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

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

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

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Incyte Corporation

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. AMMF – The Cholangiocarcinoma Charity

4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews
   a. ERG report
   b. Addendum for new PAS
   c. ERG genetic testing cost scenario

5. **Evidence Review Group – factual accuracy check**

6. **Technical engagement response** from Incyte Corporation
   a. Response form
   b. Additional evidence
   c. Updated analyses with new PAS

7. **Technical engagement responses from experts:**
   a. Chiara Braconi – clinical expert, nominated by Cholangiocarcinoma-UK and the National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists
   b. Maria Hawkins – clinical expert, nominated by Cholangiocarcinoma-UK
   c. Helen Morement – patient expert, nominated by AMMF – The Cholangiocarcinoma Charity and Cholangiocarcinoma-UK
   d. Andrea Sheardown – patient expert, nominated by AMMF – The Cholangiocarcinoma Charity

8. **Technical engagement response from consultees and commentators:**
   a. National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists

9. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews

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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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

August 2020

File name	Version	Contains confidential information	Date
ID3740_Pemigatinib Document B_redacted_V2.docx	2.0	Yes - redacted	10 November 2020

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Abbreviations

Abbreviation	Definition
1L	First-line
2L	Second-line
5-FU	5-fluorouracil; FOLFOX-4; oxaliplatin+5-FU+leucovorin
AE	Adverse event
AIC	Akaike information criterion
ASC	Active symptom control
BIC	Bayesian information criterion
BSG	British Society of Gastroenterology
BTC	Biliary tract cancer
CCA	Cholangiocarcinoma
Cis	Cisplatin
CR	Complete response
CT	Computed tomography
DCR	Disease control rate
DEBDOX	Drug-eluting beads loaded with doxorubicin
DEBIRI	Drug-eluting bead, irinotecan
DOR	Duration of response
DSU	Decision Support Unit
EBD	Endoscopic biliary drainage
eCCA	Extrahepatic cholangiocarcinoma
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMC	Electronic Medicines Compendium
EORTC QLQ-BIL21	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (CCA and gallbladder cancer)
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EPAR	European public assessment report
EQ-5D-3L	EuroQol five-dimension, three-level tool
ERCP	Endoscopic retrograde cholangiopancreatography
ESMO	European Society for Medical Oncology
ESS	Effective sample size
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FGFR2+	Fibroblast growth factor receptor 2-positive
FOLFIRI	5-fluorouracil+irinotecan; XELIRI, capecitabine+irinotecan
FOLFOX	5-fluorouracil+oxaliplatin
Gem	Gemcitabine
HCC	hepatocellular carcinoma
hCCA	Hilar cholangiocarcinoma
HCRU	Healthcare resource use

HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
iCCA	Intrahepatic cholangiocarcinoma
ICER	Incremental cost-effectiveness ratio
IDH	Isocitrate dehydrogenase
IRC	Independent review committee
ITC	Indirect comparison
IV	Intravenous
KM	Kaplan–Meier
LY	Life year
LYG	Life year gained
MAIC	Matched-adjusted indirect comparison
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX	Oxaliplatin, L-folinic acid and fluorouracil
MHRA	Medicines and Healthcare Products Regulatory Agency
MRCP	Magnetic resonance cholangiopancreatography
NA	Not available
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHB	Net health benefit
NGS	Next generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
ONS	Office for National Statistics
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PD	Progressive disease
Pemi	Pemigatinib
PF	Progression-free
PFS	Progression-free survival
PIM	Promising Innovative Medicine
PLD	Patient-level data
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Plastic stent
PSA	Probabilistic sensitivity analysis
PSM	Parametric survival model
PSS	Personal Social Services
PTC	Plasma thromboplastin component
PTDB	Percutaneous biliary drainage

QALM	Quality-adjusted life month
QALY	Quality-adjusted life year
QD	Once daily
QQ	Quantile–quantile
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
sCT	Systemic chemotherapy
SD	Standard deviation
SE	Standard error
SEMS	Self-expandable metal stent
SIRT	Selective internal radiation therapy
SLR	Systematic literature review
SmPC	Summary of product characteristics
SOC	Standard of care
TA	Technology appraisal
TACE	Transarterial chemoembolization
TEAE	Treatment-emergent adverse event
TNM	Tumour, node, metastasis classification
ToT	Time on treatment
TSD	Technical support document
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USD	United States dollar
XELIRI	Capecitabine plus irinotecan
XELOX	Capecitabine+oxaliplatin

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with advanced cholangiocarcinoma (CCA) with *FGFR2* fusion or rearrangement that is relapsed or refractory after at least one prior systemic therapy.	As per final scope	N/A
Intervention	Pemigatinib	As per final scope	N/A
Comparator(s)	• Chemotherapy • Best supportive care (including stent insertion)	As per final scope	N/A
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	As per final scope	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The use of pemigatinib is conditional on the presence of FGF/FGFR gene alteration. The economic modelling should include the costs	Cost effectiveness of the treatments specified are expressed in terms of incremental cost per quality adjusted life year. The time horizon for estimating clinical and cost effectiveness in the cohort simulation model is lifetime Costs are included from an NHS and Personal Social perspective Testing costs are not included in the base case analysis as patients will be	A sensitivity analysis is provided with an estimated cost of the genetic test.

	associated with diagnostic testing for the FGF/FGFR gene alteration in people with relapsed or refractory advanced CCA who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.	tested routinely according to NHS plans .	Incyte understands from clinician and NHS service provider input that genetic testing for CCA (including FGFR2 gene alterations) will become part of routine practice due to availability of new treatment options for this particular patient population and the current intent of the NHS Long Term Plan for the service to offer whole genome sequencing as part of routine care. Genetic testing by next generation sequencing (NGS) uses sequencing panels to detect alterations across a wide range of genes including FGFR.
Subgroups to be considered	None	As per final scope	N/A
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	As per final scope	N/A

CCA, cholangiocarcinoma; FGF, fibroblast growth factor; FGFR2, fibroblast growth factor receptor 2; NGS, next generation sequencing; NHS, National Health Service.

B.1.2. Description of the technology being appraised

A summary of pemigatinib is shown in Table 2, and the draft summary of product characteristics is included in Appendix C.

Table 2. Technology being appraised

UK approved name and brand name	Pemigatinib (Pemazyre™)
Mechanism of action	Pemigatinib is a potent and selective FGFR1, 2, and 3 inhibitor. Pemigatinib blocks autophosphorylation and activation of major FGF/FGFR signalling pathways, inhibiting the growth of cells with *FGFR2* fusions/rearrangements.
Marketing authorisation/CE mark status	MAA submitted to EMA: November 2019 CHMP opinion anticipated: December 2020 Full MAA anticipated: January 2021
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Pemigatinib monotherapy is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (*FGFR2*) fusion or rearrangement that is relapsed or refractory after at least one line of systemic therapy.
Method of administration and dosage	Pemigatinib is administered 13.5 mg QD on a 14 day-on, 7 day-off schedule. Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity.
Additional tests or investigations	Incyte understands from clinician and NHS service provider input that genomic testing for CCA patients is likely to become part of routine practice due to availability of new treatment options for this particular patient population and the current intent of the NHS Long Term Plan for the service to offer whole genome sequencing as part of routine care. As testing represents broader assessment of different oncogenic alterations the cost of the FGFR2 genetic test which represents just one target has therefore been included as scenario analysis.
List price and average cost of a course of treatment	The drug acquisition cost of pemigatinib is £37.88 per mg (£511.36 per 13.5mg tablet). Under the administration schedule of 14 days on, 7 days off, the weekly total drug cost is [redacted] and £7159 per treatment cycle (21 days).
Patient access scheme (if applicable)	A submission has been made to NHS England regarding a patient access scheme which include a simple discount arrangement.

CCA, cholangiocarcinoma; CHMP, Committee for Human Medicinal Products; FGF, fibroblast growth factor; FGFR, FGF receptor; MAA, marketing authorisation application; NHS, National Health Service; QD, once daily; UK, United Kingdom.

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Cholangiocarcinoma (CCA), also known as cancer of the bile ducts, is a rare cancer that develops from the epithelial lining of the gallbladder and bile ducts.[1,2] Based on the location of the primary tumour, CCA is classified as intrahepatic (iCCA) or extrahepatic (eCCA). Extrahepatic tumours are further subclassified as perihilar (also called Klatskin) and distal (Figure 1).[1,3] Each subtype has distinct risk factors, molecular pathogenesis, therapeutic options, and prognosis.[4] iCCAs represent approximately 34% of CCA cases.[5]

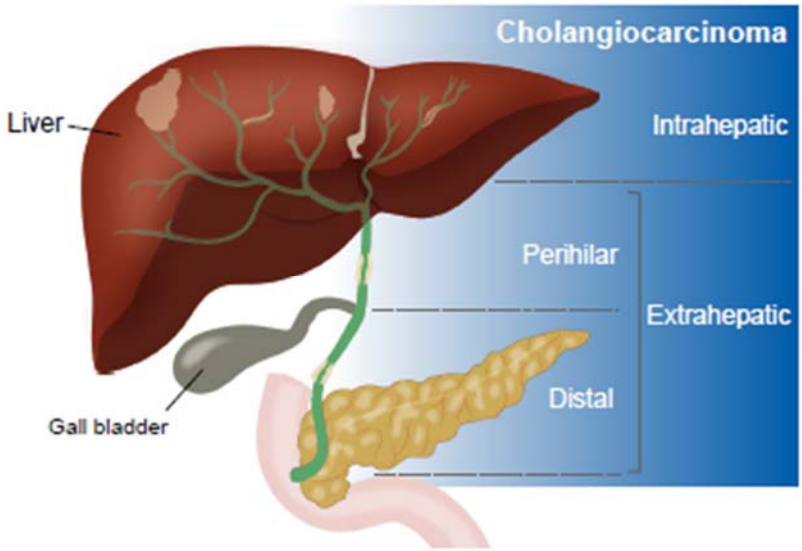


Figure 1. Classification of CCA by primary tumour location

CCA, cholangiocarcinoma.
Source: Adapted from Rizvi & Gores, 2017[6]

Most CCAs arise spontaneously, in the absence of known underlying risk factors.[1,7,8] However, there are some well-established risk factors associated with the subtypes of CCA. Congenital risk factors include Caroli disease, congenital hepatic fibrosis, and biliary cysts (types I and IV). In Western countries, the hepatitis C virus and liver cirrhosis have been identified as risk factors for iCCA.[8,9]

General risk factors for CCA may include obesity, diabetes mellitus, and metabolic disease. Certain drugs and toxins, such as alcohol, tobacco (smoking), oral contraceptive pills, dioxin, and asbestos have also been suggested as risk factors for CCA.[1,8]

CCA is a rare cancer in the UK

There are a lack of data in England and Wales regarding incidence and prevalence for the population of interest in this submission—previously treated, unresectable, locally advanced, or metastatic CCA with fibroblast growth factor receptor 2 (*FGFR2*) fusions/rearrangements.

Worldwide, CCA is the second most common primary liver tumour, after hepatocellular carcinoma (HCC). Since the mid-1990s, more deaths have been coded in England and Wales due to CCA than to HCC. Incidence and mortality rates for iCCA have risen steeply and steadily across the world over the past few decades with concomitant falls in eCCA rates.[3,10]

Recent evidence from UK data suggest that rising iCCA rates partly reflect misclassification, with perihilar ('Klatskin') tumours being incorrectly coded as intrahepatic instead of extrahepatic.[12] The overall incidence and mortality from all CCA, however, is increasing.[1] There has been a marked rise in age-standardised incidence and mortality rates for CCA in the past 17 years (p-test for trend <0.001 for both).[13] The cause of the rise is unknown and is not explained by improvements in diagnosis.[3,10] In 2001, the age-standardised incidence rate for CCAs was 2.7 per 100,000 (95% confidence interval [CI]: 2.5, 2.8).[11] In 2010–2013, the incidence rate per 100,000 in England had risen to 3.58.[12] In 2017, the reported incidence was 4.3 per 100,000, with 4.0 in females (95% CI: 3.7, 4.2) and 4.6 in males (95% CI: 4.3, 4.9).[11] Accordingly, in 2017, there were 2,187 persons diagnosed with CCA in England (1,069 males and 1,118 females). Over the same time period, the age-standardised mortality rate rose from 2.6 (95% CI: 2.4, 2.8) in 2001 to 4.7 per 100,000 in 2017, with 4.5 in females (95% CI: 4.3, 4.8) and 4.9 in males (95% CI: 4.6, 5.2).[11] The mortality rate reported was higher than the incidence rate, likely reflecting under-coding of CCAs in the incidence data as a result of misdiagnosis.[11]

Gene fusions drive oncogenesis in CCA

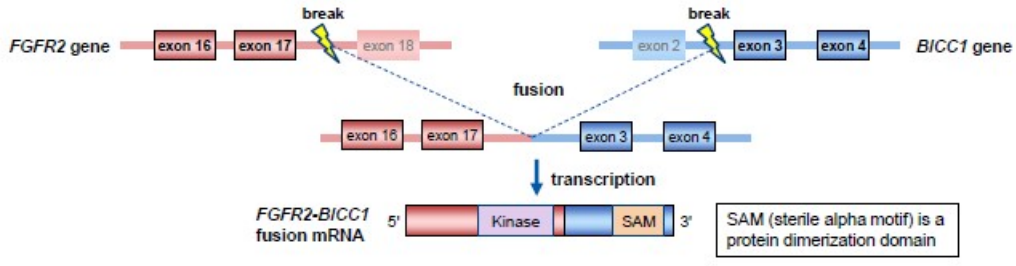
CCA is a genetically diverse cancer.[13] Several recent studies have identified different genetic fusions/rearrangements that occur in CCA.[14] Gene fusions have been shown to be drivers of oncogenesis and multiple potentially targetable genetic alterations with therapeutic implications have been identified.[13]

