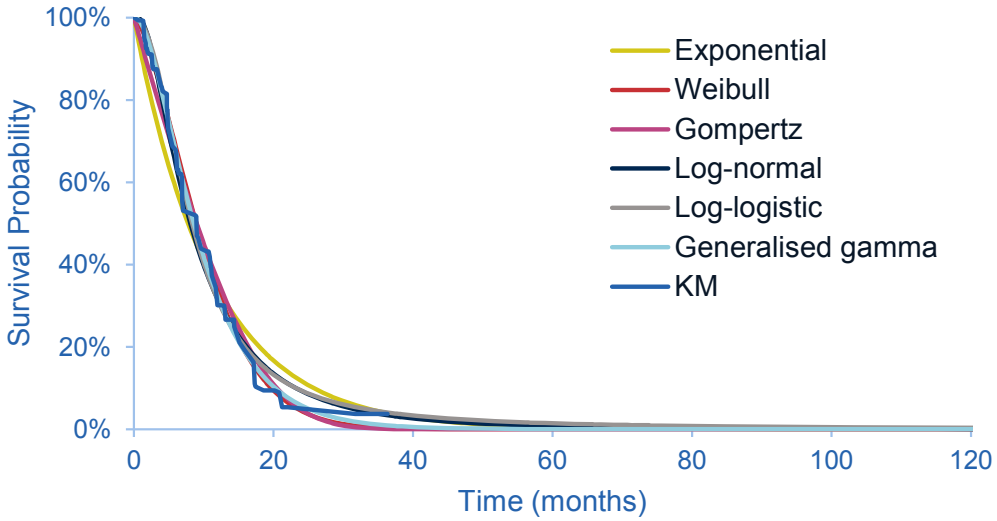
Table 4: ABC-06 ASC OS – AIC and BIC

Model	AIC	BIC
Exponential	438.89	441.28
Generalised Gamma	415.48	422.66
Gompertz	440.86	445.65
Log-logistic	**409.56**	**414.35**
Log-normal	414.16	418.95
Weibull	433.01	437.80
Key: modified folinic acid, fluorouracil, and oxaliplatin; PFS, progression-free survial; KM, Kaplan-Meier, PSM, parametric survival model		

FIGHT-202 MAIC extrapolations

Adjusted using ABC-06 mFOLFOX+ASC characteristics

Figure 5: FIGHT-202 pemigatinib PFS KM data (adjusted for ABC-06 mFOLFOX+ASC) and fitted PSM models

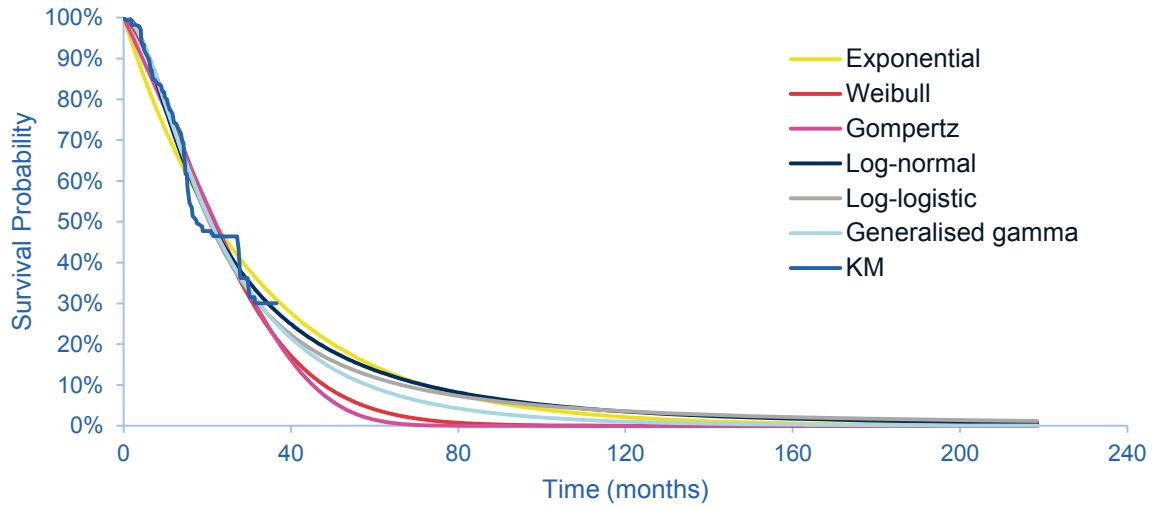


Key:mFOLFOX+ASC, modified **folinic acid, fluorouracil, and oxaliplatin**; PFS, progression-free survial; KM, Kaplan-Meier, PSM, parametric survival model

Table 5: FIGHT-202 pemigatinib PFS (adjusted for ABC-06 mFOLFOX+ASC) – AIC and BIC

Model	**AIC**	**BIC**
Exponential	375.95	378.63
Generalised Gamma	365.76	373.80
Gompertz	370.78	376.15
Log-logistic	365.81	371.17
Log-normal	366.33	371.70
Weibull	**364.80**	**370.16**
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; mFOLFOX+ASC, modified folinic acid, fluorouracil, and oxaliplatin; PFS, progression-free survial; KM, Kaplan-Meier, PSM, parametric survival model		

Figure 6: FIGHT-202 pemigatinib OS KM data (adjusted for ABC-06 mFOLFOX+ASC) and fitted PSM models



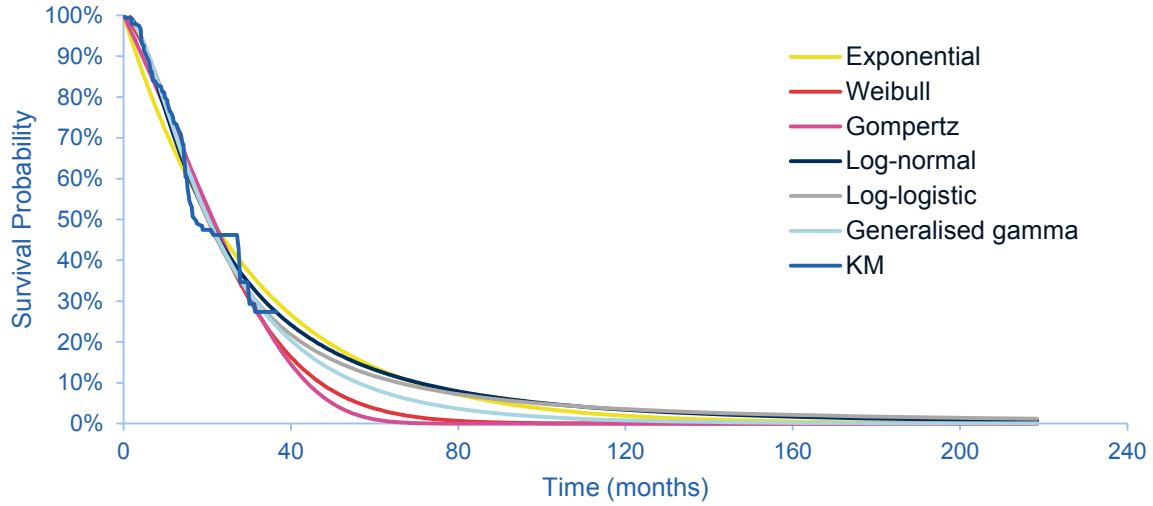
Key: mFOLFOX+ASC, modified folinic acid, fluorouracil, and oxaliplatin; PFS, progression-free survial; KM, Kaplan-Meier, PSM, parametric survival model; OS, overall survival

Table 6: FIGHT-202 pemigatinib OS (adjusted for ABC-06 mFOLFOX+ASC) – AIC and BIC

Model	AIC	BIC
Exponential	343.27	345.95
Generalised Gamma	339.07	347.11
Gompertz	342.17	347.54
Log-logistic	**336.63**	**341.99**
Log-normal	337.74	343.11
Weibull	338.47	343.83
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; mFOLFOX+ASC, modified folinic acid, fluorouracil, and oxaliplatin; KM, Kaplan-Meier, PSM, parametric survival model; OS overall survival		

Adjusted using ABC-06 ASC characteristics

Figure 7: FIGHT-202 pemigatinib OS KM data (adjusted for ABC-06 ASC) and fitted PSM models



Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; mFOLFOX+ASC, modified **folinic acid, fluorouracil, and oxaliplatin**; KM, Kaplan-Meier, PSM, parametric survival model, OS, overall survival.