Rearrangements/fusions lead to tumorigenic FGFR signalling

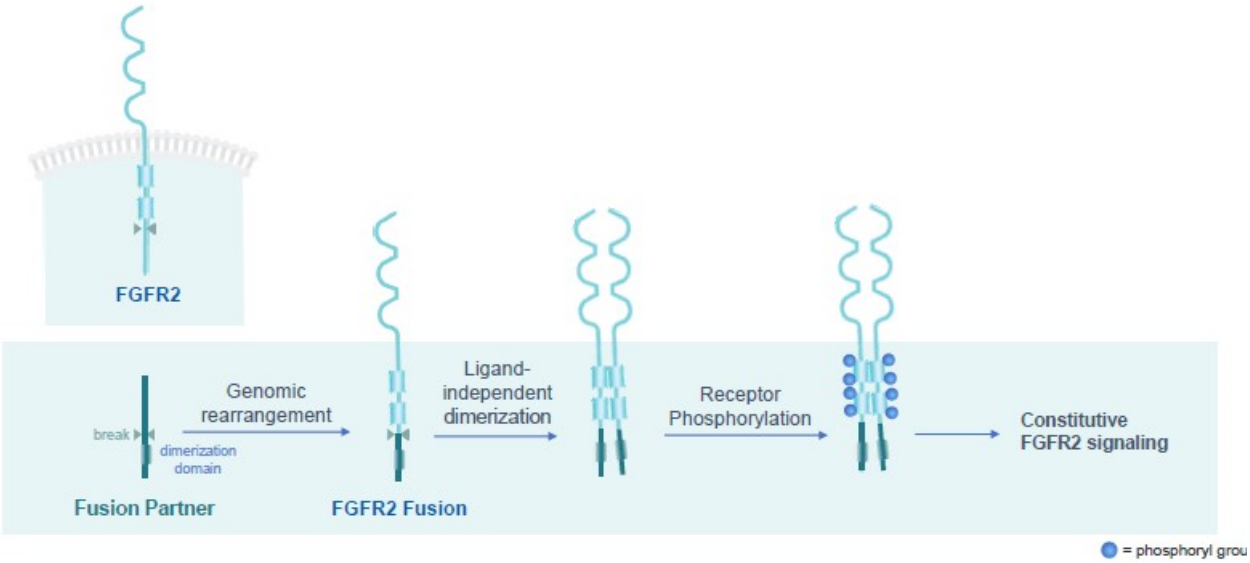
The FGF/FGFR signalling pathway plays a central role in multiple essential cellular processes, including physiological functions and embryonic development.[15-20] In normal cells, the binding of FGF ligands to their related FGF receptors (FGFR1 to FGFR4) leads to receptor dimerization, which then induces cross-phosphorylation and activation of the FGFR kinases. FGFR kinases activate downstream signalling pathways that are implicated in cellular processes, such as proliferation, survival, migration, and angiogenesis.[15,18] There is strong genetic and functional evidence that dysregulation of FGFR can lead to the initiation and progression of different cancers.[17,18] For example, gene fusions are associated with oncogenic properties and may act as driver mutations in cancers like iCCA.[15,17]

FGFR2 fusions can trigger ligand-independent receptor dimerization and constitutive FGFR signalling, potentially driving tumorigenesis in iCCA

FGFR2 fusions develop early in disease progression, suggesting they serve as oncogenic drivers and are responsible for both the initiation and maintenance of cancer.[21] Genomic mutations involving FGFR2 activation account for nearly 20% of all iCCA cases and a large number of FGFR2 alterations have been identified in iCCA as oncogenic drivers.[17] In most iCCA cases with *FGFR2* gene fusions, the fusion partner becomes attached downstream of the kinase domain of *FGFR2* (Figure 2A).[19,22] Additionally, a majority of *FGFR2* fusion partners contain a dimerization domain, which allows the *FGFR2* fusion to dimerize even in the absence of an FGF ligand.[23,24] FGFR2 dimerization activates FGFR signalling by bringing the kinase domains in close proximity, allowing cross-phosphorylation and triggering constitutive downstream signalling of cell processes involved in tumorigenesis (Figure 2B).[16,24]



A. *FGFR2* fusions with intact kinase domains in iCCA



B. *FGFR2* fusions trigger ligand-independent receptor dimerization and constitutive FGFR signalling

Figure 2. *FGFR2* fusions in iCCA

iCCA, intrahepatic cholangiocarcinoma; FGFR, fibroblast growth factor receptors.
Sources: Arai et al. 2014;[19] Goyal et al. 2017.[22]

Pre-clinical models demonstrated that *FGFR2* fusions trigger constitutive activation of the FGFR kinase, leading to tumorigenesis both in vivo and in vitro.[17,19] Tumours with activating *FGFR2* fusions may be sensitive to FGFR inhibitors, such as pemigatinib, which suggests an important role for targeted therapeutics in this patient population.[17,25]

Prognostic role of FGFR alterations

The prognostic role of *FGFR* alterations is not fully characterised in CCA. Several relationships still need to be elucidated, including: (1) the predictive role of *FGFR* alterations for response to standard chemotherapy regimens; (2) the role played by *FGFR2* fusions, as compared to other *FGFR* alterations or wildtype, on survival; and (3) if the role *FGFR2* alterations play in prognosis is constant or if it changes throughout the course of the disease.

Nevertheless, retrospective studies have shown that *FGFR* mutations (predominantly *FGFR2* fusions or rearrangements) occur more frequently in younger women and seem to confer more indolent disease.[26,27] For example, in a retrospective analysis by Jain et al. 2018, 377 patients with CCA were assessed by next-generation sequencing or fluorescence in situ hybridisation.[28] Ninety-five subjects had *FGFR* mutations, and *FGFR2* fusions were the most frequent alteration (n=63 *FGFR2* fusions, 11 with other *FGFR2* alterations). Patients with *FGFR* alterations tended to be younger females who presented at an earlier disease stage (tumour, node, metastasis classification [TNM] I/II vs III/IV

35.8% vs 22%, respectively; p=0.001) and were associated with longer survival compared with patients without *FGFR* mutations (median overall survival [OS] from date of initial CCA diagnosis until death 37 vs 20 months, respectively; p<0.001).[28] This difference remained significant after excluding 36 patients treated with FGFR inhibitors (30 vs 20 months, respectively; p=0.03).[28] The limitations of this analysis to fully characterise the prognostic role of *FGFR* alterations are worth highlighting - one being the cohort analyses included patients with early-stage disease who were likely to receive curative treatment options like surgery and/or radiation.

Further, there appears to be no scientific controversy that patients with *FGFR2*-altered disease are afforded additional survival with exposure to FGFR-targeted therapy. Patients with any *FGFR* mutation had a better OS with FGFR-targeted therapy (44.8 months) than those who did not received FGFR-targeted therapy (24.3 months; p=0.01).[28] This is further confirmed with the results of the pemigatinib trial (FIGHT-202, Sections B.2.6.4 and B.2.6.5), which reported an overall response rate (ORR) of 35.5% and a duration of response (DOR) of 7.5 months in patients with *FGFR2* fusions/rearrangements.[29] Despite lack of a comparator arm in the trial, it is understood that these patients are benefiting from targeted therapy.

B.1.3.2 Burden to patients, carers, and society

CCA has a poor prognosis

CCA is a rare, aggressive disease with a poor prognosis. In the UK, survival data from large scale, retrospective, database analyses are lacking. Approximately 70% of patients are diagnosed late with unresectable, locally advanced, or metastatic disease—these patients have an estimated 5-year survival rate of ≤10%.[14,30-33] In patients with BTC who have progressed on first-line (1L) treatment, median OS is 6.2 months when treated with systemic chemotherapy (mFOLFOX+active symptom care [ASC]).[34]

Data are scarce on the disease burden and health-related quality of life (HRQoL) of patients with CCA in the UK, and even less is known about the impact on carers and society. CCA patients with advanced disease are likely burdened by secondary symptoms of bile duct or gastrointestinal obstruction such as jaundice, itching, abdominal pain, and nausea.[35] In addition, they potentially face the harmful side effects of systemic chemotherapy, which are discussed further in the following section.

B.1.3.3 Unmet need in the treatment of CCA

Surgery is the only curative treatment option for patients with CCA; however, only approximately 30% of patients are candidates for resection at diagnosis.[14] Of those, another 10% to 45% are determined to be unresectable during explorative laparotomy.[1] For patients with localised disease who undergo curative resection surgery, relapse rates are high—60%.[14]

Unresectable but localised disease may be eligible for loco-regional therapies such as radioembolism or radiotherapy. Evidence for radioembolism, also known as selective internal radiation therapy (SIRT), is currently restricted to iCCA patients with limited disease advancement (locally advanced but non-metastatic). The National Institute for Care and Health Excellence (NICE) Interventional Procedures Programme published the *Interventional procedure overview of selective internal radiation for unresectable primary intrahepatic CCA* (IPG630). The guidance notes that the current evidence on the safety of SIRT for unresectable primary iCCA shows that there are well-recognised, serious, but rare safety concerns, and NICE recommends the procedure be used only in the context of research.[36]

Treatment for unresectable, locally advanced, or metastatic patients is limited to chemotherapy for patients with Eastern Cooperative Oncology Group (ECOG) performance status 0–1. The standard 1L chemotherapy is a combination of cisplatin-gemcitabine.[37,38] Patients who progress on 1L chemotherapy often have a rapidly worsening performance status and only a small proportion of patients may remain suitable for further systemic treatment.

Current SOC for 1L treatment

Patients in the UK have no approved targeted therapeutic options for CCA with *FGFR2* fusions/rearrangements. Most patients are diagnosed with advanced or metastatic disease and, in these patients, systemic chemotherapy is associated with modest clinical success. Current standard of care (SOC) for 1L therapy in patients with BTC was established in 2009/2010 following the results of the ABC-02 trial.[37] ABC-02 was a phase 3, UK study of 410 patients with locally advanced or metastatic disease. The study compared combination treatment with cisplatin-gemcitabine (Cis-Gem cohort) vs gemcitabine (Gem cohort) alone. The patient cohorts were not restricted specifically to patients with CCA (Gem cohort: n=119/206; Cis-Gem cohort: n=122/204), but also included patients with

gallbladder (Gem cohort: n=76/206; Cis-Gem cohort n=73/204) and ampullary carcinoma (Gem cohort: n=11/206; Cis-Gem cohort: n=9/204). Median OS was 11.7 months (95% CI: 9.5,14.3 months) for the Cis-Gem cohort and 8.1 months for the Gem cohort (95% CI: 7.1, 8.7 months; p<0.001) (Figure 3a). Median progression-free survival (PFS) was 8.0 months (95% CI: 6.6, 8.6 months) for the Cis-Gem cohort and 5.0 months for the Gem cohort (95% CI: 4.0, 5.9 months; p<0.001) (Figure 3b).[37]

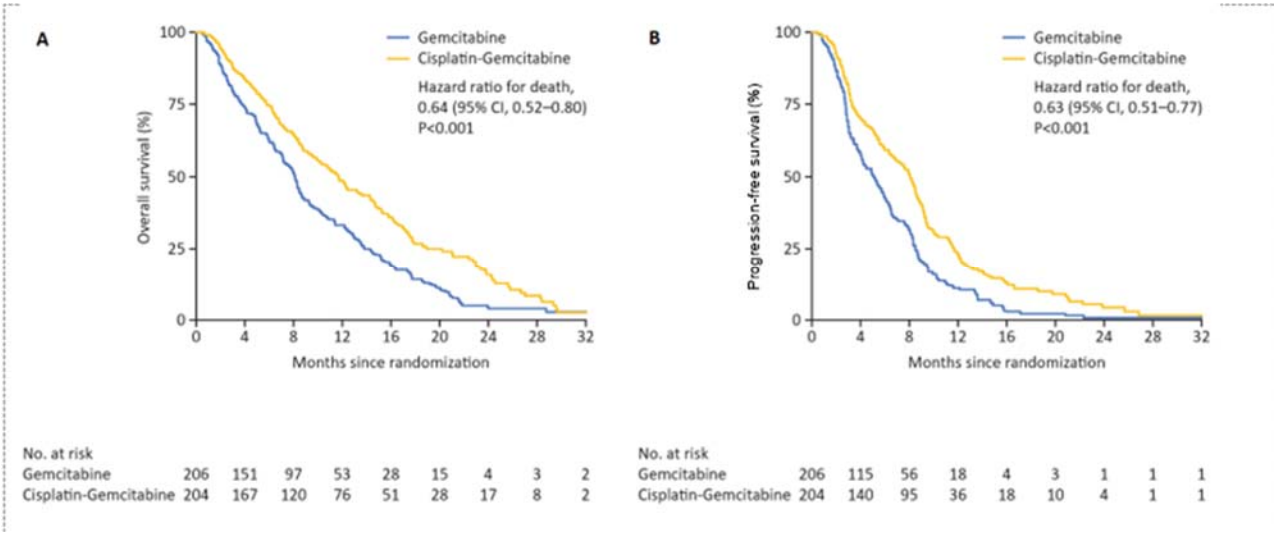


Figure 3. Outcomes for patients with BTC who received cisplatin-gemcitabine vs gemcitabine alone in ABC-02; A. OS, B. PFS

BTC, biliary tract cancer; OS, overall survival; PFS, progression-free survival.
Source: Valle et al. 2010.[37]

No approved therapy for second-line CCA

There are no data on the efficacy of second-line (2L) systemic chemotherapy in previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements—the target population of this submission. Treatment options are limited to older chemotherapy regimens with no approved 2L therapies for CCA.[39] Patients who commonly present with advanced disease may have substantial comorbidity including advanced age, intercurrent sepsis, and poor performance status score.[40] For those patients who progress on 1L, 2L chemotherapy options yield limited benefit, with low response rates and rapid progression.[15,37]

A systematic review of 2L chemotherapy in advanced biliary cancer evaluated 14 phase 2 clinical trials.[39] The authors concluded that there was insufficient evidence to establish a SOC for 2L chemotherapy due to the small patient cohorts, variation in chemotherapy regimens, lack of consensus on primary endpoint, heterogeneity of patients, and poor

outcomes. Figure 4 illustrates the poor survival outcomes of 2L chemotherapy treatment of advanced biliary cancer from Lamarca et al. 2014.[39]

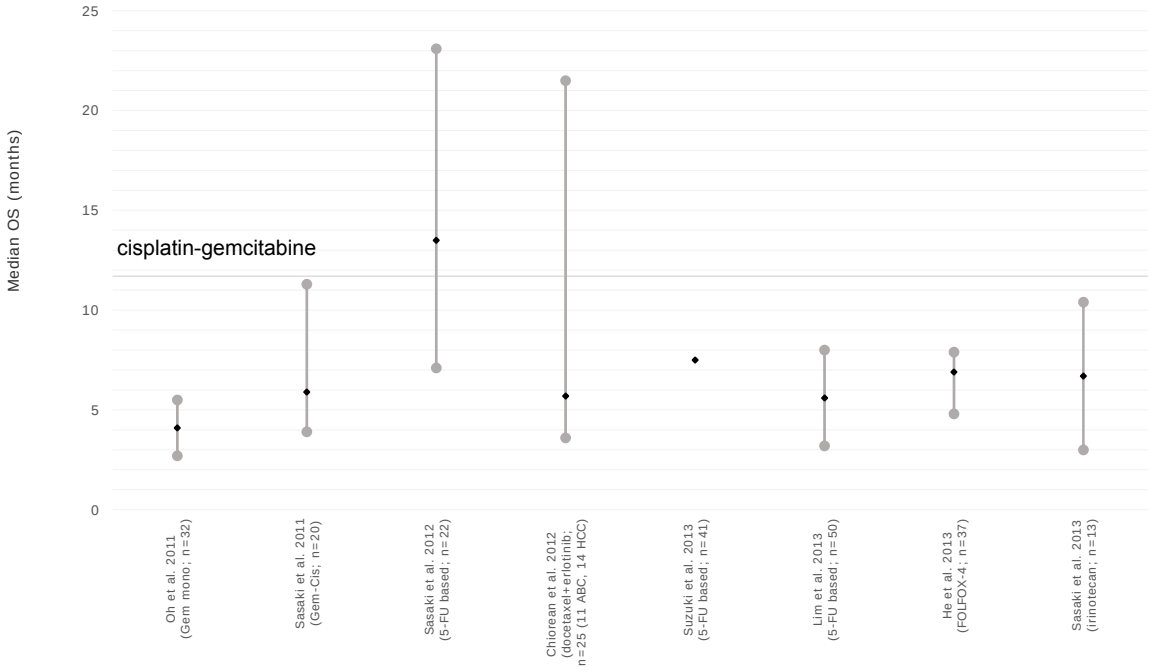


Figure 4. Median OS in phase 2 single arm clinical trials of second-line chemotherapy treatment of advanced biliary cancer

5-FU, 5-fluorouracil; FOLFOX-4; oxaliplatin+5-FU+leucovorin; Gem-Cis, gemcitabine-cisplatin; HCC, hepatocellular carcinoma; mono, monotherapy; OS, overall survival.
Source: Lamarca et al. 2014.[39]

Toxicity of systemic chemotherapy

Current systemic chemotherapies can result in high rates of serious adverse events (SAEs), leading to high discontinuation rates. The most common SAEs are severe haematological abnormalities or toxicities (Table 3).[41-46] In a retrospective analysis of 1L chemotherapy outcomes for unresectable iCCA and perihilar CCA, 30% of patients receiving cisplatin-gemcitabine discontinued therapy due to toxicity prior to disease progression, with the most common reason being elevated creatinine.[47]

Table 3. SAEs reported across studies with regimens including systemic chemotherapy

Frequently experienced SAEs across studies	Patients experiencing event (%)
Anaemia	6.8%–54%[43,44,46]
Haematologic abnormalities or toxicities	38.5%–52.2%[41,45]
Neutropenia	20%–36%[43,46]
Asthenia	6.8%–33%[42,44]
Fatigue	11.4%–20%[41,43]
Hepatic toxicity	20%[44]
Performance status decrease	11.3%–15.5%[44]
Skin toxicity	6.6%–13.6%[41,44]

SAE, serious adverse event.

Limitations of real-world treatment in unresectable, locally advanced, or metastatic patients

There are no studies evaluating real-world treatment patterns specifically in patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements.

A retrospective, multicentre study in Italy explored 2L treatment outcomes for patients with advanced biliary cancer between 2004 and 2013.[48] A wide range of 2L chemotherapies were found to be used in the real-world setting, demonstrating that there is no SOC (Table 4).

Table 4. Second-line chemotherapy for patients with advanced CCA across 10 Italian institutions between 2004 and 2013

Chemotherapy regimen
Monotherapy with 5-fluorouracil or capecitabine
Gemcitabine plus 5-fluorouracil or capecitabine
Capecitabine plus mitomycin-C
FOLFIRI or XELIRI
Retreatment with gemcitabine plus cisplatin or oxaliplatin
FOLFOX or XELOX
Epirubicin plus cisplatin plus 5-flurouracil
Gemcitabine plus irinotecan
Monotherapy with gemcitabine
Other regimens

n, number; FOLFIRI, 5-fluorouracil+irinotecan; XELIRI, capecitabine+irinotecan; FOLFOX, 5-fluorouracil+oxaliplatin; XELOX, capecitabine+oxaliplatin.
Source: Fornaro et al. 2015.[48]

The study also presented a pooled analysis of 2L treatment outcomes for patients with advanced BTCs. The results illustrated the limited efficacy of 2L chemotherapy (Table 5).

Other retrospective analyses in the US, Italy, and Canada confirm these poor outcomes.[49-51] Such retrospective analyses highlight the limited value of 2L chemotherapy after a 1L cisplatin-gemcitabine combination therapy in advanced BTC.[48-51]

Table 5. Outcomes of BTC patients receiving second-line chemotherapy: comparing a retrospective multicentre analysis in Italy and a pooled analysis of published data

Analysis	Response rate (%; 95% CI)	Median PFS (months; 95% CI)	Median OS (months; 95% CI)
Retrospective multicentre (n=174)	3.4 (0.7, 6.1)	3.0 (2.7, 3.4)	6.6 (5.1, 8.1)
Published literature (n=499)	10.2 (7.3, 13.1)	3.1 (2.9, 3.4)	6.3 (5.6, 7.0)

BTC, biliary tract cancer; CI, confidence intervals; OS, overall survival; PFS, progression-free survival.
Source: Fornaro et al. 2015. [48]

ABC-06 trial: advanced biliary cancer in patients previously treated with cisplatin-gemcitabine chemotherapy

ABC-06 was a phase 3, randomised controlled trial evaluating ASC alone or ASC with oxaliplatin/5-FU chemotherapy (mFOLFOX+ASC) for patients with locally advanced or metastatic BTC who were previously treated with cisplatin-gemcitabine chemotherapy.[34] A total of 162 patients, from 20 sites in the UK, were randomised to receive mFOLFOX+ASC (n=81) or ASC alone (n=81). The study met its primary endpoint; the adjusted hazard ratio (HR) was 0.69 (95% CI: 0.50, 0.97; p=0.031) for OS in favour of mFOLFOX+ASC vs ASC alone.[34] Despite this, the study showed limited efficacy in 2L patients, with adverse events (AEs) in line with systemic treatment. The median OS was 5.3 months and 6.2 months for the ASC alone and mFOLFOX+ASC groups, respectively. The 6-month and 12-month survival rates for the mFOLFOX+ASC group were 50.6% and 25.9%, respectively. The ORR in the mFOLFOX+ASC group was 5% and the disease control rate (DCR) was 33%. The radiological median PFS reported for patients treated with mFOLFOX+ASC was 4.0 months (95% CI: 3.2, 5.0).[34]

The safety profile from ABC-06 reported toxicities expected with systemic chemotherapy treatment. Fifty-nine percent of patients in the mFOLFOX+ASC group had a grade 3/4 AE.[34] The most common grade 3/4 AEs were fatigue/lethargy (19%; n=15/81); decreased neutrophil count (12%; n=10/81); infection, including lung, urinary, fever, or unspecified (14%; n=11/81); and biliary events, such as obstruction, infection, liver infection, increased bilirubin/alkaline phosphatase, and hepatitis (19%; n=15/82).[34] Three chemotherapy-related deaths (due to renal failure/diabetic ketoacidosis, febrile

neutropaenia, and acute kidney injury) were reported.[34] ABC-06 is the first prospective trial evaluating the efficacy and safety of 2L chemotherapy in advanced biliary cancer patients; the results support the findings of the retrospective studies summarised in the previous section, and further highlight the overall poor outcomes for these patients.

Given the rapid progression seen with CCA, patients urgently need a therapy that can reduce or stabilise disease burden. Historically, systemic chemotherapies in 2L treatment have limited efficacy and can result in significant toxicity. Findings from the recent ABC-06 trial in BTC patients, showed limited efficacy and significant toxicity in 2L with mFOLFOX+ASC chemotherapy.[34] The results of ABC-06 were not reported in subpopulations by genetic mutation. To date, there is no evidence for the efficacy of existing 2L systemic therapy in CCA patients with *FGFR2* fusions/rearrangements.

B.1.3.4 Clinical pathway of care

Management of CCA in the UK

The British Society for Gastroenterology (BSG) published guidelines on the management of CCA, which are summarised in Table 6.[3,38]

Table 6. Summary of the key British Society for Gastroenterology treatment guidelines for CCA

Treatment	Recommendation
Early stage	
	Patients with early stage disease who are candidates for surgery should undergo resection—the only curative treatment.*
	All operable patients should be offered adjuvant treatment trials (Grade B).
Locally advanced and metastatic	
	Not candidates for resection
	Cisplatin-gemcitabine combination chemotherapy is recommended for locally advanced or metastatic unresectable CCA (Grade A).
	Locoregional therapies, such as radioembolization and transcatheter arterial chemoembolization, need prospective randomised data to assess their true value.
	All patients who have inoperable tumours, or who are operable but have not been rendered disease-free, or those patients with recurrences should be actively encouraged to participate in chemotherapy and/or radiotherapy clinical trials (Grade B).

CCA, cholangiocarcinoma.
*Special consideration for resection: routine pre-operative biliary drainage (stent) should be avoided except in certain situations such as acute cholangitis, with modification of antibiotic prophylaxis according to patient characteristics and local microbiological specialist advice (Grade B).
Source: Khan et al. 2012.[3]

The European Society for Medical Oncology (ESMO) published clinical practice guidelines for the diagnosis, treatment, and follow-up of biliary cancer in 2016.[38] The BSG and ESMO guidelines overlap in their recommendations for the management of CCA, and both highlight the lack of 2L treatment options in CCA patients.[3,38]

Figure 5A shows the current pathway of care and Figure 5B shows the proposed pathway of care for patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements in England and Wales. Following approval by the European Medicines Agency (EMA), pemigatinib will provide a targeted treatment option for CCA patients with *FGFR2* fusions/rearrangements who are unresectable and relapsed or refractory to first line treatment.

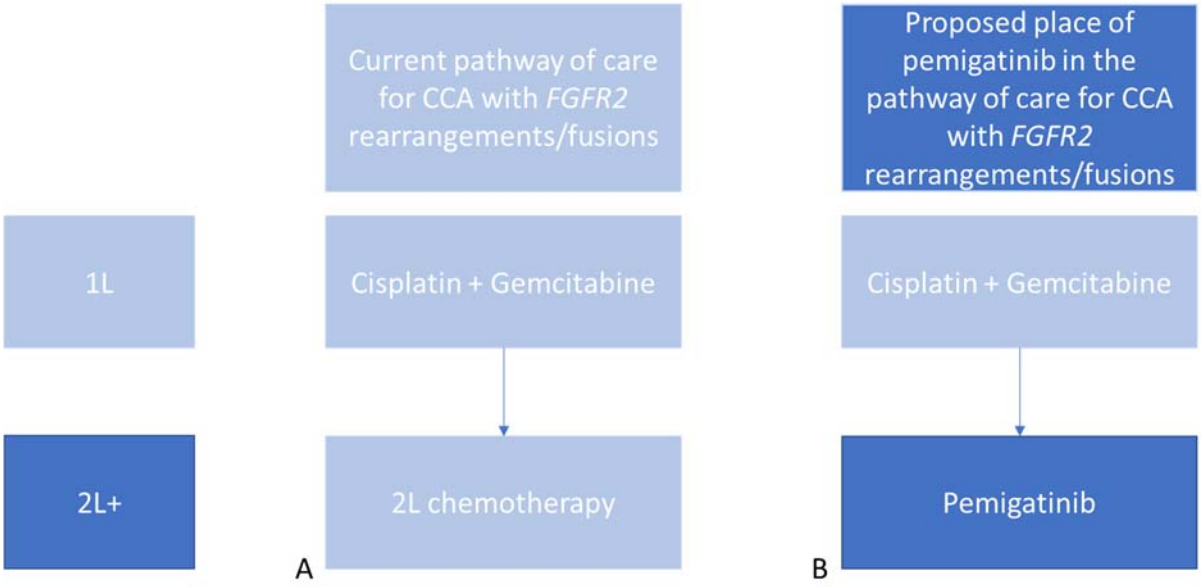


Figure 5. Proposed place of pemigatinib in the pathway of care for previously treated, unresectable, locally advanced, or metastatic CCA patients with *FGFR2* fusions/rearrangements in England and Wales

1L, first line; 2L, second line.

Until recently, the use of genetic testing in CCA was not considered clinically relevant due to a lack of targeted therapies. However, the significance of this has become more pertinent due to increased research and development of treatments such those targeting *FGFR* fusions and isocitrate dehydrogenase (IDH) mutations. That said, genetic testing for CCA is not currently part of routine care.

As highlighted in the NHS Long Term Plan,[52] beginning this year (2020/21) the NHS aims to extend the use of genomic testing so it will be routinely available to all cancer patients. Their initial goal is that by 2023 over 100,000 patients will have received a genomic test for their cancer. Furthermore, by targeting investment in areas of innovation, particularly genomics, the NHS hopes to be the first national health care system to offer whole genome sequencing as part of routine care. This process has already begun with the establishment of seven genomic hubs across England, each having access to various testing technologies including gold standard next generation sequencing (NGS) technology. Indeed, some FGFR testing is currently available and being undertaken across a number of oncological, haematological and neurological malignancies, for example FGFR4 in paediatric solid tumours.

As per the NHS's goals to offer a world-leading service with regards to their genomics offering The National Genomic Test Directory for Cancer[53] is updated annually. Due to the COVID-crisis the directory was not updated in April 2020 as originally planned. However, as a result of conversations with providers based at some of the hubs, it is our understanding that a wider range of FGFR tests will be added imminently including *FGFR2* fusions/arrangements for CCA. Considering this, it is worth noting that pemigatinib is not the sole FGFR inhibitor in development for the treatment of CCA. It is likely other such molecules will soon be introduced to the UK thus the availability of genetic testing for this indication will not solely support pemigatinib.

Additionally, since the *FGFR2* fusion/rearrangement occurs at onset of disease[17] genomic testing of this type has greater clinical relevance when assessing optimal patient treatment and management options for CCA to support their personalised care plan.[54]

B.1.4. Equality considerations

There are no known equality issues relating to the use of pemigatinib in patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was conducted in 2018 to identify relevant clinical evidence in previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements. A total of 6,996 articles were identified in the original search on 9 November 2018. Eight non-comparative studies and one retrospective observational study were included from 24 publications.

Subsequently, the inclusion criteria were revised and updated searches were conducted on 22 April 2020 to identify studies in previously treated, unresectable, locally advanced, or metastatic CCA without restriction on alteration. A total of 2,382 articles were identified. The original searches were also screened with the expanded criteria.

A total of 209 studies were included from 108 unique studies, including five randomised controlled trials from 14 publications, and 103 single-arm trials and observational studies from 197 publications. Six trials were flagged as ongoing and had not yet reported results. The original and expansion/update search results are presented in Figure 6 and Figure 7, respectively. The five randomised controlled trials are summarised in Table 7. Additional details of the methodology and results are summarised in Appendix D.