Table 7: FIGHT-202 pemigatinib OS (adjusted for ABC-06 ASC) – AIC and BIC

Model	AIC	BIC
Exponential	346.42	349.10
Generalised Gamma	342.50	350.55
Gompertz	344.95	350.31
Log-logistic	**340.26**	**345.62**
Log-normal	341.33	346.69
Weibull	341.60	346.96
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; mFOLFOX+ASC, modified folinic acid, fluorouracil, and oxaliplatin; KM, Kaplan-Meier, PSM, parametric survival model, OS, overall survival.		

Appendix 4 – Updated cost-effectiveness results

Updated company deterministic base case and scenario analyses

The company ACD response describes the company's preferences on each of the committee's key concerns. Some of these preferences require an update to the company base case cost-effectiveness results while for other assumptions, following clinical validation there was found to be no clear justification for a change to the base case. In addition, the company has proposed

an update to the existing patient access scheme, reducing the price per pack of pemigatinib to [commercial in confidence information removed]. The results using the company's updated preferrred assumptions and PAS are shown in Table 8.

Table 8: Updated company deterministic base case and scenario analyses results [commercial in confidence information removed]

	ICER vs. mFOLFOX		ICER vs. ASC		3-year OS			5-year OS		
	ACM1 PAS [redacted]	Updated PAS [redacted]	ACM1 PAS [redacted]	Updated PAS [redacted]	Pemi-gatinib	ASC	ASC+ mFOLFOX	Pemi-gatinib	ASC	ASC+ mFOLFOX
ACM1 company base case	£49,186	£41,265	£51,952	£44,240	24.8%	0.1%	0.4%	12.5%	0.0%	0.0%
+ addition of OCT monitoring costs	£49,663	£41,743	£52,417	£44,705	24.8%	0.1%	0.4%	12.5%	0.0%	0.0%
+ addition of FGFR2 testing costs	£49,996	£42,076	£52,741	£45,029	24.8%	0.1%	0.4%	12.5%	0.0%	0.0%
Updated company base case	**£49,996**	**£42,076**	**£52,741**	**£45,029**	**24.8%**	**0.1%**	**0.4%**	**12.5%**	**0.0%**	**0.0%**
+ generalised gamma for OS extrapolation	£59,141	£49,629	£62,127	£52,916	24.2%	0.1%	0.3%	9.9%	0.0%	0.0%
+ exponential for OS and PFS extrapolation	£55,751	£46,935	£57,889	£49,371	27.1%	0.2%	0.5%	11.4%	0.0%	0.0%
Independent survival models: log-logistic OS for all arms (unadjusted FIGHT-202)	£53,729	£45,123	£51,999	£44,411	24.8%	0.9%	3.3%	12.5%	0.3%	1.2%
Independent survival models: log-logistic OS for all arms (FIGHT-202 adjusted using ASC ABC-06)	£54,528	£45,808	£52,691	£45,010	25.2%	0.9%	3.3%	11.6%	0.3%	1.2%

	ICER vs. mFOLFOX		ICER vs. ASC		3-year OS			5-year OS		
	ACM1 PAS [redacted]	**Updated PAS** [redacted]	**ACM1 PAS** [redacted]	**Updated PAS** [redacted]	**Pemi-gatinib**	**ASC**	**ASC+ mFOLFOX**	**Pemi-gatinib**	**ASC**	**ASC+ mFOLFOX**
Independent survival models: log-logistic OS for all arms (FIGHT-202 adjusted using ASC+mFOLFOX ABC-06)	£53,612	£45,051	£51,912	£44,354	25.8%	0.9%	3.3%	11.9%	0.3%	1.2%
Independent survival models: generalised gamma OS for all arms (unadjusted FIGHT-202)	£61,607	£51,622	£62,058	£52,866	24.2%	1.0%	1.7%	9.9%	0.2%	0.2%
Independent survival models: generalised gamma OS for all arms (FIGHT-202 adjusted using ASC ABC-06)	£62,169	£52,116	£62,575	£53,323	24.3%	1.0%	1.7%	8.4%	0.2%	0.2%
Independent survival models: generalised gamma OS for all arms (FIGHT-202 adjusted using ASC+mFOLFOX ABC-06)	£59,593	£49,987	£60,180	£51,307	25.5%	1.0%	1.7%	9.3%	0.2%	0.2%

Key: ASC, active symptom control; ACM, appraisal committee meeting; optical coherence tomography; FGFR, fibroblast growth factor receptor 2; OS, overall survival

Updated company probabilistic base case

The company has also updated the probabilistic base case cost-effectiveness results. These results align closely with the deterministic results (Table 9 and Figure8), and estimate that pemigatinib has a [commercial in confidence information removed] probability of being cost-effective at a willingness-to-pay threshold of £50,000 (Figure9).

Table 9: Updated company deterministic and probabilistic base case results [commercial in confidence information removed]

	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER (£/QALY)
Deterministic results							
ASC	[redacted]	0.60	[redacted]				
mFOLFOX+ASC	[redacted]	0.66	[redacted]	[redacted]	0.06	[redacted]	Extendedly dominated
Pemigatinib	[redacted]	2.44	[redacted]	[redacted]	1.84	[redacted]	45,029
Probabilistic results							
ASC	[redacted]	0.60	[redacted]				
mFOLFOX+ASC	[redacted]	0.66	[redacted]	[redacted]	0.06	[redacted]	Extendedly dominated
Pemigatinib	[redacted]	2.46	[redacted]	[redacted]	1.86	[redacted]	43,736

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality adjusted life years.

Figure 8: Updated company base case cost-effectiveness plane [commercial in confidence information removed]

Key: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; WTP, willingness to pay.

Figure 9: Updated company base case CEAC [commercial in confidence information removed]

Key: CEAC, cost-effectiveness acceptability curve.

Updated company base case one-way sensitivity analysis

The updated one-way sensitivity analyses show the same key parameters as drivers of model results: pemigatinib OS HR, baseline utility and the cost of IV administration for mFOLFOX (Figure 10, Figure 11).

Figure 10: Updated company base case one-way sensitivity analysis vs. ASC [commercial in confidence information removed]

Key: ICER, incremental cost-effectiveness ratio.

Figure 11: Updated company base case one-way sensitivity analysis vs. ASC+mFOLFOX [commercial in confidence information removed]

Key: ICER, incremental cost-effectiveness ratio.

References

1. Lamarca A, Palmer DH, Wasan HS, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *The Lancet Oncology*. 2021.

2. Lowery MA, Goff LW, Keenan BP, et al. Second-line chemotherapy in advanced biliary cancers: A retrospective, multicenter analysis of outcomes. *Cancer*. 2019; 125(24):4426-34.

3. Incyte Corporation. Clinical Study Report Addendum: A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects With Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including FGFR2 Translocations Who Failed Previous Therapy (FIGHT-202) (data cut-off: 7 April 2020). 2020.

4. Incyte. Summary of Product Characteristics (SPC). Pemigatinib (Pemazyre). 2021. Accessed: 13 April 2021.

5. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2020; 21(5):671-84.

6. Kim BJ, Yoo C, Kim KP, et al. Efficacy of fluoropyrimidine-based chemotherapy in patients with advanced biliary tract cancer after failure of gemcitabine plus cisplatin: Retrospective analysis of 321 patients. *Br J Cancer*. 2017; 116(5):561-7.

7. Lamarca A, Palmer DH, Wasan HS, et al. ABC-06 | A randomised phase III, multi-centre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC+mFOLFOX) for patients (pts) with locally advanced / metastatic biliary tract cancers (ABC) previously-treated with cisplatin/gemcitabine (CisGem) chemotherapy. *Journal of Clinical Oncology*. 2019; 37(15_suppl):4003-.

8. Zheng Y, Tu X, Zhao P, et al. A randomised phase II study of second-line XELIRI regimen versus irinotecan monotherapy in advanced biliary tract cancer patients progressed on gemcitabine and cisplatin. *Br J Cancer*. 2018; 119(3):291-5.