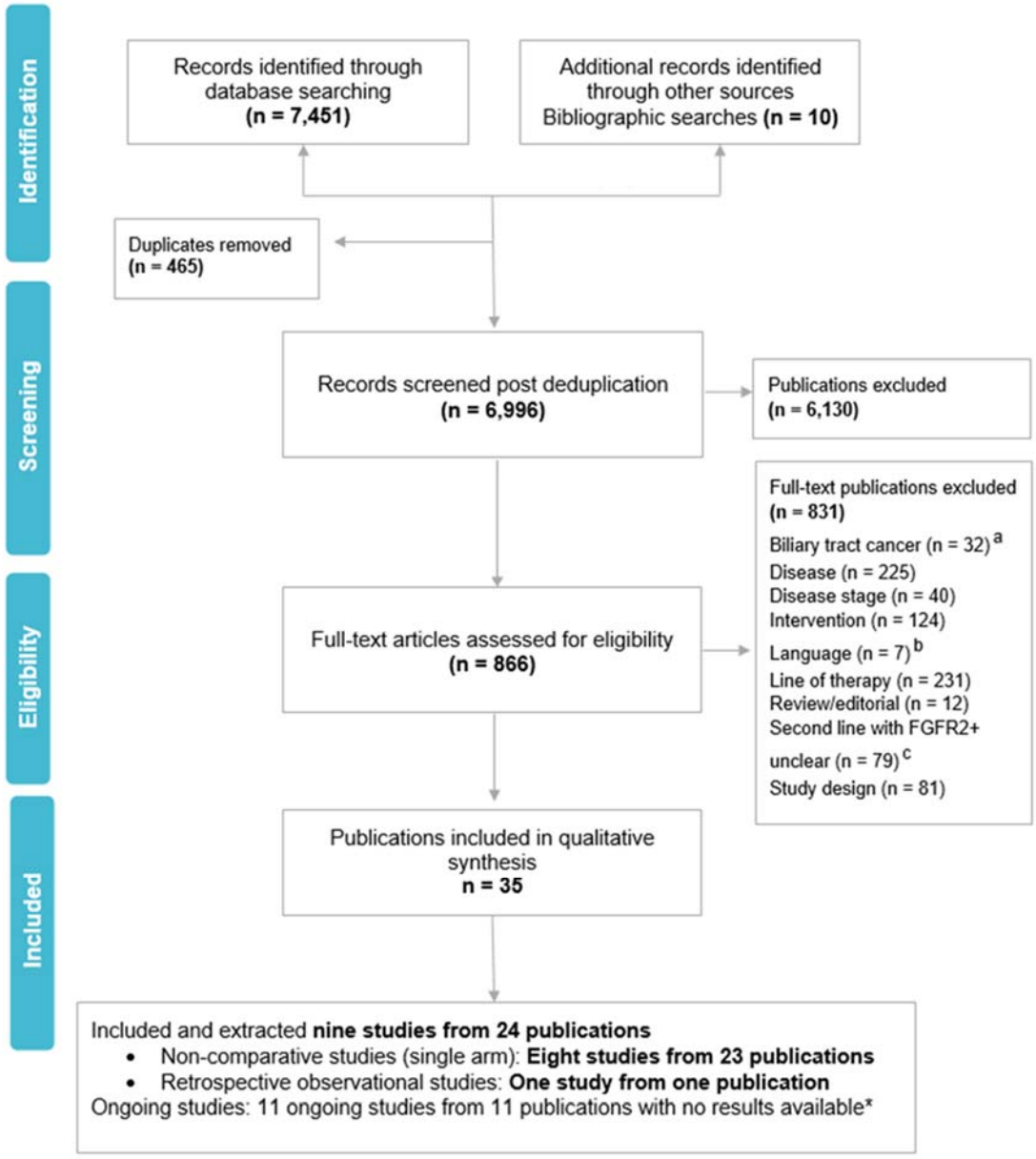


Figure 6. PRISMA diagram for the clinical evidence SLR – original 2018 SLR

FGFR2+, fibroblast growth factor receptor 2-positive; SLR, systematic literature review.

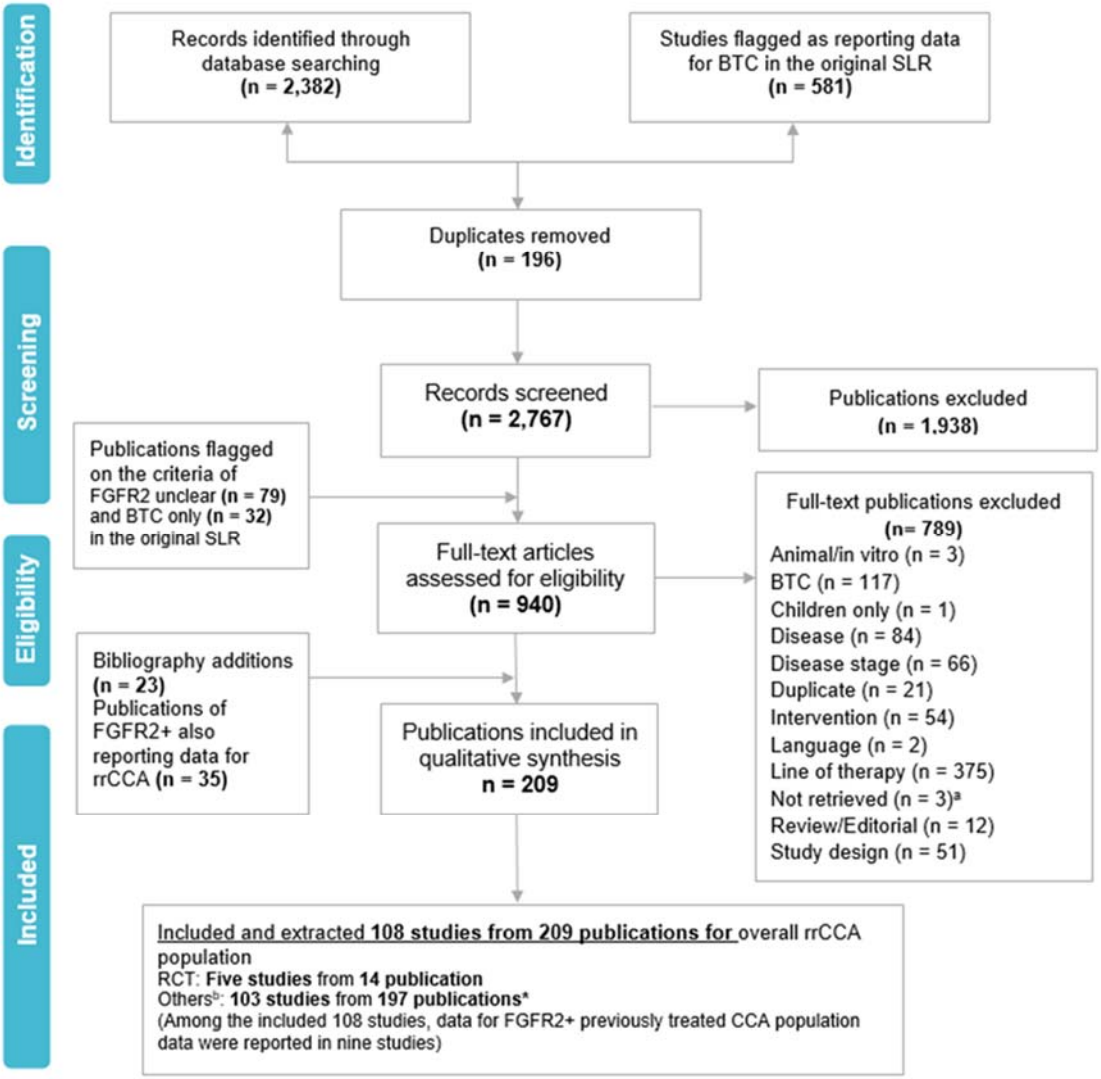


Figure 7. PRISMA diagram for the clinical evidence SLR – April 2020 expansion and update SLR

FGFR2+, fibroblast growth factor receptor 2-positive; SLR, systematic literature review.

Table 7. Summary of published clinical effectiveness evidence from randomised controlled trials

Study name (trial name/NCT)	Study phase Study centre	Relapsed or refractory CCA 2L+ (N)/ FGFR2+ identified (N)	Treatment/comparator	CCA type N (%) Intrahepatic, extrahepatic, Hilar
Lamarca 2019[34] **(ABC-06/NCT01926236)**	Phase 3 UK	117/NR	mFOLFOX+ASC ASC	mFOLFOX+ASC • iCCA: 34 (56.6) • eCCA: 26 (43.3) • Hilar CCA: NR
				ASC • iCCA: 38 (66.6) • eCCA: 19 (33.3) • Hilar CCA: NR
Abou-Alfa 2020[55] **(ClarIDHy/NCT02989857)**	Phase 3 France, Italy, South Korea, Spain, the UK, and the US	185/NR	Ivosidenib (AG-120)/ placebo	Ivosidenib (AG-120) • iCCA: 111 (90) • eCCA: 1 (1) • Hilar CCA: 4 (3)
				Placebo • iCCA: 58 (95) • eCCA: 1 (2) • Hilar CCA: 0
Demols 2019[56] **(REACHIN/NCT02162914)**	Phase 2 NR	66/NR	Regorafenib + best supportive care Placebo + best supportive care	Regorafenib + best supportive care • iCCA: 23 (69.69) • eCCA: 3 (9.09) • Hilar CCA: 3 (9.09)
				Placebo + best supportive care • iCCA: 19 (57.57) • eCCA: 6 (18.2) • Hilar CCA: 3 (9.09)
				•
				Active symptom control • iCCA: 38 (66.6) • eCCA: 19 (33.3) • Hilar CCA: NR
Zheng 2018[57] **(NCT02558959)**	Phase 2 China	48/NR	Irinotecan + capecitabine (XELIRI-arm) Irinotecan (IRI-arm)	Irinotecan + capecitabine (XELIRI-arm) • iCCA: 20 (66.7) • eCCA: 3 (10) • Hilar CCA: NR
				Irinotecan (IRI-arm)

				• iCCA: 21 (70) • eCCA: 4 (13.3) • Hilar CCA: NR
Venturini 2016[58] (NR)	NR NR	10/NR	TACE + DEBDOX (irinotecan)/ TACE + DEBIRI (doxorubicin)	TACE + DEBDOX (irinotecan) • iCCA: NR • eCCA: NR • Hilar CCA: NR
				TACE + DEBIRI (doxorubicin) • iCCA: NR • eCCA: NR • Hilar CCA: NR

ASC, active symptom control; CCA, cholangiocarcinoma; DEBDOX, drug-eluting beads loaded with doxorubicin; DEBIRI, drug-eluting bead, irinotecan; iCCA, intrahepatic cholangiocarcinoma; eCCA, extrahepatic, cholangiocarcinoma; NR, not reported; TACE, transarterial chemoembolization; UK, United Kingdom; US, United States; XELIRI, capecitabine plus irinotecan.

B.2.2. List of relevant clinical effectiveness evidence

The submission is supported by data from the ongoing phase 2 FIGHT-202 study (NCT02924376; INCB 54828-202). Data sources for this submission include Abou-Alfa et al. 2020,[29] the FIGHT-202 clinical study report,[59] and Incyte data on file.[60,61] All sources reported the data as of the 22 March 2019 cutoff date.

Table 8. Clinical effectiveness evidence

Study	FIGHT-202				
Study design	Open-label, single-arm, multicentre, phase 2 study				
Population	Subjects with advanced/metastatic or surgically unresectable CCA including *FGFR2* fusions/rearrangements who failed previous therapy				
Intervention(s)	Pemigatinib				
Comparator(s)	NA				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	Efficacy data from FIGHT-202 is used in the economic model because this is the only study that provides data for pemigatinib in the population and line of relevance to this submission.				
Reported outcomes specified in the decision problem	• OS • PFS • Response rates (ORR) • AEs • HRQoL				
All other reported outcomes	• DOR • DCR • EORTC QLQ-C30, BIL21				

AEs, adverse events; CCA, cholangiocarcinoma; DCR, disease control rate; DOR, duration of response; EORTC QLQ-BIL21, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (CCA and gallbladder cancer); EORTC QLQ-C30, EORTC QLQ Core 30; FGFR2, fibroblast growth factor receptor; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival.
Source: Abou-Alfa et al. 2020[29]

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

A summary of FIGHT-202 methodology is provided in Table 9.

Table 9. FIGHT-202 methodology

Trial number(s)	NCT02924376, EudraCT Number 2016 002422-36, JapicCTI-184218
Location (number of centres in which patients were randomised to pemigatinib)	FIGHT-202 enrolled participants at 67 study sites in the United Kingdom, United States, South Korea, France, Italy, Thailand, Germany, Belgium, Israel, Spain, Japan, and Taiwan.
Study design	A phase 2, open-label, single-arm, multicentre study to evaluate the efficacy and safety of pemigatinib in patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements.
Study objectives	Primary: To evaluate the efficacy of pemigatinib in participants with advanced/metastatic or surgically unresectable cholangiocarcinoma with *FGFR2* fusions/rearrangements who have progressed on at least one previous treatment.
Key inclusion/exclusion criteria	Key inclusion criteria: • Patients with histologically or cytologically confirmed CCA who failed one prior treatment • Documentation of *FGF/FGFR* gene alteration status • Radiographically measurable disease per RECIST v1.1 • ECOG PS ≤2 • Adequate hepatic function (total bilirubin <1.5 x ULN; <2.5 X ULN for patients with Gilbert syndrome or metastatic disease involving liver; aminotransferases ≤2.5 x ULN; ≤5 x ULN for patients with liver metastases) • Adequate renal function (CrCl >30 mL/min) • Serum phosphate ≤ institutional ULN • Serum calcium within institutional normal range Key exclusion criteria: • Prior treatment with select FGFR inhibitors • History of calcium phosphate homeostasis or ectopic mineralisation/calcification • Current evidence of clinically significant corneal or retinal disorder confirmed by ophthalmologic examination
Trial drugs	Pemigatinib
Permitted and disallowed concomitant medication	Concomitant medications were permitted to treat comorbidities or AEs during the study, except: • Potent cytochrome P450 3A4 inhibitors and inducers (note: there were no restrictions on topical ketoconazole) • Another selective FGFR inhibitor • Investigational study drug for any indication • Any anticancer medications other than the study drug
Primary outcomes	ORR in participants with *FGFR2* fusions/rearrangements based on the central genomics laboratory results (Cohort A).
Secondary outcomes	• DOR: time from the date of CR or PR until PD (all cohorts).