9. Zhu AX, Macarulla T, Javle MM, et al. Final results from ClarIDHy, a global, phase III, randomized, double-blind study of ivosidenib (IVO) versus placebo (PBO) in patients (pts) with previously treated cholangiocarcinoma (CCA) and an isocitrate dehydrogenase 1 (IDH1) mutation. *Journal of Clinical Oncology*. 2021; 39(3_suppl):266-.

10. Walter T, Horgan AM, McNamara M, et al. Feasibility and benefits of second-line chemotherapy in advanced biliary tract cancer: A large retrospective study. *European Journal of Cancer*. 2013; 49(2):329-335

NICE National Institute for Health and Care Excellence

Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations [ID3740]

Consultation on the appraisal consultation document – deadline for comments by **5pm** on **Wednesday 26 May 2021** via NICE DOCS.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**AMMF – The Cholangiocarcinoma Charity**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	Comments

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	AMMF – the Cholangiocarcinoma Charity, advocates for all those with cholangiocarcinoma. As such, we would like to express huge disappointment and dissatisfaction at the decision made by the NICE committee in not recommending Pemigatinib.
1	To illustrate the effectiveness of pemigatinib, on 14.04.2021 AMMF received the following in an email from one of our consultant oncologist contacts, "One of my patients came for a second opinion. In brief he has an intrahepatic cholangiocarcinoma, received cisplatin and gemcitabine (first-line) and oxaliplatin-capecitabine (second line). His cancer was impossible to biopsy for molecular profiling. In the end we had an available trial slot for liquid biopsy (ctDNA) and found an FGFR fusion. We had to apply to Incyte for pemigatinib and the whole time he was deteriorating. Finally, he started treatment in February and within a week started feeling better – his scan has shown a remarkable improvement after 3 cycles. He walked 150 Km last week! I suggested that he should share his story and have signposted him to AMMF …"
2	Pemigatinib is a treatment that is very much needed by those who are eligible within the cholangiocarcinoma community. It is hard to imagine patients with more unmet needs than those with cholangiocarcinoma. Frequently diagnosed at a late stage, for those cholangiocarcinoma patients who are inoperable this is indeed a death sentence – their survival time will be very limited. There is pitifully little in the treatment armoury for these inoperable patients: a first line chemotherapy combination that hasn't changed in over a decade and which may or may not gain them a few extra months of life, and clinical trials for some.
3	Until recently there was no standard 2nd line treatment at all for those for whom the first line treatment failed, or those who had relapsed. Since the ABC-06 study, a further chemotherapy combination is now offered. However, once again this may or may not work for the patient and they will not know this until they have endured several cycles of treatment and various difficult, stressful side effects.
4	However, we now know that if a patient is found to have the FGFR2 alteration, then the therapy pemigatinib will be helpful for them. Plus, this treatment has very manageable toxicities and so offers significant overall benefit for these patients.
5	NICE committee's decision means that for cholangiocarcinoma patients with an FGFR2 alteration, who may have received very little effective treatment since their diagnosis, this therapy which would extend their life is to be denied to them. This decision will seem incomprehensible and unjustifiable, even more so if it is perceived to be on grounds of cost. Because there is so little in the way of treatments available to CCA patients, overall they probably cost the NHS considerably less than treating patients with other cancers, added to which it is such an aggressive cancer, most inoperable patients will survive a very short time anyway – again less cost on the NHS.
6	The use of targeted therapies in cholangiocarcinoma represents the single most valuable advance in the management of this cancer in the last decade. Pemigatinib has shown proven efficacy for those with an FGFR2 alteration, manageable toxicities, and offers significant overall benefit for eligible patients. Therefore, AMMF asks the committee, on behalf of all cholangiocarcinoma patients, to reconsider their decision.

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[None]
Name of commentator person completing form:	Andrea Sheardown – Cholangiocarcinoma Patient Expert

Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I am genuinely concerned and deeply saddened by the recent decision made by the NICE committee in not recommending Pemigatinib.
2	As a patient that has directly been impacted by cholangiocarcinoma, this decision has a huge impact on not only my own future but that of other cholangiocarcinoma patients too. Currently the only potential curative treatment available here in the UK for patients diagnosed with cholangiocarcinoma is a liver resection. Due to the aggressive nature of this type of cancer and the fact it is exceedingly difficult to diagnose early enough for treatment, most patients die before being able to receive any form of treatment plan.
3	The chemotherapy used for this cancer has not changed in a number of years and has been proven to have little to no success. Also patients that have been lucky enough to have had a liver resection, still have an extremely high chance of recurrence going forward too.
4	Pemigatinib, would allow patients that have the FGFR2 mutation the chance of extra valuable time with their families. This treatment has proven to have very manageable toxicities too, allowing patients to continue with their normal activities and quality of life. Through molecular profiling and then administration of this more targeted therapy, it would be the first step in the right direction for cholangiocarcinoma patients, who are normally resigned to a terminal diagnosis from the outset.
5	With the increasing incidence of this cancer across all age groups, and mortality that parallels that incidence, it is critical new treatments like this are given the chance to be used. All cancer patients regardless of whether their cancer is a rarer cancer, or one of the more well- known cancers, should be offered the right to a treatment that has proven success in prolonging life, regardless of cost. The small minority of patients that would be eligible for this treatment, should not be discriminated against, because there isn't a bigger pool of data to substantiate the effectiveness of this drug due to the low survival rates. Other highly respected health authorities have already approved this treatment due to its success. The cost should be put into perspective of saving/extending lives of those people eligible for this treatment.
6	This therapy has recently been approved in both the USA and Europe, offering cholangiocarcinoma patients there, the opportunity for this first targeted treatment, specifically aimed at cholangiocarcinoma patients and giving them valuable extra time with their families. With the success of this treatment in these other countries, it is unjust to expect those patients with this mutation here in the UK, to have to travel to other countries to seek this treatment. It could be easily available to them here too, so I really hope the committee will reconsider its decision and give

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	those diagnosed with cholangiocarcinoma a chance of life!

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Maastricht University

Pemigatinib for the treatment of relapsed or refractory advanced cholangiocarcinoma with *FGFR2* alterations

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Declared competing interests of the authors
None.

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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors
Marie Westwood and Nigel Armstrong acted as joint project leads and systematic reviewers on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Hannah Penton acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report and provided general guidance. Pim Wetzelaer, Charlotte Ahmadu and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Janine Ross critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al critiqued the company's economic evaluation, contributed to the writing of the report, and provided general health economic guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Introduction

This addendum contains the ERGs critique of the company's updated survival analyses and base-case assumptions, provided in the company's response to the Appraisal Consultation Document (ACD).[1] The company's updated cost effectiveness results and scenarios are provided in Section 2, followed by the ERG's updated cost effectiveness results and scenarios in Section 3.

1. Updated survival analyses

1.1 Updated survival analyses

The ACD summarised a number of concerns raised by the committee regarding the survival analyses in the model, including:

- The committee considered it inappropriate to apply the hazard ratio (HR) to the treatment arm to generate parametric curves for comparator survival, as this required the assumption of proportional hazards (PH) and it noted that the company's preferred log-logistic extrapolation is not a PH model. The committee considered that it would have been more appropriate to fit independent models to the treatment and comparator arms.[1]
- Using data from two comparators in the indirect comparison produces two weighted datasets for pemigatinib. They considered that subsequent analyses should select one dataset and the committee would like to see evidence that both datasets are similar.[1]

The committee requested to see:

- Clinical expectations of survival at 3 and 5 years in all treatment groups
- External data on expected comparator survival
- An assessment of the empirical hazard function over time

In response to the committee's requests, the company sought further expert opinion on survival expectations and sources of literature which could provide external validation of survival extrapolations. Further survival analyses were also conducted by updating the independently fit extrapolations available in the model using the April 2020 data cut.

Clinical expectations of survival at 3 and 5 years

The company conducted a further clinical expert opinion elicitation exercise with one clinician, detailed in Appendix 1 of the ACD response.[2] The clinician suggested that on active symptom control (ASC), 3-year survival would be close to 0% and 5-year survival 0%. The clinician's predicted 3-year survival estimate on mFOLFOX+ASC was approximately 3%, while at 5-years it was considered that survival would be very low, but likely slightly higher than the model predicted 0.1%. For pemigatinib, the extrapolations were presented. The clinician considered that while the estimates of 3-year survival from the extrapolated models seemed very good, these were acceptable given the observed follow-up data from FIGHT-202. For predicted survival at 5-years the clinician considered that estimates between 10-13% would be appropriate.