	• PFS: first dose to progressive disease or death (all cohorts). • ORR in participants with other *FGF/FGFR* alterations (Cohort B). • ORR in all participants with *FGF/FGFR* alterations (Cohorts A and B). • DCR: CR + PR + stable disease (all cohorts). • OS: first dose to death due to any cause (all cohorts)
PROs	HRQoL evaluation (EORTC QLQ-C30 and EORTC QLQ-BIL21)
Safety assessments	Safety and tolerability assessed by evaluating the frequency, duration, and severity of AEs
Pre-planned subgroups	N/A

AEs, adverse events; CCA, cholangiocarcinoma; CR, complete response; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FGF, fibroblast growth factor; FGFR, FGF receptor; HRQoL, health-related quality of life; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limits of normal.
Source: Incyte, data on file.[59]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis population

Analysis populations in FIGHT-202 included:

- For Cohort A and B: efficacy evaluable population includes all patients who received at least one dose of pemigatinib and have a known FGF/FGFR alteration. All efficacy analyses were conducted using the efficacy evaluable population.[59]

- Safety population includes all enrolled participants who received at least one dose of pemigatinib. All safety analyses were conducted using the safety population. The database for the pooled safety analyses includes data from participants in FIGHT-101, -102, -201, -202, and -203 who received pemigatinib as monotherapy and are included in the modified safety population. Safety analyses of the pooled safety population are also presented in this submission, as the FGF/FGFR fusions/rearrangements should not impact the safety profile of pemigatinib.[59]

- The per protocol population includes participants in the efficacy evaluable population who were considered to be sufficiently compliant with the study protocol. The clinical team identified the participants for exclusion from the per protocol population and documented the rationales for exclusion before database lock based

on the procedures described in the FIGHT-202 Statistical Analysis Plan. The per protocol population was used for sensitivity analyses of ORR.[59]

B.2.4.2 Statistical Analyses

Cohort determination was based on FGF/FGFR status from the central genomics laboratory and subjects were summarised by cohorts.[59]

Efficacy analyses

Primary endpoint analyses

The primary endpoint of the study is ORR in participants with tumours with *FGFR2* fusions or rearrangements (Cohort A) based on the central genomics laboratory results. The primary endpoint—ORR—was defined as the proportion of participants who achieved a complete response (CR) or a partial response (PR) based on RECIST v1.1. Tumour response of CR or PR is determined by an independent review committees (IRC) based on confirmed response. Participants who did not have sufficient baseline or on-study data to be assessed for tumour response were included in the denominator for the calculation of ORR. The 95% CI for ORR was calculated using exact method for binomial distribution. The primary analysis of ORR is based on IRC-assessed confirmed tumour responses. It was predetermined that the study outcome would be considered positive if the lower limit of the 95% CI for ORR exceeded 15%. A sensitivity analysis of ORR was performed in the per protocol population. Secondary analyses of ORR in Cohorts A and B combined, Cohort B, and Cohort C were performed in the same way as the primary analysis of ORR.[59]

Secondary endpoint analyses

Secondary endpoints included duration of response (DOR), PFS, DCR, and OS. DOR was defined as the time from the first overall response contributing to an IRC-assessed tumour response to the earlier of death or the first overall response of progressive disease (PD). PFS, DOR, and OS were analysed using the Kaplan–Meier (KM) method. DCR was calculated in the same way as ORR with the exception that participants who achieved stable disease for a minimum of 39 days, in addition to those who achieved a CR and PR, were included in the calculation.[59]

Safety analyses

Safety data were listed and summarised descriptively for the safety population. AEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.02. If the toxicity was not included in CTCAE v4.03, it was rated on a scale of 1 to 4 as follows: 1=mild, 2=moderate, 3=severe, and 4=life-threatening.[59]

Pharmacology

Pharmacokinetic data were analysed using standard population PK methods and software.[59]

B.2.4.3 Patient withdrawals

Patients were allowed to withdraw from treatment at any time at their own request, or withdraw at the discretion of the investigator or sponsor due to safety or behavioural reasons, or to the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.[59] Patient disposition including withdrawals is discussed in detail in Section B.2.6.1.

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

The quality assessment of FIGHT-202 (Abou-Alfa et al. 2020) is summarised in Table 10. Quality assessments of the studies identified by the SLR are summarised in Appendix D.

Table 10. Quality assessment for Abou-Alfa et al., 2020

Category	Question	Abou-Alfa et al., 2020[29]
Reporting	1. Is the hypothesis/aim/objective of the study clearly described?	Y
	2. Are the main outcomes to be measured clearly described in the introduction or methods section?	Y
	3. Are the characteristics of the patients included in the study clearly described?	Y
	4. Are the interventions of interest clearly described?	Y
	5. Are the distributions of principal confounders in each group of patients to be compared clearly described?	Y

Category	Question	Abou-Alfa et al., 2020[29]
	6. Are the main findings of the study clearly described?	Y
	7. Does the study provide estimates of the random variability in the data for the main outcomes?	Y
	8. Have all important adverse events that may be a consequence of the intervention been reported?	Y
	9. Have the characteristics of patients lost to follow-up been described?	Y
	10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Y
External validity	11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Y
	12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Y
	13. Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	N
Internal validity	14. Was an attempt made to blind study subjects to the intervention they have received?	NA
	15. Was an attempt made to blind those measuring the main outcomes of the intervention?	N
	16. If any of the results of the study were based on 'data dredging', was this made clear?	Y
	17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Y
	18. Were the statistical tests used to assess the main outcomes appropriate?	Y
	19. Was compliance with the intervention(s) reliable?	Y
	20. Were the main outcome measures used accurate (valid and reliable)?	Y
Internal validity – confounding	21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Y
	22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Y

Category	Question	Abou-Alfa et al., 2020[29]
	23. Were study subjects randomised to intervention groups?	NA
	24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	NA
	25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Y
	26. Were losses of patients to follow-up considered?	Y
Power	27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Y

Note: Adapted from Downs and Black checklist.[62]

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1 Study population

B.2.6.1.1 Patient disposition

Figure 8 summarises the patient disposition from FIGHT-202 (22 March 2019 data cutoff).

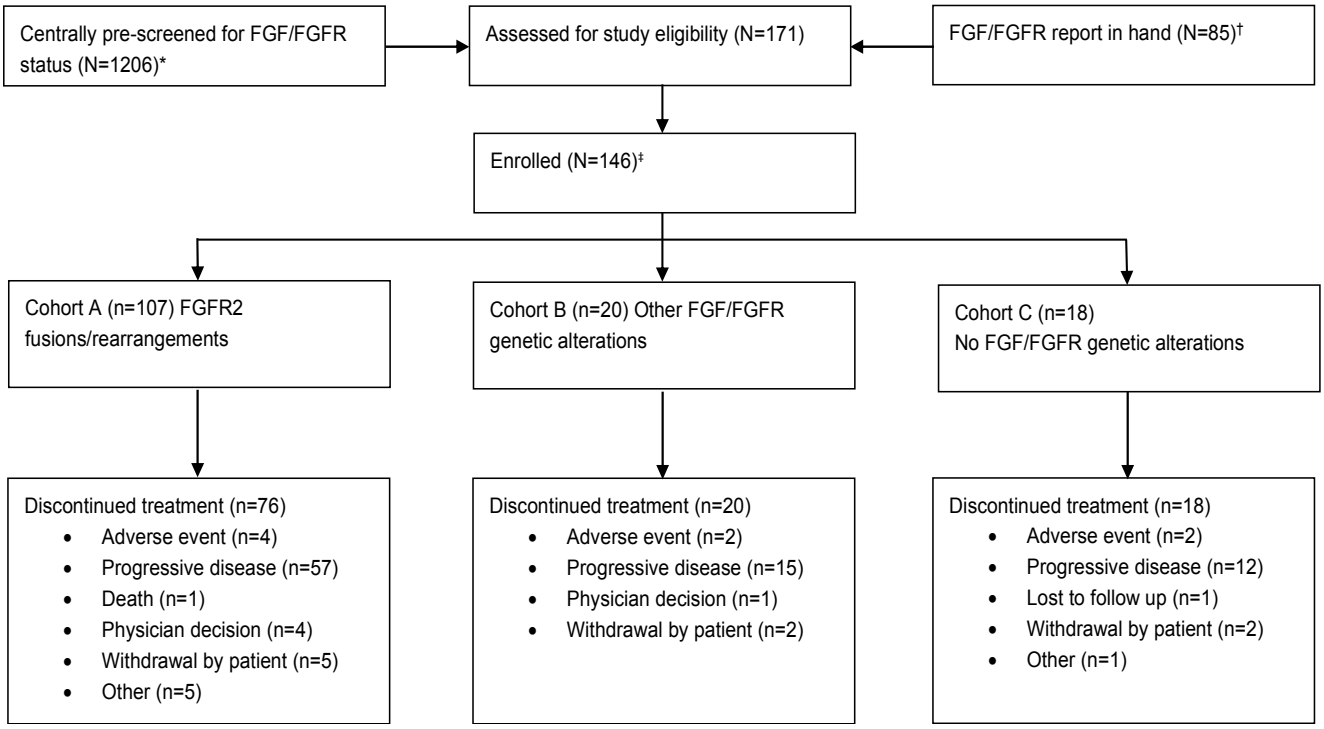


Figure 8. Patient disposition FIGHT-202

FGF/FGFR, fibroblast growth factor/FGF receptors.
*FoundationOne®, Foundation Medicine.
†Most patients with report in hand had undergone FoundationOne® testing for FGF/FGFR status.
‡One patient received pemigatinib but had undetermined FGF/FGFR status; analysed for safety but not efficacy and was not assigned to a cohort.
Source: Incyte, Data on file (Summary of clinical efficacy)[61]

As of the 22 March 2019 data cutoff, 76 patients (71.0%) from Cohort A had discontinued treatment. The median duration of follow-up for Cohort A was 15.44 months (range, 7.0–24.7 months).[29,61]

B.2.6.2 Baseline characteristics

Table 11 presents the baseline demographics and disease characteristics of the CCA patients enrolled in FIGHT-202. Cohort A (n=107) reflects the patients with CCA and *FGFR2* fusions/rearrangements.

Table 11. Baseline demographics and disease characteristics (FIGHT-202; data cutoff, 22 March 2019)

	Cohort A *FGFR2* fusions/rearrangements	Cohort B Other *FGF/FGFR* fusions/rearrangements	Cohort C No *FGF/FGFR* fusions/rearrangements	Total*
N	107	20	18	146
Age, median (range), y	56 (26–77)	63 (45–78)	65 (31–78)	59 (26–78)
<65, n (%)	82 (77)	10 (50)	7 (39)	100 (68)
65–<75, n (%)	20 (19)	7 (35)	8 (44)	35 (24)
≥75, n (%)	5 (5)	3 (15)	3 (17)	11 (8)
Sex, n (%)				
Men	42 (39)	9 (45)	10 (56)	62 (42)
Women	65 (60)	11 (55)	8 (44)	84 (58)
Region, n (%)				
North America	64 (60)	6 (30)	18 (100.0)	88 (60)
Western Europe	32 (30)	3 (15)	0	35 (24)
Rest of world†	11 (10)	11 (55)	0	22 (15)
ECOG PS, n (%)				
0	45 (42)	7 (35)	7 (39)	59 (40)
1	57 (53)	10 (50)	8 (44)	76 (52)
2	5 (5)	3 (15)	3 (17)	11 (8)
Number of prior regimens,‡ n (%)				
1	65 (61)	12 (60)	12 (67)	89 (61)
2	29 (27)	7 (35)	2 (11)	38 (26)
≥3	13 (12)	1 (5)	4 (22)	19 (13)
Prior cancer surgery, n (%)	38 (36)	6 (30)	4 (22)	48 (33)
Prior radiation, n (%)	28 (26)	3 (15)	5 (28)	36 (25)
CCA location, n (%)				
Intrahepatic	105 (98)	13 (65)	11 (61)	130 (89)
Extrahepatic	1 (1)	4 (20)	7 (39)	12 (8)
Other/missing	1 (1)	3 (15)§	0	4 (3)

FGF/FGFR, fibroblast growth factor/FGF receptors.
*The total includes one patient who received pemigatinib but had undetermined FGF/FGFR status; analysed for safety but not for efficacy and was not assigned to a cohort.
†Includes Israel, South Korea, Taiwan, Thailand, and Japan.
‡Maximum number of five therapies in cohort A and three in cohort B/C.
§Includes gallbladder (n=2) and ampulla of Vater (n=1) cancer.
Source: Abou-Alfa et al. 2020[29]

B.2.6.3 Duration of treatment

The median duration of treatment with pemigatinib for Cohort A was 219 days (range 7–730 days) at the 22 March 2019 data cutoff.[61]

B.2.6.4 Primary efficacy outcomes

The primary endpoint of FIGHT-202 is ORR in participants with *FGFR2* fusions/rearrangements. The ORR is defined as the proportion of patients who achieved a confirmed CR or a confirmed PR based on RECIST v1.1 criteria.[59]

Responses achieved with pemigatinib were unprecedented, clinically meaningful, and durable. Patients with CCA and *FGFR2* fusions/rearrangements treated in the 2L+ with pemigatinib (FIGHT-202, Cohort A) had an ORR of 35.5% (95% CI: 26.5%, 45.4%), including 3 CRs (2.8%) and 35 PRs (32.7%; Table 12).[29] The study achieved the predetermined threshold for a positive outcome (lower limit of the 95% CI for ORR >15%). No patients from Cohort B or C had a PR or CR. Table 12 summarises the treatment response results from all three cohorts.[59]

Table 12. Primary endpoint: ORR

Variable	Cohort A (n=107) *FGFR2* fusions/rearrangements	Cohort B (n=20) Other *FGF/FGFR* fusions/rearrangements	Cohort C (n=18) No *FGF/FGFR* fusions/rearrangements
ORR (95% CI), %	35.5 (26.5, 45.4)	0	0
Best OR,* n (%)			
CR	3 (2.8)	0	0
PR	35 (32.7)	0	0
Stable disease	50 (46.7)	8 (40.0)	4 (22.2)
PD	16 (14.9)	7 (35.0)	11 (61.1)
Not evaluable	3 (2.8)	5 (25.0)	3 (16.7)

CI, confidence interval; CR, complete response; FGF/FGFR, fibroblast growth factor/FGF receptors; FGFR2, fibroblast growth factor receptors 2; OR, overall response; ORR, overall response rate; PD, progressive disease; PR, partial response.
Note: The FIGHT-202 trial was not designed to compare cohorts. FIGHT-202 (data cutoff, 22 March 2019).
*Assessed and confirmed by independent central review.
†Postbaseline tumour assessment was not performed owing to study discontinuation (2 participants in Cohort A, 4 participants in Cohort B, 3 participants in Cohort C) or was performed prior to the minimum interval of 39 days for an assessment of stable disease (1 participant in Cohort A, 1 participant in Cohort B).
Source: Abou-Alfa et al. 2020[29]

A majority of participants in Cohort A (88%; 91 of 103 participants with post-baseline target lesion measurements) had IRC-assessed best percentage reductions in the sum of target lesion diameters from baseline, including 45 participants with reductions of >30% (Figure

9).[29] Seven participants with reductions of >30% did not have tumour assessments that met RECIST v1.1 criteria for confirmed PR. Median best percentage change from baseline in the sum of target lesion diameters was –24.6% (range: –100%, 55%).[59]

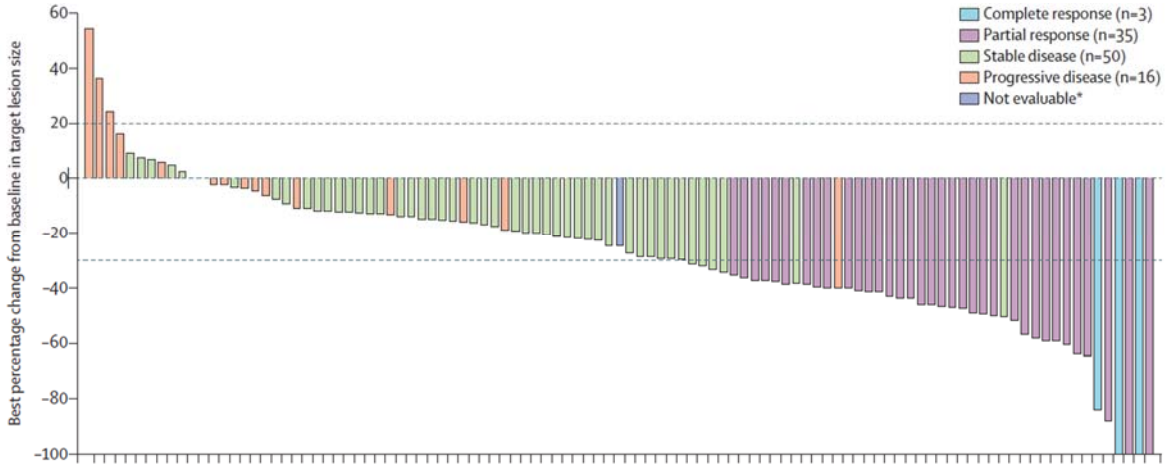


Figure 9. Best percentage change from baseline in target lesions size (FIGHT-202, Cohort A; data cutoff, 22 March 2019)

RECIST, Response Evaluation Criteria in Solid Tumors.
Note: Coloured bars are confirmed responses per RECIST.
*Patient had decrease in target lesion size but was not evaluable for response per RECIST.
Source: Abou-Alfa et al. 2020[29]

ORR was similar in patients who had received 1, 2, or ≥3 lines of prior therapy and in patients harbouring *FGFR2-BCC1* vs any other *FGFR2* fusions or rearrangements (Figure 10).[59]

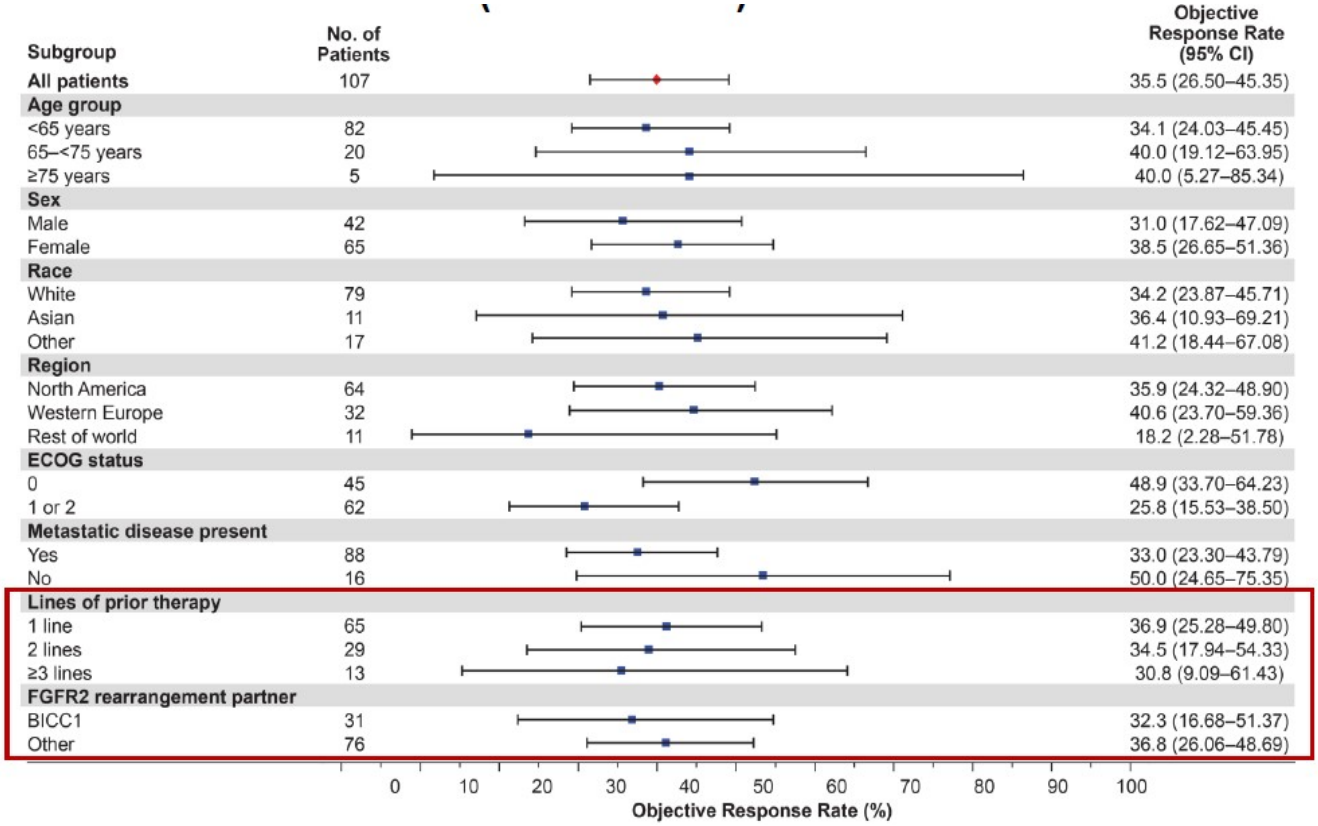


Figure 10. ORR by subgroup (Cohort A)

CI, confidence interval; FGFR2, fibroblast growth factor receptors 2.

Source: Abou-Alfa et al. 2020[29]

B.2.6.5 Secondary efficacy outcomes

The key secondary endpoint is DOR, defined as the time from the date of CR or PR until PD. Median DOR among responders was 7.5 months (95% CI: 5.7 months, 14.5 months) in Cohort A (Table 13). The median time to first response was 2.7 months (interquartile range: 1.4, 3.9).[29] No patients in Cohort B or C achieved a response.

Table 13. Key secondary endpoint: DOR

Variable	Cohort A (n=107) *FGFR2* fusions/rearrangements	Cohort B (n=20) Other *FGF/FGFR* fusions/rearrangements	Cohort C (n=18) No *FGF/FGFR* fusions/rearrangements
Median DOR (95% CI), mo	7.5 (5.7, 14.5)	–	–
Patients with events, n (%)	21/38 (55)	0	0
Patients censored, n (%)	17/38 (45)	0	0
KM estimated probability of retaining a response			
At 6 months, % (range)	68 (49, 82)	–	–
At 12 months, % (range)	37 (19, 56)	–	–

CI, confidence interval; DOR, duration of response; FGF, fibroblast growth factor; FGFR, FGF receptor; KM, Kaplan–Meier.
Source: Abou-Alfa et al. 2020.[29]

Additional secondary endpoints included PFS, DCR, and OS are summarised in Table 14. Median PFS results were 6.9 months (95% CI: 6.2 months, 9.6 months) for Cohort A, 2.1 months (95% CI: 1.2 months, 4.9 months) for Cohort B, and 1.7 months (1.3 months, 1.8 months) for Cohort C.[29] Figure 11 shows the KM estimates for PFS in Cohort A.[29]

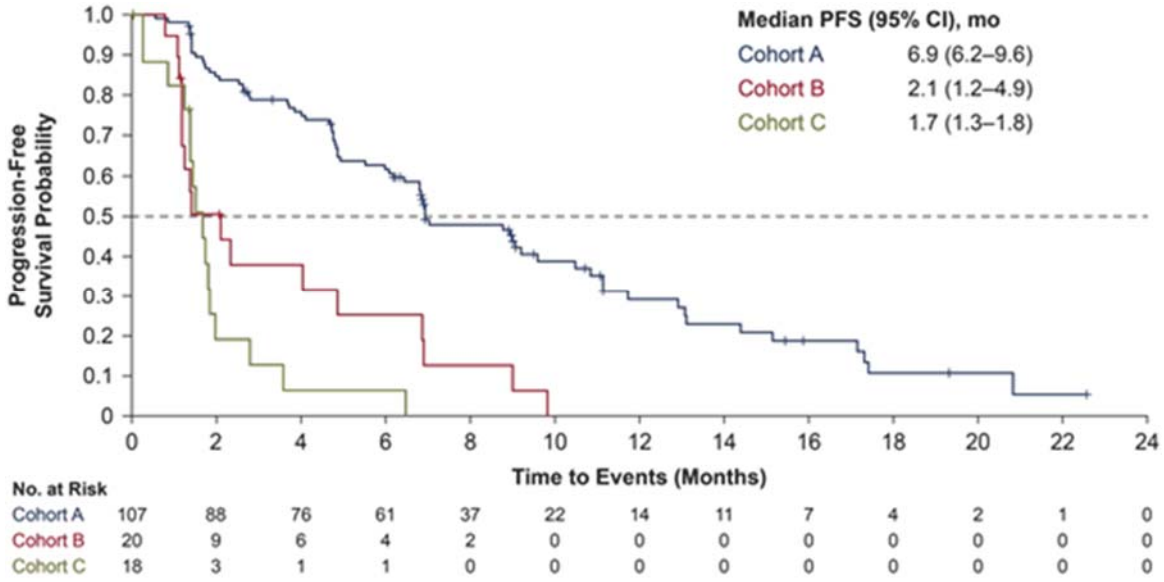


Figure 11. KM estimates of PFS in all cohorts of FIGHT-202 (data cutoff, 22 March 2019)

FGFR, fibroblast growth factor receptor; KM, Kaplan–Meier; PFS, progression-free survival.
Source: Vogel et al, 2019[63]

The DCR was calculated as the sum of CR, PR, and stable disease, and indicates the percentage of patients who were able to achieve at minimum disease stabilisation.[29,39] The proportion of patients with DCR were 82% (95% CI: 74%, 89%) for Cohort A, 40% (95% CI: 19%, 64%) for Cohort B, and 22% (95% CI: 6%, 48%)(Table 14).[29]

OS data were not mature at the time of data cutoff. In Cohort A, 67 of 107 patients (63%) were alive and censored for OS at the last date known alive with a median follow-up of 15.44 months (range: 7.0 months, 24.7 months) at the time of data cutoff. The median OS was 21.1 months (95% CI: 14.8, not estimable; Table 14). The OS was 6.7 months (95% CI: 2.1 months, 10.6 months) and 4.0 months (95% CI: 2.3 months, 6.5 months), for Cohort B and Cohort C, respectively.[29] Figure 12 shows the KM estimates of OS for Cohort A.[29]

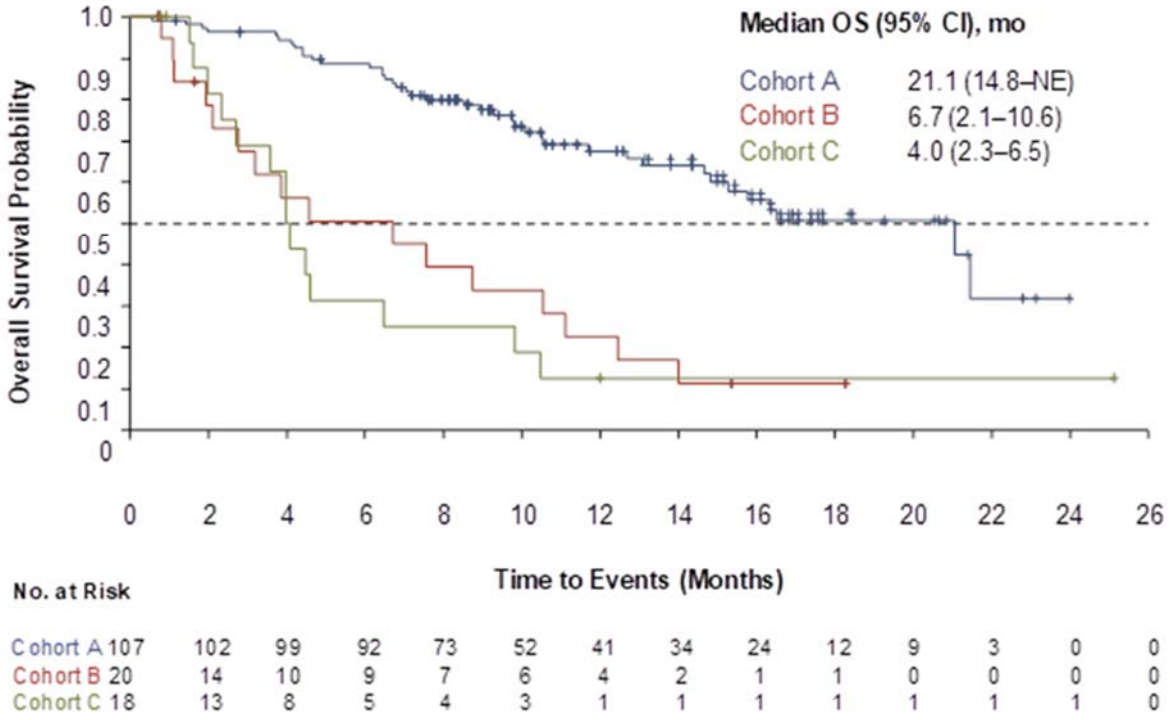


Figure 12. KM estimates of OS in all cohorts of FIGHT-202 (data cutoff, 22 March 2019)

FGFR, fibroblast growth factor receptor; KM, Kaplan–Meier; OS, overall survival.
Source: Vogel et al, 2019[63]

Table 14. Secondary endpoints

Variable	Cohort A (n=107) *FGFR2* fusions/rearrangements	Cohort B (n=20) Other *FGF/FGFR* fusions/rearrangements	Cohort C (n=18) No *FGF/FGFR* fusions/rearrangements
PFS, median (months)	6.9 (6.2, 9.6)	2.1 (1.2, 4.9)	1.7 (1.3, 1.8)
Patients with events, n (%)	71 (66)	17 (85)	16 (89)
Patients censored, n (%)	36 (34)	3 (15)	2 (11)
KM estimated probability of retaining a response			
At 6 months, % (range)	62 (52, 70)	25 (8, 47)	6 (<1, 25)
At 12 months, % (range)	29 (19, 40)	0	0
DCR, % (95% CI)	82 (74, 89)	40 (19, 64)	22 (6, 48)
OS, median (months)	21.1 (14.8, NE)	6.7 (2.1, 10.6)	4.0 (2.3, 6.5)
Patients with events, n (%)	40 (37)	16 (80)	14 (78)
Patients censored, n (%)	67 (63)	4 (20)	4 (22)
KM estimated probability of retaining a response			
At 6 months, % (range)	89 (81, 93)	51 (26, 71)	31 (11, 54)
At 12 months, % (range)	68 (56, 76)	23 (7, 43)	13 (2, 33)

DCR, disease control rate; FGF, fibroblast growth factor; FGFR, FGF receptor; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival.
Source: Abou-Alfa et al. 2020[29]

B.2.6.6 Additional outcomes

Health-related quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the EORTC QLQ-BIL21 (CCA and gallbladder cancer). Mean and median changes from baseline in EORTC QLQ-C30 and QLQ-BIL21 scores were variable, and no consistent trends were observed. Similar results were observed across all cohorts.[59]

B.2.6.7 Efficacy conclusions

Efficacy data from FIGHT-202 demonstrate that pemigatinib 13.5 mg once daily (QD) on a 14 days-on/7 days-off schedule has meaningful and durable antitumour activity in

participants with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements (Cohort A, n=107). The study achieved the predetermined threshold for a positive outcome (lower limit of the 95% CI for ORR exceeded 15%). In Cohort A, the ORR based on IRC-assessed, confirmed tumour responses was 35.5% (95% CI: 26.5%, 45.4%).[29] Three participants (2.8%) had CRs and 35 participants (32.7%) had PRs.[29] No patients from Cohort B or C had a PR or CR. The antitumour activity in patients with *FGFR2* fusions/rearrangements was observed across demographic and disease subgroups assessed.[29]

Persistence of efficacy was demonstrated by the duration of the IRC-assessed, confirmed tumour responses; median DOR in participants with advanced/metastatic or surgically unresectable CCA with *FGFR2* fusions/rearrangements was 7.5 months (95% CI: 5.7 months, 14.5 months) with a median follow-up of 15.44 months.[29]

The PFS data further support the persistence of clinical benefit elicited by pemigatinib. In Cohort A of FIGHT-202, median PFS with pemigatinib was 6.9 months (95% CI: 6.2 months, 9.6 months). KM estimates of PFS at 9 and 12 months were 62% and 29%, respectively.[29] Median PFS in participants with other molecular subtypes was shorter (2.1 and 1.7 months in Cohorts B and C, respectively) with no overlapping 95% CIs, demonstrating that antitumour activity from pemigatinib treatment is persistent in the targeted population for this submission. The observed proportion of patients with an ORR and the PFS in this study suggest that pemigatinib has encouraging clinical activity in patients with *FGFR2* fusions/rearrangements.[29]

While caution should be taken in comparing data across studies (due to differences in study designs and patient populations), the antitumour activity of pemigatinib in patients with *FGFR2* fusions/rearrangements compare favourably with 2L chemotherapy and targeted therapy (reported in Section Unmet need in the treatment of CCA).[29] The efficacy of pemigatinib will further be explored in Section Indirect and mixed treatment comparisons.