ERG Comment: The new clinical opinion estimate of survival at 5 years on pemigatinib of 10-13% aligns well with the estimates given by the clinicians in the first ACM of 10% survival at 5-years, although includes a slightly higher range. The ERG therefore considers that the lower end of the 10-13% range may be more credible.

External datasets

During the first committee meeting, it was mentioned that a publication of further ABC-06 data was expected soon. In their ACD response, the company reported that while the updated ABC-06 publication

did not include additional follow-up it did include additional detail on patient outcomes by tumour site, which showed that intrahepatic cholangiocarcinoma (iCCA) patients had no better, and possibly worse prognosis than extrahepatic cholangiocarcinoma (eCCA), with lower median PFS, OS and 6-month OS results compared to eCCA, shown in Figure 1.1 below.[3]

The clinician consulted by the company also mentioned 2 studies which provided estimates based on retrospective database analysis, Lowery et al 2019 and Walter et al.[4, 5] The company also reported outcomes from the ClarlDHy trial, which they considered an appropriate source of validation because of the high proportion of patients with iCCA disease (95%).[6] This trial was also for a molecular subpopulation i.e. IDH1 mutation. The company report that once the ClarlDHy placebo arm is adjusted for crossover, the outcomes, including those presented in Table 1 and Figure 2 of the ACD response, and the median OS of 5.1 months, are consistent with outcomes from ABC-06.[7]

Figure 1.1: ABC-06 patient outcomes by tumour site

	All patients	iCCA	eCCA
n (ASC-alone)	81	38	19
n (ASC+FOLFOX)	81	34	26
Overall survival			
Adjusted* HR (95% CI) OS	0.69 (0.50-0.97)	0.64 (0.38-1.06)	0.84 (0.45-1.57)
Median OS months (ASC-alone); months (95% CI)	5.3 (95% CI 4.1-5.8)	5.2 (3.7-5.8)	5.4 (3.9-6.4)
Median OS months (ASC+FOLFOX); months (95% CI)	6.2 (95% CI 5.4-7.6)	5.7 (4.1-7.4)	6.2 (4.0-7.9)
6m OS rate (ASC-alone) (%)	35.5%	30.8%	36.8%
6m OS rate (ASC+FOLFOX) (%)	50.6%	44.1%	53.9%
12m OS rate (ASC-alone) (%)	11.4%	11.2%	10.5%
12m OS rate (ASC+FOLFOX) (%)	25.9%	26.5%	15.4%
Progression-free survival			
Median PFS (ASC+FOLFOX); months (95% CI)	4.0 months (3.2-5.0)	3.3 months (2.5-5.2)	4.0 months (2.9-5.9)

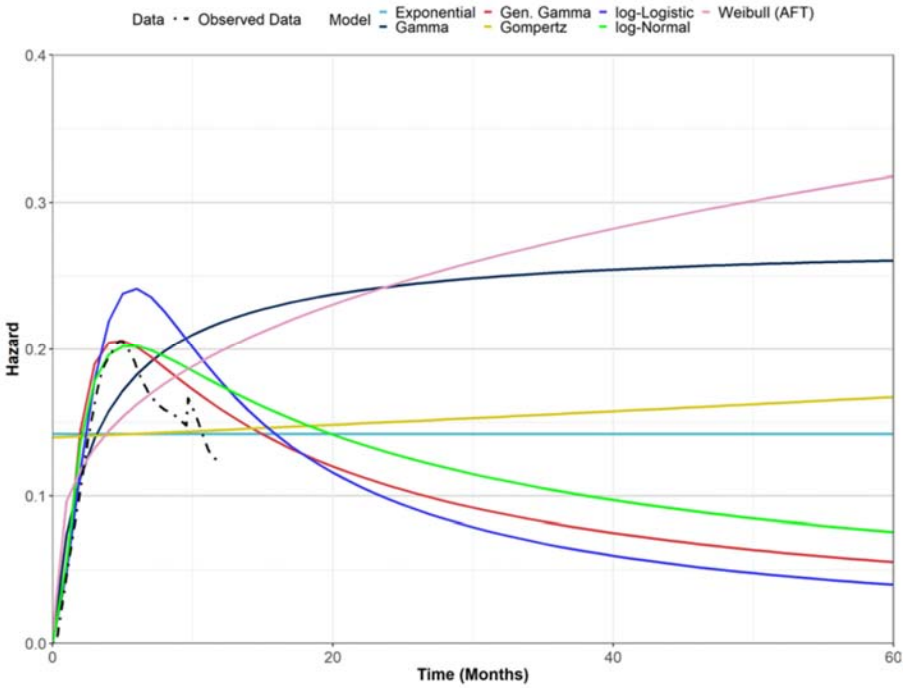
Source: Figure 1 of the Company's Response to the ACD.[7]
ASC = active symptom control; eCCA = extrahepatic cholangiocarcinoma; HR = hazard ratio; iCCA = intrahepatic cholangiocarcinoma; PFS = progression free survival; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; OS = overall survival.

ERG Comment: The ERG notes that while 6-month and median outcomes all favour eCCA patients, the 12-month OS rates favour iCCA. However more importantly, the ERG does not feel this evidence reduces the uncertainty surrounding the populations in this appraisal, as it involves a comparison between a different mutation subgroup and the unselected ABC-06 population. Similarity between the iDH1 and FGFR2 mutation populations in terms of proportion of patients with iCCA, does not mean that we would expect similar survival characteristics in patients with the FGFR2 mutation.

Assessment of the empirical hazard function over time

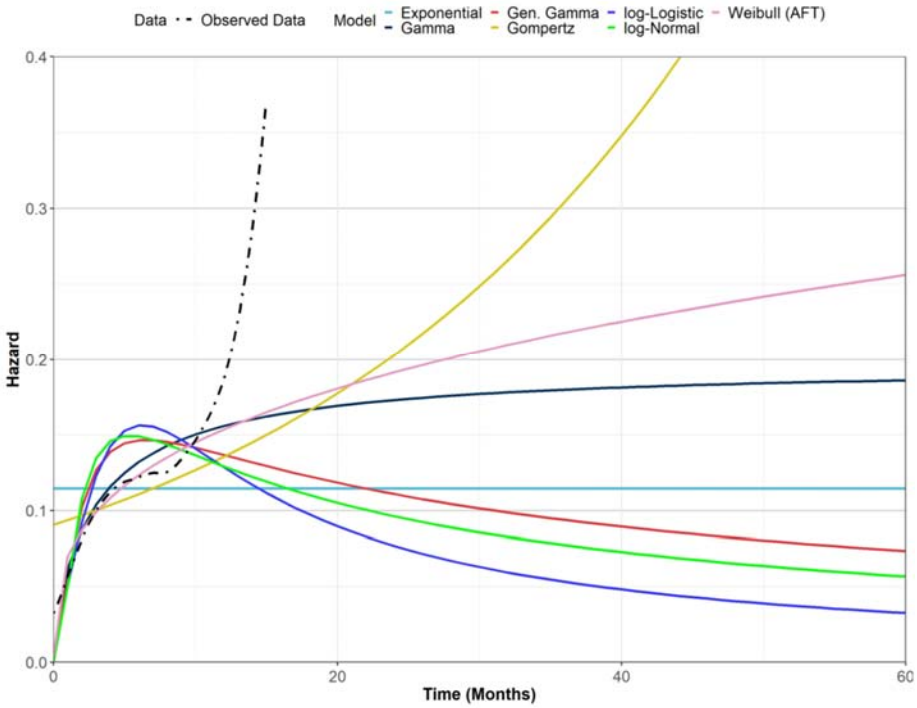
The company provided plots of the smoothed hazards over time for patients on ASC and mFOLFOX, displayed in Figures 1.2 and 1.3 below, to complement the curves for pemigatinib provided at Technical Engagement.[1] The OS smoothed hazard plots for both arms of ABC-06 show increasing hazards initially, before plateauing. After this, the smoothed hazard for ASC decreases, but increases for mFOLFOX+ASC. The company consider that the increase observed for mFOLFOX is likely due to small patient numbers. The company state that the published evidence showing decreasing probability of death over time would also apply to the comparator arm, and therefore a model with declining hazards would be appropriate in the base-case.