B.2.7. Subgroup analysis

There were no pre-specified subgroup analyses based on baseline demographics and characteristics.

B.2.8. Meta-analysis

There is only one relevant study (FIGHT-202) for the indicated population relevant to this submission, therefore a meta-analysis was not performed.

B.2.9. Indirect and mixed treatment comparisons

In the absence of randomised controlled trials comparing the efficacy of pemigatinib directly to that of SOC, an indirect treatment comparison (ITC) was warranted to provide relative treatment effect evidence. FIGHT-202 being single-arm increases the complexity of assessing treatment efficacy against other relevant comparators, because standard techniques such as Bucher ITCs and network meta-analyses require a common comparator to estimate relative treatment effects.[64] Therefore, it was necessary to consider alternative methods for making these comparisons. A matching-adjusted indirect comparison (MAIC) was conducted in line with NICE Decision Support Unit (DSU) technical support document (TSD 18), as it enables the calculation of adjusted relative treatment effect estimates (e.g., HRs) in one direct step and allows a set of weights to be derived; the same set of weights can be used for all relevant outcome models (e.g., OS and PFS).[65]

Sources of information for the efficacy of the current SOC were identified through a clinical SLR. As detailed in Appendix D, there was one appropriate trial for the MAIC analyses: ABC-06. ABC-06 was a randomised phase 3, multicentre, open-label study of ASC alone or mFOLFOX+ASC for patients with locally advanced/metastatic BTCs previously treated with cisplatin/gemcitabine chemotherapy. Although these data indicated that mFOLFOX+ASC significantly improves OS versus ASC alone, it is unclear whether this has resulted in a universal change in the SOC for this patient population. Clinical experts consulted on this issue did indicate that, based on the available data, mFOLFOX is likely to be used in a second-line setting.[66] For this reason, both the mFOLFOX+ASC arm and the ASC alone arm were considered in the MAIC and model.

Details of the comparison between FIGHT-202 and ABC-06 studies and baseline patient characteristics are provided in Table 15 and Table 16, respectively. There was some observed heterogeneity across studies with regard to trial design and patient population. Key differences included:

- FIGHT-202 was a phase 2, single-arm clinical trial, whereas ABC-06 was a randomised phase 3, multicentre, open-label study
- FIGHT-202 was a multinational study, whereas ABC-06 was based in the UK
- ABC-06 investigated all BTCs, whereas the population of FIGHT-202 investigated patients with advanced/metastatic or surgically unresectable CCA who had progressed on at least one line of prior systemic therapy and included a majority of patients with iCCA
- Cohort A of FIGHT-202 included only patients with *FGFR2* fusions or rearrangements; the proportion of patients with these mutations was not reported in ABC-06

Table 15: Comparative summary of studies considered for indirect treatment comparison

	FIGHT-202	ABC-06
Study design	Phase 2, single-arm clinical trial	Randomised, phase 3, multicentre, open-label study
Population	Cholangiocarcinoma including *FGFR2* alterations	Biliary tract cancers, UK only
Intervention	Pemigatinib	mFOLFOX+ASC
Comparator	N/A	ASC alone
Primary endpoint	Objective response rate	Overall survival
Secondary endpoints	Duration of response, progression-free survival (RECIST 1.1), disease control rate, overall survival	Progression-free survival (RECIST 1.1), radiological response, adverse events, quality of life
Median follow-up duration	15.4 months	21.7 months

ASC, active symptom control; FGFR2, fibroblast growth factor receptor 2; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; N/A, not applicable; RECIST, Response Evaluation Criteria in Solid Tumors.
Sources: Abou-Alfa et al, 2020;[29] Lamarca et al., 2019.[34]

Table 16: Patient characteristics at baseline for studies considered for indirect treatment comparison

Study	FIGHT-202	ABC-06	ABC-06
Patients, N	107	81	81
Treatment	Pemigatinib	ASC	mFOLFOX+ASC
FGFR2+, N (%)	107 (100)	NR	NR
Median age, years (range)	56 (26–77)	65 (26–81)	65 (26–84)
Men, N (%)	42 (39)	37 (46)	43 (53)
Intrahepatic CCA, N (%)	105 (98)	38 (47)	34 (42)
ECOG PS 0–1, N (%)	102 (95)	81 (100)	81(100)
Albumin <35 g/L, N (%)	21 (20)	21 (26)	19 (23)

ASC, active symptom control; CCA, cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; *FGFR2*, fibroblast growth factor receptor 2; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; NR, not reported; PS performance status.
Sources: Abou-Alfa et al, 2020;[29] Lamarca et al., 2019.[34]

B.2.9.1 Matching-adjusted indirect comparison – methods

Full details of the methods adopted for the MAIC are provided in Appendix D and follow NICE technical guidance.[65] In summary, patient-level data (PLD) from FIGHT-202 were matched to aggregate data from ABC-06, and comparisons were carried out by performing weighted analysis (parametric survival models [PSMs] and Cox proportional hazard models).

The following factors (based on all covariates reported/ available from both trials) were included in the adjustment:

[redacted]

B.2.9.2 Matching-adjusted indirect comparison – results

Table 17 presents the baseline characteristics of the pemigatinib arm from FIGHT-202 (unadjusted and weighted) and the resulting effective sample size of the comparisons. The MAIC weighting was based on age, sex, ECOG performance status and albumin. There were nine patients from FIGHT-202 who had a missing value for albumin and were

excluded from the MAIC analyses. After performing the matching to the ABC-06 trial cohort characteristics, the weighted FIGHT-202 patients were approximately 10 years older, a higher proportion were male, a higher proportion had an ECOG performance status of 0–1, and lower albumin levels. Based on these characteristics, it was not clear how the matching would affect the weighted analyses compared to the naïve comparison, as the changes in some characteristics were likely to improve the relative effect when using weighted data (e.g. increase in ECOG 0–1 and decrease in albumin levels) whereas others were likely to decrease the relative effect (e.g. increase in age). The effective sample size was reduced by approximately half of the original sample size.

Table 17: Comparison of baseline characteristics – pemigatinib (FIGHT-202) unadjusted and weighted

Treatment (study)	N/ESS	Mean age (years)	Male %	ECOG PS 0–1 %	Albumin ≥35 g/L %
Pemigatinib unadjusted (FIGHT-202)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemigatinib weighted to mFOLFOX+ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemigatinib weighted to ASC only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ASC; active symptom control; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size.
Sources: Abou-Alfa et al, 2020;[29] Lamarca et al., 2019.[34]

B.2.9.3 FIGHT-202 vs ABC-06 (mFOLFOX+ASC) overall survival

Unadjusted and weighted KM plots, KM summary of number of events and median, and the HRs for OS are presented in Figure 13, Table 18, and Table 19, respectively. These results show that the patients receiving pemigatinib demonstrated significantly greater improvements in OS compared with patients receiving mFOLFOX+ASC (unweighted HR: [redacted]; 95% CI: [redacted]). Weighting the pemigatinib patients to match the mFOLFOX+ASC arm of ABC-06 resulted in an increase in the relative treatment effect (weighted HR: [redacted]; 95% CI: [redacted]).

[redacted]

Figure 13: KM plot of OS – Pemigatinib (FIGHT-202) vs mFOLFOX+ASC (ABC-06)

ASC, active symptom control; KM, Kaplan-Meier; OS, overall survival; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; Pemi, pemigatinib.

Table 18: KM summary of OS –pemigatinib (FIGHT-202) vs mFOLFOX+ASC (ABC-06)

Treatment (study)	N/ ESS	Events	Median (95% CI)
Pemigatinib unadjusted (FIGHT-202)	[redacted]	[redacted]	[redacted]
Pemigatinib weighted (FIGHT-202)	[redacted]	[redacted]	[redacted]
mFOLFOX+ASC (ABC-06)	[redacted]	[redacted]	[redacted]

ASC, active symptom control; CI, confidence interval; ESS, effective sample size; KM, Kaplan–Meier; mFOLFOX; oxaliplatin, L-folinic acid and fluorouracil; NA, not available; OS, overall survival.

Table 19: Hazard ratios for OS – pemigatinib (FIGHT-202) vs mFOLFOX+ASC (ABC-06)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	Pemigatinib vs mFOLFOX+ASC	[redacted]
Weighted bootstrapped CI	Pemigatinib vs mFOLFOX+ASC	[redacted]

ASC, active symptom control; CI, confidence interval; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; OS, overall survival.

B.2.9.4 FIGHT-202 vs ABC-06 (mFOLFOX+ASC) progression-free survival

Unadjusted and weighted KM plots, KM summary of number of events and median and the HRs for PFS are presented in Figure 14, Table 20 and Table 21, respectively. These results show that the patients receiving pemigatinib demonstrated significantly greater improvements in PFS compared with patients receiving mFOLFOX+ASC (unweighted HR: [redacted]; 95% CI: [redacted]). Weighting the pemigatinib patients to match the mFOLFOX+ASC arm of ABC-06 resulted in a slight increase in the relative treatment effect (weighted HR: [redacted]; 95% CI: [redacted]).

[redacted]

Figure 14: KM plot of PFS – Pemigatinib (FIGHT-202) vs mFOLFOX+ASC (ABC-06)

ASC, active symptom control; KM, Kaplan-Meier; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; Pemi, pemigatinib; ; Pemi, pemigatinib; PFS, progression-free survival.

Table 20: KM summary of PFS – pemigatinib (FIGHT-202) vs mFOLFOX+ASC (ABC-06)

Treatment (study)	N/ESS	Events	Median (95% CI)
Pemigatinib unadjusted (FIGHT-202)	[redacted]	[redacted]	[redacted]
Pemigatinib weighted (FIGHT-202)	[redacted]	[redacted]	[redacted]
mFOLFOX+ASC (ABC-06)	[redacted]	[redacted]	[redacted]

ASC, active symptom control; CI, confidence interval; KM, Kaplan–Meier; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; PFS, progression-free survival.

Table 21: Hazard ratios for PFS – Pemigatinib (FIGHT-202) vs mFOLFOX+ASC (ABC-06)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	Pemigatinib vs mFOLFOX+ASC	[redacted]
Weighted bootstrapped CI	Pemigatinib vs mFOLFOX+ASC	[redacted]

ASC, active symptom control; CI, confidence interval; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; PFS, progression-free survival.

B.2.9.5 FIGHT-202 vs ABC-06 (ASC only) overall survival

Unadjusted and weighted KM plots, KM summary of number of events and median, and the HRs for OS are presented in Figure 15, Table 22 and Table 23, respectively. These results show that the patients receiving pemigatinib demonstrated significantly greater improvements in OS compared with patients receiving ASC (unweighted HR: [redacted]; 95% CI: [redacted]). Weighting the pemigatinib patients to match the ASC arm of ABC-06 resulted in a slight increase in the relative effect (weighted HR: [redacted]; 95% CI: [redacted]).

Figure 15: KM plot of OS – Pemigatinib (FIGHT-202) vs ASC (ABC-06)

ASC, active symptom control; KM, Kaplan-Meier; Pemi, pemigatinib; PFS, progression-free survival.

Table 22: KM summary of OS – Pemigatinib (FIGHT-202) vs ASC (ABC-06)

Treatment (study)	N/ESS	Events	Median (95% CI)
Pemigatinib unadjusted (FIGHT 202)	[redacted]	[redacted]	[redacted]
Pemigatinib weighted (FIGHT 202)	[redacted]	[redacted]	[redacted]
ASC (ABC-06)	[redacted]	[redacted]	[redacted]

ASC, active symptom control; CI, confidence interval; ESS; effective sample size; KM, Kaplan–Meier; NA, not available; OS, overall survival.

Table 23: Hazard ratios for OS – Pemigatinib (FIGHT-202) vs ASC (ABC-06)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	Pemigatinib vs ASC	[redacted]
Weighted bootstrapped CI	Pemigatinib vs ASC	[redacted]

ASC, active symptom control; CI, confidence interval OS, overall survival.

The KM plot of PFS was not available for ASC, so this comparison was not possible.

Uncertainties in the indirect and mixed treatment comparisons

There was marked heterogeneity between FIGHT-202 and ABC-06, particularly in respect to subtypes of BTC considered and FGFR2 status. Where possible, heterogeneity was addressed by using matching methods so that the patient characteristics in the weighted FIGHT-202 data matched those in ABC-06. However, it was not possible to match on FGFR2 status or subtype of BTC, as Cohort A in FIGHT-202 included only CCA patients with *FGFR2* fusions or rearrangements, and this level of granularity in the patient population was not reported in ABC-06. The available evidence regarding the potential prognostic effect of FGFR2 status is discussed further in Section B.3.3.3.

When using MAIC methods, there is some uncertainty around the weights as these are estimated rather than fixed and known.[65] This uncertainty has been accounted for using bootstrap estimates to calculate the CIs for the HR.

Sensitivity analyses included in the economic model around the indirect treatment comparisons include the use of the naïve hazard ratios, based on no matching, which provide a more conservative estimate of the treatment effects. Sensitivity analyses have also been included to use weighted parametric survival models, which do not rely on the proportional hazard's assumption.

B.2.10. Adverse reactions

B.2.10.1 Extent of exposure

A total of 562 patients have been treated with at least one dose of pemigatinib as monotherapy, including 484 patients with advanced malignancies and 78 healthy participants.[60]

Eighteen of the 484 participants in the safety population did not meet criteria for the modified safety population and were excluded from the All Cancer Population (n=466).