Figure 1.2: ABC-06 ASC, Overall survival smoothed hazard plots



Source: Figure 4 of the Company's Response to the ACD.[7]
ASC = active symptom control.

Figure 1.3: ABC-06 mFOLFOX, Overall survival smoothed hazard plots



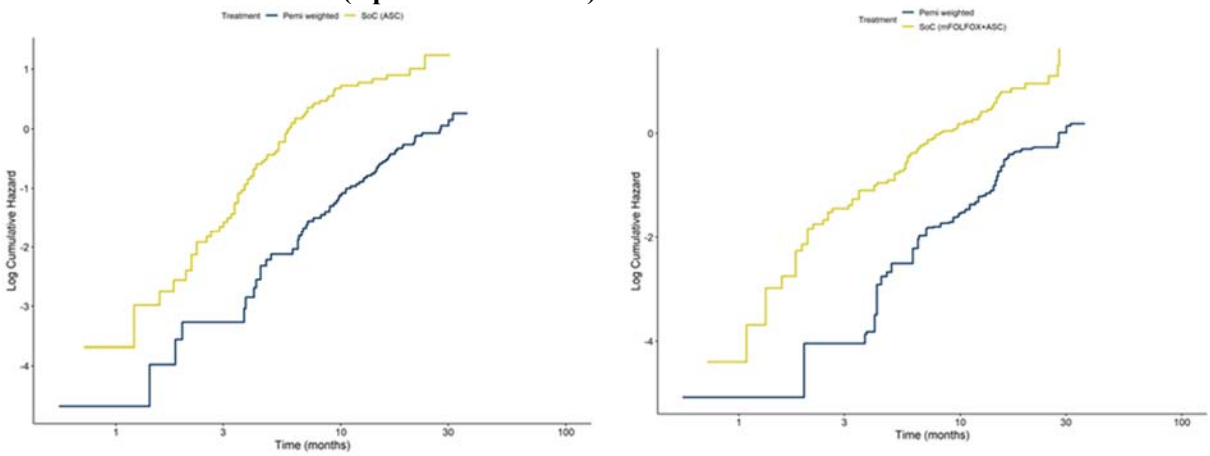
Source: Figure 5 of the Company's Response to the ACD.[7]
mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil.

ERG Comment: The additional empirical hazard plots for ASC and mFOLFOX provided by the company show that the predicted hazards for the log-logistic, generalised gamma and log-normal fit quite well, while other extrapolations, including the Weibull considered in the first committee meeting do not appear to fit well. For the mFOLFOX arm, none of the curves appear to fit the empirical hazards well, but it is unclear to what extent this is due to small patient numbers.

Fitting independent models to each group

In response to the committee's comment that using HRs to generate comparator survival curves was inappropriate, the company argued that while assessment of proportional hazards is somewhat subjective, they consider based on Figure 1.4 below that it was a reasonable assumption. They therefore consider the application of a HR to generate parametric curves for comparator survival appropriate. The company note that independently fit models were available in the economic model at CS and were tested as scenarios.[7] At technical engagement, when extrapolations were updated with the April 2020 data cut, only the unadjusted FIGHT-202 extrapolation and the MAIC HRs were updated, as the independent models had not been considered in either the ERG base case or scenario analyses. These models have now been updated with April 2020 data and are presented as scenarios in Appendix 4 of the company ACD response.[2]

Figure 1.4: Log-cumulative hazard plots for MAIC adjusted pemigatinib overall survival versus ASC and mFOLFOX+ASC (April 2020 data cut)



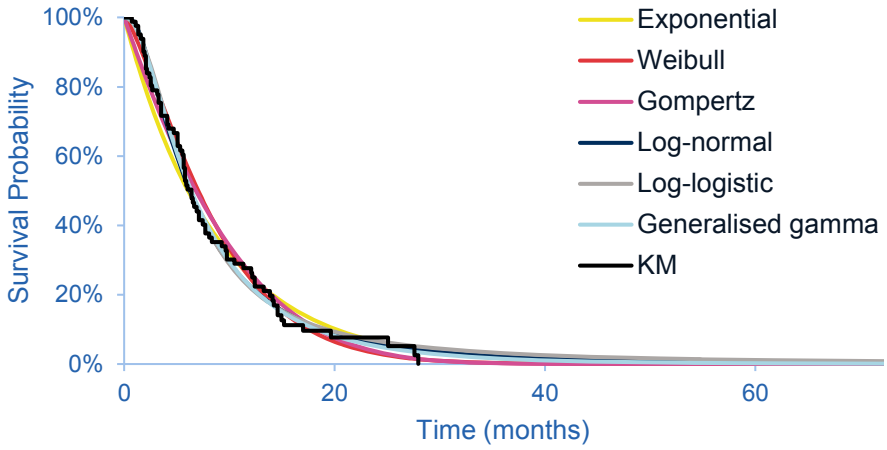
Source: Figure 3 of the Company's Response to the ACD.[7]
ASC = active symptom control; MAIC = matching adjusted indirect comparison; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil.

The company conducted several scenario analyses using the independently fit extrapolations. For the pemigatinib OS extrapolation, three options for extrapolation were considered:

1. Extrapolation using unadjusted FIGHT-202 trial data (as per the company base case)
2. Extrapolation using FIGHT-202 trial data that has been adjusted using a MAIC and the patient characteristics from the ASC arm of ABC-06
3. Extrapolation using FIGHT-202 trial data that has been adjusted using a MAIC and the patient characteristics from the mFOLFOX+ASC arm of ABC-06

Kaplan Meier (KM) and extrapolation curves for ASC, mFOLFOX and pemigatinib (matched to either ASC or mFOLFOX) as well as fit statistics and 3- and 5-year survival estimates are presented below in Tables 1.1-1.4 and Figures 1.5-1.8.

Figure 1.5: ABC-06 mFOLFOX+ASC OS KM data and fitted PSM models



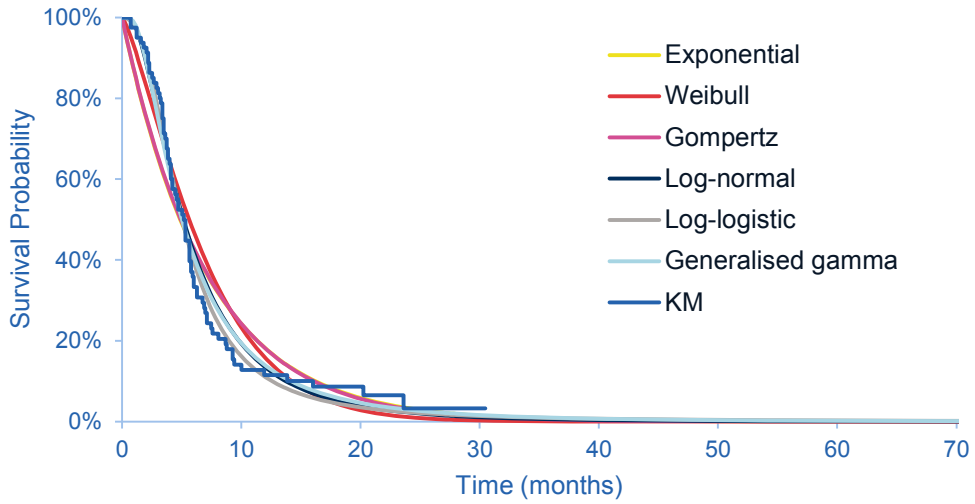
Source: Figure 3 of Appendix 3 of the Company's Response to the ACD.[2]
ASC = active symptom control; KM = Kaplan Meier; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; OS = overall survival; PSM = parametric survival model.

Table 1.1: ABC-06 mFOLFOX+ASC OS – AIC and BIC

Model	AIC	BIC	3-year survival estimate	5-year survival estimate
Exponential	477.08	479.48	1.6%	0.1%
Generalised gamma	467.94	475.12	1.5%	0.2%
Gompertz	475.96	480.75	0.2%	0.0%
Log-logistic	468.91	473.70	3.1%	1.2%
Log-normal	**466.22**	**471.01**	2.1%	0.4%
Weibull	470.81	475.60	0.3%	0.0%

Source: Table 3 of Appendix 3 of the Company's Response to the ACD.[2]
AIC = Akaike information criterion; ASC = active symptom control; BIC = Bayesian information criterion; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; OS = overall survival.

Figure 1.6: ABC-06 ASC OS KM data and fitted PSM models



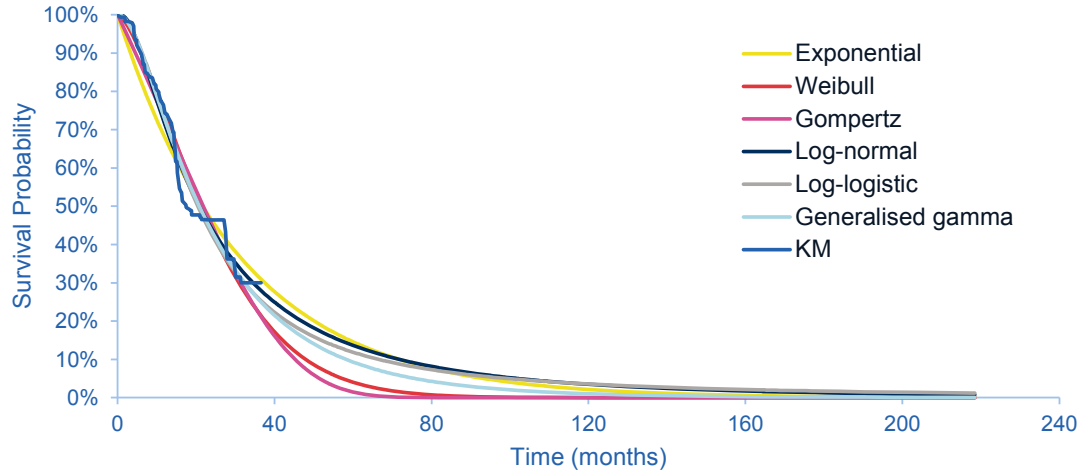
Source: Figure 4 of Appendix 3 of the Company's Response to the ACD.[2]
ASC = active symptom control; KM = Kaplan Meier, OS = overall survival; PSM = parametric survival model.

Table 1.2: ABC-06 ASC OS – AIC and BIC

Model	AIC	BIC	3-year survival estimate	5-year survival estimate
Exponential	438.89	441.28	0.6%	0.0%
Generalised gamma	415.48	422.66	1.0%	0.2%
Gompertz	440.86	445.65	0.5%	0.0%
Log-logistic	**409.56**	**414.35**	0.9%	0.3%
Log-normal	414.16	418.95	0.6%	0.1%
Weibull	433.01	437.80	0.0%	0.0%

Source: Table 4 of Appendix 3 of the Company's Response to the ACD.[2]
ASC = active symptom control; AIC = Akaike information criterion; BIC = Bayesian information criterion; OS = overall survival.

Figure 1.7: FIGHT-202 pemigatinib OS KM data (adjusted for ABC-06 mFOLFOX+ASC) and fitted PSM models



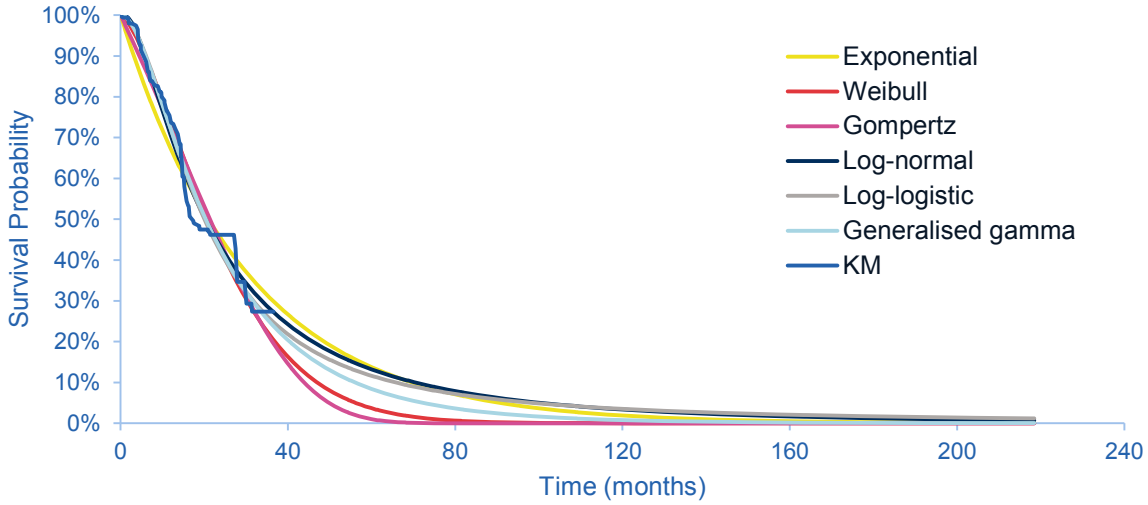
Source: Figure 6 of Appendix 3 of the Company's Response to the ACD.[2]
ASC = active symptom control; KM = Kaplan Meier; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; OS = overall survival; PSM = parametric survival model.

Table 1.3: FIGHT-202 pemigatinib OS (adjusted for ABC-06 mFOLFOX+ASC) – AIC and BIC

Model	AIC	BIC	3-year survival estimate	5-year survival estimate
Exponential	343.27	345.95	31.4%	14.6%
Generalised gamma	339.07	347.11	25.5%	9.3%
Gompertz	342.17	347.54	21.9%	1.5%
Log-logistic	**336.63**	**341.99**	25.8%	11.9%
Log-normal	337.74	343.11	28.4%	13.6%
Weibull	338.47	343.83	22.0%	4.0%

Source: Table 6 of Appendix 3 of the Company's Response to the ACD.[2]
AIC = Akaike information criterion; ASC = active symptom control; BIC = Bayesian information criterion; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; OS = overall survival.

Figure 1.8: FIGHT-202 pemigatinib OS KM data (adjusted for ABC-06 ASC) and fitted PSM models



Source: Figure 7 of Appendix 3 of the Company's Response to the ACD.[2]
ASC = active symptom control; KM = Kaplan Meier; OS = overall survival; PSM = parametric survival model.

Table 1.4: FIGHT-202 pemigatinib OS (adjusted for ABC-06 ASC) – AIC and BIC

Model	AIC	BIC	3-year survival estimate	5-year survival estimate
Exponential	346.42	349.10	30.3%	13.8%
Generalised gamma	342.50	350.55	24.3%	8.4%
Gompertz	344.95	350.31	20.3%	1.0%
Log-logistic	**340.26**	**345.62**	25.2%	11.6%
Log-normal	341.33	346.69	27.6%	13.2%
Weibull	341.60	346.96	21.0%	3.7%

Source: Table 7 of Appendix 3 of the Company's Response to the ACD.[2]
AIC = Akaike information criterion; ASC = active symptom control; BIC = Bayesian information criterion; OS = overall survival.

ERG Comment: The company conducted updates of the independent models at the request of the committee, providing results according to both matching possibilities (ASC or mFOLFOX+ASC arm).

The ERG agree that the plots presented in Figure 1.1 would suggest that the proportional hazards assumption is met.

Pemigatinib extrapolations according to either matching arm suggest that either the generalised gamma or log logistic could be plausible according to 5-year survival estimates of 10% from the clinicians in the committee meeting and 10-13% from the clinical validation conducted by the company, although the generalised gamma predicts a lower 5-year survival of 8.4% when matching using the ASC arm. It is

difficult to choose between these curves given fairly similar 5-year survival rates, which sit either just below 10% (generalised gamma) or higher within (log logistic) the range of plausible 5-year survival provided by experts.

When considering clinical survival predictions in the ASC and mFOLFOX arms, the log logistic curve provides the closest fit to the clinicians estimate of 3% survival at 3 years on mFOLFOX. However it is unclear whether the 1.2% survival on mFOLFOX at 5 years predicted by the log logistic curve is an overestimate as the clinician stated that survival in this group would be very low, but likely slightly higher than 0.1% (generalised gamma predicts 0.2%). The generalised gamma and log logistic predict very similar 3- and 5-year survival rates at 3 and 5 years for patients receiving ASC only. At 5 years the generalised gamma predicted survival of 0.2% is slightly closer to zero than the log logistic 0.3%, but again there is very little to differentiate the curves here.

Given the lack of a strong argument in favour of one curve over another, the ERG will provide scenarios for OS estimated using the log logistic and generalised gamma curves. Despite the committee having considered the Weibull function in the first meeting, the ERG feels that the additional clinical validation and the observed hazard functions over time suggest that the Weibull is a less suitable candidate and therefore Weibull scenarios were not included. Scenarios will be run using the HR weighted, independently fit unadjusted, independently fit ASC adjusted and independently fit mFOLFOX adjusted approaches to show the impact of extrapolation approach on results.

Company base-case survival choice

The company considered that their choice of the log logistic curve in the base-case had been fully justified in their technical engagement response and appendices using the following criteria:

- Decreasing probability of death over time for cholangiocarcinoma patients was presented, alongside the smoothed hazards from FIGHT-202
- Best AIC/BIC of the updated extrapolations
- Considered to be clinically plausible regarding long-term survival (10-13% at 5 years) (the company note that while the generalised gamma also meets this criteria, the Weibull does not as it predicts only 5% survival at 5 years)
- Applying the MAIC HR predicts long-term survival in line with clinical expectation and other published evidence for similar populations of chemotherapy- and ASC-treated patients (Appendix 2 of the ACD response[2]).

They noted that the application of the MAIC HR to the log-logistic extrapolation of FIGHT-202 data was criticised at the ACM, due to the accelerated failure time (AFT) assumption of the log-logistic (and generalised gamma) survival models. Although the non-AFT survival models from FIGHT-202 OS data all show hazards that do not decrease, they presented an additional scenario, displayed in Table 2.3, using the exponential function for OS (and PFS) extrapolation of FIGHT-202 data. They reported that this scenario showed similar cost-effectiveness results to the company base case, and should alleviate the committee's technical concerns regarding application of the MAIC HR to an AFT model.

The company reported that regardless of which arm was used for the MAIC, the log logistic remained a good candidate curve. However, generalised gamma was also explored in additional scenarios. For PFS, log-normal remained a good visual and statistical fit when using the MAIC-adjusted FIGHT-202 data and, in order to keep consistency with the unadjusted extrapolations and the comparator arm (see below), log-normal remained as the base case for MAIC-adjusted extrapolations of FIGHT-202 PFS data. TOT remained unchanged from the company base case, as TOT was not adjusted in the MAIC. The results of scenarios are displayed in Section 2.2. The company argue that these results show that it is the choice of extrapolation model, not the extrapolation method that drives results. However, although the ICERs are similar, all scenarios using independent survival models predict a small number of ASC patients alive at 3 and 5 years. This is contrary to clinical expectation, which suggests that these extrapolations may overestimate ASC survival. For the ASC+mFOLFOX arm, the company base case model does slightly underpredict 3- and 5-year survival compared to clinical expectation (0.4% versus 3% at 3 years, and 0.0% versus 0.1% at 5 years). On the other hand, the independent survival models may overpredict long-term ASC+mFOLFOX survival compared to clinical opinion (1.2% versus 0.1% at 5 years), also at the expense of changing the modelled patient population by adjusting the FIGHT-202 clinical trial data to match the ABC-06 patient characteristics.[7] The company made no change to their preferred base-case curves.

ERG Comment: Given the lack of a strong argument in favour of one curve over another, the ERG will provide scenarios for OS estimated using the log logistic and generalised gamma curves. As the company note, different extrapolation approaches appear to either under or overestimate certain elements of survival, with no set being strictly preferred. Therefore survival analysis results will be provided using the HR weighted, independent unadjusted, independent ASC adjusted and independent mFOLFOX adjusted approaches, for the committee's consideration.

1.2 FGFR2 Genetic testing costs

The company considered the source of the prevalence estimate of 10% provided by NHSE to be unclear. Therefore, the company chose to include the NHSE cost of £34 per test in their updated company base-case using the reported prevalence in the UK from FIGHT-202 of 8.6% which was validated by clinical experts.

ERG Comment: The ERG agrees with the inclusion of the genetic testing cost from NHSE. The ERG has no further opinion of whether the 8.6% or 10% prevalence estimate is more appropriate, but given that 10% was preferred by the committee, this will be included in the updated ERG base-case.

1.3 Costs of optical coherence tomography

The committee considered that the costs of optical coherence tomography (OCT) should be included in the cost-effectiveness analysis as pemigatinib treatment can sometimes cause retinal pigment epithelial detachment. The Cancer Drugs Fund (CDF) clinical lead advised that ophthalmological examination using optical coherence tomography would be required before and after starting treatment with pemigatinib in the NHS.[1]

In their ACD response, the company reported that the licensed indication for pemigatinib now includes guidance that an optical tomography scan should be considered at pemigatinib treatment initiation; followed

by every 2 months for the first 6 months of treatment; then every 3 months while on treatment and urgently at any time for visual symptoms.[8]

The company reported that clinical opinion was that these observations would typically be done as part of a standard clinical exam and that it was not clear what additional benefit there was from increased monitoring when these events would be picked up routinely.[9] However costs of OCT monitoring consistent with that recommended in the pemigatinib license were included in the company's updated base-case. The unit cost was sourced from the NHS reference costs[5] and the frequency of visual symptoms taken from Cohort A of FIGHT-202, assuming the prevalence of blurred vision.

ERG Comment: The ERG agrees with the inclusion of the costs of OCT monitoring in the updated base-case.

2. Company's updated cost effectiveness results

2.1 Company's updated deterministic results

The company's updated base-case assumptions were the same as their base-case at the first committee meeting with the exception of:

- Monitoring costs for OCT were added
- FGFR2 genetic testing costs were added according to a unit cost per test of £34 and a prevalence of 8.6%
- An updated patient access scheme (PAS) of [redacted] which decreased the price of a pack of pemigatinib to [redacted] was included.

The updated survival analyses did not cause the company to change their preferred extrapolation curve or approach for either OS or PFS.

The deterministic results of the company's updated base-case are displayed in Table 2.1. Again mFOLFOX+ASC is extendedly dominated by pemigatinib. Pemigatinib is more costly and more effective than ASC, with incremental costs of £[redacted] and [redacted] quality adjusted life years (QALYs) gained, resulting in an incremental cost effectiveness ratio (ICER) of £45,029 per QALY gained.

Table 2.1: Company base-case fully incremental deterministic results (PAS [redacted], discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ASC	[redacted]	0.60	[redacted]				
mFOLFOX+ASC	[redacted]	0.66	[redacted]	[redacted]	0.06	[redacted]	Extendedly dominated
Pemigatinib	[redacted]	2.44	[redacted]	[redacted]	1.84	[redacted]	45,029

Source: Table 9 of Appendix 4 of the Company's Response to the ACD.[2]
ASC = active symptom control; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYG = life years gained; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; PAS = patient access scheme; QALY(s) = quality-adjusted life year(s).

The probabilistic base-case results shown in Table 2.2 aligned with the deterministic results. Again mFOLFOX+ASC was extendedly dominated. Incremental costs and QALYs were [redacted] and [redacted] respectively when comparing pemigatinib to ASC, resulting in a probabilistic ICER of £43,736. The cost-effectiveness plane in Figure 2.1 shows that the majority of the simulations fall below the £50,000 threshold line. The CEAC presented in Figure 2.2 shows that at thresholds of £30,000 and £50,000 per QALY gained, pemigatinib has a [redacted]% and [redacted]% probability of being considered cost effective.

Table 2.2: Company base-case fully incremental probabilistic results (PAS [redacted], discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ASC	[redacted]	0.60	[redacted]				
mFOLFOX+ASC	[redacted]	0.66	[redacted]	[redacted]	0.06	[redacted]	Extendedly dominated
Pemigatinib	[redacted]	2.46	[redacted]	[redacted]	1.86	[redacted]	43,736

Source: Table 9 of Appendix 4 of the Company's Response to the ACD.[2]
ASC = active symptom control; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYG = life years gained; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; PAS = patient access scheme; QALY(s) = quality-adjusted life year(s).

Figure 2.1: Company updated base-case cost effectiveness plane

Source: Figure 8 of Appendix 4 of the Company's Response to the ACD.[2]
QALYs = quality adjusted life years.

Figure 2.2: Company updated CEAC

Source: Figure 9 of Appendix 4 of the Company's Response to the ACD.[2]
ASC = active symptom control; CEAC = cost effectiveness acceptability curve; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil

The company's one-way sensitivity analyses, shown in Figures 10 and 11 of Appendix 4 of the Company's ACD Response, demonstrate that the main drivers of model results are still the assumed HR for pemigatinib OS and baseline utility.[2]

2.2 Company scenario analyses

The company scenario analyses are shown in Table 2.3. The scenario which had the largest impact on results was extrapolating OS using the independently fit generalised gamma curves for all arms, with the FIGHT-202 data adjusted using the ASC arm of ABC-06, which increased the ICERs comparing pemigatinib to mFOLFOX and ASC respectively by approximately £10,000 and £8,000 respectively.

Table 2.3: Results of the company's scenario analyses

Scenario	ICER vs. mFOLFOX		ICER vs. ASC		3-year OS			5-year OS		
	ACM1 PAS ([redacted]%)	Updated PAS ([redacted]%)	ACM1 PAS ([redacted]%)	Updated PAS ([redacted]%)	Pem	ASC	ASC+ mFOL	Pem	ASC	ASC+ mFOL
ACM1 company base case	£49,186	£41,265	£51,952	£44,240	24.8%	0.1%	0.4%	12.5%	0.0%	0.0%
+ addition of OCT monitoring costs	£49,663	£41,743	£52,417	£44,705	24.8%	0.1%	0.4%	12.5%	0.0%	0.0%
+ addition of FGFR2 testing costs	£49,996	£42,076	£52,741	£45,029	24.8%	0.1%	0.4%	12.5%	0.0%	0.0%
Updated company base case	**£49,996**	**£42,076**	**£52,741**	**£45,029**	**24.8%**	**0.1%**	**0.4%**	**12.5%**	**0.0%**	**0.0%**
+ generalised gamma for OS extrapolation	£59,141	£49,629	£62,127	£52,916	24.2%	0.1%	0.3%	9.9%	0.0%	0.0%
+ exponential for OS and PFS extrapolation	£55,751	£46,935	£57,889	£49,371	27.1%	0.2%	0.5%	11.4%	0.0%	0.0%
Independent survival models: log-logistic OS for all arms (unadjusted FIGHT-202)	£53,729	£45,123	£51,999	£44,411	24.8%	0.9%	3.3%	12.5%	0.3%	1.2%
Independent survival models: log-logistic OS for all arms (FIGHT-202 adjusted using ASC ABC-06)	£54,528	£45,808	£52,691	£45,010	25.2%	0.9%	3.3%	11.6%	0.3%	1.2%
Independent survival models: log-logistic OS for all arms (FIGHT-202 adjusted using	£53,612	£45,051	£51,912	£44,354	25.8%	0.9%	3.3%	11.9%	0.3%	1.2%

Scenario	ICER vs. mFOLFOX		ICER vs. ASC		3-year OS			5-year OS		
	ACM1 PAS ([redacted]%)	Updated PAS ([redacted]%)	ACM1 PAS ([redacted]%)	Updated PAS ([redacted]%)	Pem	ASC	ASC+ mFOL	Pem	ASC	ASC+ mFOL
ASC+mFOLFOX ABC-06)										
Independent survival models: generalised gamma OS for all arms (unadjusted FIGHT-202)	£61,607	£51,622	£62,058	£52,866	24.2%	1.0%	1.7%	9.9%	0.2%	0.2%
Independent survival models: generalised gamma OS for all arms (FIGHT-202 adjusted using ASC ABC-06)	£62,169	£52,116	£62,575	£53,323	24.3%	1.0%	1.7%	8.4%	0.2%	0.2%
Independent survival models: generalised gamma OS for all arms (FIGHT-202 adjusted using ASC+mFOLFOX ABC-06)	£59,593	£49,987	£60,180	£51,307	25.5%	1.0%	1.7%	9.3%	0.2%	0.2%

Source: Table 8 of Appendix 4 of the Company's Response to the ACD.[2]
AE = adverse event; ASC = active symptom control; HR = hazard ratio; ICER = incremental cost effectiveness ratio; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; OS = overall survival.

3. Exploratory and scenario analyses undertaken by the ERG

The ERG agreed with the inclusion of OCT monitoring costs and NHSE provided genetic testing costs in the base-case, however they applied a prevalence of 10%, to align with that estimated by NHSE as preferred by the committee, rather than the 8.6% used by the company. This change in prevalence change has very little impact on the ICER (<£50 change on the company base-case ICER).

The ERG agreed with the committee than fitting independent curves to each arm was preferred to applying a weighted HR to generate comparator survival curves. However the ERG did not feel that given the data and the estimates of clinical plausibility available that there was a strong case for preferring either the log logistic or generalised gamma over the other, or preferring the use the weighted MAIC from either the ASC only group or mFOLFOX group over the other. Therefore, a range of scenarios have been provided, reflecting this uncertainty for the committee to consider.

Results of the plausible survival scenarios are displayed in Table 3.1. ICERs for the comparison of pemigatinib with ASC range between £44,310 and £44,984 when using log logistic extrapolations and from £51,255 to £53,268 when using generalised gamma. In a direct comparison between pemigatinib and mFOLFOX (which was extendedly dominated in all strategies run), ICERs range between £42,029 and £45,757 when using log logistic extrapolations and from £49,573 to £52,057 when using generalised gamma.

Table 3.1: Plausible extrapolations of OS (PAS [redacted], discounted)

OS Extrapolation	Pemigatinib		mFOLFOX + ASC		ASC		Pemigatinib vs. mFOLFOX+ASC			Pemigatinib vs. ASC		
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£)	Incr. Costs (£)	Incr. QALYs	ICER (£)
Weighted HR approach (as per company base-case)												
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42,029	[redacted]	[redacted]	44,984
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,573	[redacted]	[redacted]	52,862
Independently fit extrapolations (unadjusted)												
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,072	[redacted]	[redacted]	44,366
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,563	[redacted]	[redacted]	52,812
Independently fit extrapolations (adjusted using ASC group)												
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,757	[redacted]	[redacted]	44,965
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	52,057	[redacted]	[redacted]	53,268
Independently fit extrapolations (adjusted using mFOLFOX+ASC group)												
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,001	[redacted]	[redacted]	44,310
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,931	[redacted]	[redacted]	51,255

Based on the model provided with the company's ACD Response.[7]

ASC = active symptom control; HR = hazard ratio; ICER = incremental cost effectiveness ratio; Incr. = incremental; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; OS = overall survival; QALY = quality-adjusted life year.

References

[1] National Institute for Health and Care Excellence. *Appraisal consultation document. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement*. London: NICE. 18p.

[2] Incyte Biosciences UK Ltd. *Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations [ID3740]: consultation on the appraisal consultation document. ACD response Appendices [Word document]*, n..d. [accessed 2.6.21]. 19p.

[3] Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *Lancet Oncol* 2021;22(5):690-701.

[4] Lowery MA, Goff LW, Keenan BP, Jordan E, Wang R, Bocobo AG, et al. Second-line chemotherapy in advanced biliary cancers: a retrospective, multicenter analysis of outcomes. *Cancer* 2019;125(24):4426-4434.

[5] Walter T, Horgan AM, McNamara M, McKeever L, Min T, Hedley D, et al. Feasibility and benefits of second-line chemotherapy in advanced biliary tract cancer: a large retrospective study. *Eur J Cancer* 2013;49(2):329-35.

[6] Zhu A, Macarulla T, Javle M, et al. Final results from ClarIDHy, a global, phase III, randomized, double-blind study of ivosidenib (IVO) versus placebo (PBO) in patients (pts) with previously treated cholangiocarcinoma (CCA) and an isocitrate dehydrogenase 1 (IDH1) mutation. *J Clin Oncol* 2021;39(Suppl 2):266-.

[7] Incyte Biosciences UK Ltd. *Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations [ID3740]: consultation on the appraisal consultation document [Word document]*, n..d. [accessed 2.6.21]. 9p.

[8] Incyte Corporation. *Pemigatinib (Pemazyre). Summary of Product Characteristics (SPC)*, 2021

[9] Incyte Corporation. *Scottish Clinical Validation*: Dr McNamara, 2021