Four of these patients had CCA, including 3 patients from FIGHT-202, and were excluded from the Cholangiocarcinoma Population (n=161).[60]

One hundred and forty-six patients with advanced/metastatic or surgically unresectable CCA were enrolled in FIGHT-202 and received at least one dose of pemigatinib in FIGHT-202 (13.5 mg intermittent dose). The median duration of pemigatinib exposure, including scheduled dose holds, for participants in FIGHT-202 was 181.0 days (range: 7–730 days; N=146), and 81.6 patient-years of exposure have been administered as of the data cutoff date. A total of 71 participants (48.6%) had >6 months of exposure to pemigatinib, and 23 participants (15.8%) had >12 months of exposure.[59]

The Cholangiocarcinoma Population included 161 patients. Exposure duration was similar to that seen in the FIGHT-202 population, 49.1% of patients had >6 months of exposure to pemigatinib, and 16.1% had >12 months of exposure. The median final dose among participants in the Cholangiocarcinoma Population was 13.5 mg (range: 6.0–20.0 mg).[60]

Of the 466 patients in the All Cancer Population (all dose regimens), a total of 30.7% of patients in the All Cancer Population had >6 months of exposure to pemigatinib, and 8.6% had >12 months of exposure. For participants in the All Cancer Population, 191.96 patient-years of treatment with pemigatinib have been administered as of the data cutoff date.[60]

B.2.10.2 Incidence of adverse events

The overall incidences of treatment-emergent AEs (TEAE) in FIGHT-202 and each of the pooled populations were similar, with most participants reporting at least one TEAE and the majority of patients having at least one TEAE considered treatment-related. Incidences of TEAEs ≥grade 3 in severity and serious TEAEs, as well as incidences of TEAEs leading to dose modifications, were similar across the populations. TEAEs with a fatal outcome occurred at higher frequency in the All Cancer Population than in FIGHT-202 and the Cholangiocarcinoma Population. Only one serious TEAE with fatal outcome (cerebrovascular accident in a participant with a concurrent cardiovascular condition, obesity, and hypothyroidism) was considered related to pemigatinib by the investigator. Table 24 summarises the TEAEs for FIGHT-202, Cholangiocarcinoma Population, and All Cancer Population.

Table 24. Overall summary of TEAEs

Category, n (%)	FIGHT-202 (N=146)	Cholangiocarcinoma Population (N=161)	All Cancer Population (N=466)
Any TEAE	146 (100.0)	161 (100.0)	465 (99.8)
Any treatment-related TEAE	134 (91.8)	152 (94.4)	441 (94.6)
Any serious TEAE	65 (44.5)	67 (41.6)	194 (41.6)
Any ≥grade 3 TEAE	93 (63.7)	100 (62.1)	284 (60.9)
Any fatal TEAE	6 (4.1)	7 (4.3)	36 (7.7)
Any TEAE leading to discontinuation	13 (8.9)	13 (8.1)	45 (9.7)
Any TEAE leading dose interruption	62 (42.5)	68 (42.2)	202 (43.3)
Any TEAE leading to dose reduction	20 (13.7)	23 (14.3)	70 (15.0)

TEAE, treatment-emergent adverse event.
Source: Incyte, data on file.[59,60]

B.2.10.3 Most frequent adverse events

Among participants in FIGHT-202, the most frequently reported TEAEs were associated with the MedDRA System Order Classes of gastrointestinal disorders (91.1%), metabolism and nutrition disorders (84.9%), skin and subcutaneous tissue disorders (73.3%), and general disorders and administration site conditions (71.2%). Consistent with the pharmacology of pemigatinib, the most frequently occurring TEAE was hyperphosphatemia (58.2%). Other events occurring in ≥30% of participants in FIGHT-202 were consistent with FGFR inhibition and/or the population under study and included alopecia, diarrhoea, fatigue, dysgeusia, nausea, constipation, stomatitis, dry mouth, and decreased appetite. The majority of these events were grade 1 or 2 in severity. Table 25 summarises the most common TEAEs reported in FIGHT-202.

Table 25. Summary of TEAEs Occurring in ≥10% of patients in FIGHT-202

MedDRA Preferred Term, n (%)	Pemigatinib 13.5 mg intermittent dose*					
	Cohort A (n=107)	Cohort B (n=20)	Cohort C (n=18)	Undetermined (n=1)	Total (N=146)	
					All grades	≥grade 3
Hyperphosphataemia	59 (55.1)	13 (65.0)	12 (66.7)	1 (100.0)	85 (58.2)	0
Alopecia	63 (58.9)	4 (20.0)	4 (22.2)	1 (100.0)	72 (49.3)	0
Diarrhoea	56 (52.3)	5 (25.0)	6 (33.3)	1 (100.0)	68 (46.6)	4 (2.7)
Fatigue	48 (44.9)	5 (25.0)	9 (50.0)	0	62 (42.5)	7 (4.8)
Dysgeusia	51 (47.7)	3 (15.0)	4 (22.2)	1 (100.0)	59 (40.4)	0
Nausea	43 (40.2)	7 (35.0)	8 (44.4)	0	58 (39.7)	3 (2.1)
Constipation	43 (40.2)	5 (25.0)	3 (16.7)	0	51 (34.9)	1 (0.7)
Stomatitis	41 (38.3)	6 (30.0)	3 (16.7)	1 (100.0)	51 (34.9)	8 (5.5)
Dry mouth	41 (38.3)	5 (25.0)	2 (11.1)	1 (100.0)	49 (33.6)	0
Decreased appetite	32 (29.9)	8 (40.0)	7 (38.9)	1 (100.0)	48 (32.9)	2 (1.4)
Vomiting	33 (30.8)	3 (15.0)	4 (22.2)	0	40 (27.4)	2 (1.4)

MedDRA Preferred Term, n (%)	Pemigatinib 13.5 mg intermittent dose*					
	Cohort A (n=107)	Cohort B (n=20)	Cohort C (n=18)	Undetermined (n=1)	Total (N=146)	
					All grades	≥grade 3
Dry eye	34 (31.8)	1 (5.0)	1 (5.6)	1 (100.0)	37 (25.3)	1 (0.7)
Arthralgia	31 (29.0)	4 (20.0)	1 (5.6)	0	36 (24.7)	9 (6.2)
Abdominal pain	24 (22.4)	4 (20.0)	4 (22.2)	1 (100.0)	33 (22.6)	7 (4.8)
Hypophosphataemia	26 (24.3)	4 (20.0)	2 (11.1)	0	32 (21.9)	18 (12.3)
Back pain	24 (22.4)	1 (5.0)	4 (22.2)	0	29 (19.9)	4 (2.7)
Dry skin	27 (25.2)	0	1 (5.6)	1 (100.0)	29 (19.9)	1 (0.7)
Pain in extremity	25 (23.4)	3 (15.0)	0	0	28 (19.2)	3 (2.1)
Oedema peripheral	16 (15.0)	4 (20.0)	6 (33.3)	0	26 (17.8)	1 (0.7)
Weight decreased	18 (16.8)	4 (20.0)	1 (5.6)	1 (100.0)	24 (16.4)	3 (2.1)
Headache	20 (18.7)	1 (5.0)	2 (11.1)	0	23 (15.8)	0
Urinary tract infection	17 (15.9)	2 (10.0)	4 (22.2)	0	23 (15.8)	4 (2.7)
Dehydration	17 (15.9)	1 (5.0)	3 (16.7)	1 (100.0)	22 (15.1)	5 (3.4)
Hypercalcaemia	16 (15.0)	5 (25.0)	1 (5.6)	0	22 (15.1)	3 (2.1)
Palmar-plantar erythrodysaesthesia syndrome	21 (19.6)	1 (5.0)	0	0	22 (15.1)	6 (4.1)
Anaemia	16 (15.0)	2 (10.0)	3 (16.7)	0	21 (14.4)	5 (3.4)
Epistaxis	19 (17.8)	1 (5.0)	0	0	20 (13.7)	0
Pyrexia	13 (12.1)	4 (20.0)	3 (16.7)	0	20 (13.7)	1 (0.7)
Asthenia	14 (13.1)	4 (20.0)	1 (5.6)	0	19 (13.0)	2 (1.4)
Dizziness	17 (15.9)	1 (5.0)	1 (5.6)	0	19 (13.0)	1 (0.7)
Myalgia	15 (14.0)	1 (5.0)	2 (11.1)	0	18 (12.3)	2 (1.4)
Blood creatinine increased	9 (8.4)	2 (10.0)	5 (27.8)	0	16 (11.0)	2 (1.4)
Gastroesophageal reflux disease	13 (12.1)	1 (5.0)	2 (11.1)	0	16 (11.0)	1 (0.7)
Hyponatraemia	7 (6.5)	5 (25.0)	4 (22.2)	0	16 (11.0)	8 (5.5)
Musculoskeletal pain	9 (8.4)	4 (20.0)	2 (11.1)	0	15 (10.3)	0

FGF/FGFR, fibroblast growth factor/fibroblast growth factor receptor; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily.
Notes: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory. Cohort A: *FGFR2* fusions or rearrangements; Cohort B: other FGF/FGFR alterations; Cohort C: negative for FGF/FGFR alterations; Undetermined: undetermined FGF/FGFR status.
*Pemigatinib was administered QD on a 14 days on, 7 days off schedule.
Source: Incyte, data on file.[59]

B.2.10.4 Most frequent treatment-related adverse events

Treatment-related TEAEs occurred with similar incidences in FIGHT-202 (91.8%; n=134/146), the Cholangiocarcinoma Population (94.4%), and the All Cancer Population (94.6%). The most common treatment-related TEAEs across the populations were similar to the most common TEAEs overall (Table 26).

Table 26. Most common treatment-related TEAEs across populations

Treatment-related TEAE, n (%)	FIGHT-202 (N=146)	Cholangiocarcinoma Population (N=161)	All Cancer Population (N=466)
Hyperphosphataemia	78 (53.4)	92 (57.1)	245 (52.6)
Alopecia	67 (45.9)	76 (47.2)	186 (39.9)
Dysgeusia	55 (37.7)	62 (38.5)	140 (30.0)
Diarrhoea	53 (36.3)	55 (34.2)	148 (31.8)
Fatigue	47 (32.2)	51 (31.7)	129 (27.7)
Stomatitis	47 (32.2)	52 (32.3)	148 (31.8)

TEAE, treatment-emergent adverse event.
Source: Incyte, data on file.[59,60]

Comparison of the most frequently occurring treatment-related TEAEs for the continuous and intermittent dose regimens in the All Cancer Population suggests higher incidence (>10% difference) of hyperphosphatemia (64.3% vs 50.5%) for continuous dosing and diarrhoea (21.4% vs 33.6%) for intermittent dosing.[60]

B.2.10.5 Serious adverse events

Serious TEAEs (including serious events with a fatal outcome) occurred in similar proportions of participants in FIGHT-202 (44.5%) and in the Cholangiocarcinoma and All Cancer Populations (41.6% for both pooled populations; Table 27); a small proportion of participants in each population had at least one serious TEAE that was considered related to pemigatinib by the investigator (4.1%, 3.7%, and 6.8%, respectively). In the context of the diseases under study and the common TEAEs that were observed, no additional safety concerns were identified based on serious TEAEs.[60]

In FIGHT-202, serious TEAEs were most commonly events in the System Order Class of gastrointestinal disorders (15.8%), and infections and infestations (12.3%). Abdominal pain and pyrexia (4.8% each), and cholangitis and pleural effusion (3.4% each) were the most common serious events by MedDRA preferred term.[59]

Serious events unique to the Cholangiocarcinoma Population (i.e., events that occurred in these three participants) included hyponatraemia in two participants and acute respiratory failure, ascites, atrial fibrillation, oesophageal varices haemorrhage, blood alkaline

phosphatase increased, blood bilirubin increased, dehydration, fatigue, hypotension, and leucocytosis in a single participant each.[60]

For the All Cancer Population, the most frequently occurring serious TEAEs were associated with the System Order Class of gastrointestinal disorders (10.9%), infections and infestations (10.5%), and general disorders and administrative site conditions (9.0%).[60] Serious TEAEs by MedDRA preferred term occurring in >2% of participants in the All Cancer Population were urinary tract infection, acute kidney injury, abdominal pain, pneumonia, and pyrexia.[60] Acute kidney injuries occurred most often in participants with urothelial carcinoma and were unrelated to pemigatinib with the exception of the event in a participant in FIGHT-202 described above.[60] Table 27 summarises the serious TEAEs in ≥2% of patients for each analysed population.

Table 27. Serious TEAEs in ≥2% of participants in FIGHT-202, the Cholangiocarcinoma Population, or the All Cancer Population

MedDRA System Organ Class preferred term, n (%)	FIGHT-202 (N=146)	Cholangiocarcinoma Population (N=161)	All Cancer Population (N=466)
Any serious TEAE	65 (44.5)	67 (41.6)	194 (41.6)
Gastrointestinal disorders	23 (15.8)	23 (14.3)	51 (10.9)
Abdominal pain	7 (4.8)	7 (4.3)	13 (2.8)
Small intestinal obstruction	3 (2.1)	2 (1.2)	6 (1.3)
General disorders and administration site conditions	8 (5.5)	9 (5.6)	42 (9.0)
Pyrexia	7 (4.8)	7 (4.3)	13 (2.8)
Hepatobiliary disorders	8 (5.5)	8 (5.0)	12 (2.6)
Cholangitis	5 (3.4)	5 (3.1)	7 (1.5)
Infections and infestations	18 (12.3)	18 (11.2)	49 (10.5)
Pneumonia	2 (1.4)	2 (1.2)	13 (2.8)
Urinary tract infection	3 (2.1)	3 (1.9)	15 (3.2)
Metabolism and nutrition disorders	13 (8.9)	14 (8.7)	29 (6.2)
Failure to thrive	3 (2.1)	3 (1.9)	3 (0.8)
Hypercalcemia	3 (2.1)	2 (1.2)	5 (1.1)
Hyponatremia	3 (2.1)	5 (3.1)	9 (1.9)
Renal and urinary disorders	3 (2.1)	2 (1.2)	26 (5.6)
Acute kidney injury	3 (2.1)	2 (1.2)	14 (3.0)
Respiratory, thoracic, and mediastinal disorders	8 (5.5)	8 (5.0)	22 (4.7)
Pleural effusion	5 (3.4)	4 (2.5)	7 (1.5)

TEAE, treatment-emergent adverse event.
Source: Incyte, data on file.[59,60]

B.2.10.6 Treatment-related serious adverse events

In FIGHT-202, treatment-related serious TEAEs occurred in six unique participants and included anaemia, acute kidney injury, hyponatraemia, abdominal pain, dysphagia, decreased appetite, and thrombosis in one participant each. Causality assessment for each of these cases was confounded by the general condition of the participant, underlying CCA, and/or medical history (e.g., chronic stable anaemia and chronic renal insufficiency in the participant with anaemia; ascites, hyperkalaemia, and renal stent in the participant with acute kidney injury).[60]

Thirty participants (6.4%) in the All Cancer Population had at least one treatment-related SAE. The most frequent treatment-related events were similar to those in FIGHT-202 and included anaemia, diarrhoea, nausea, and hyponatraemia in two participants (0.4%) each. In the All Cholangiocarcinoma Population, treatment-related serious TEAEs were considered related to pemigatinib by the investigator.[60]

B.2.10.7 Deaths

In FIGHT-202, six patients with TEAEs had a fatal outcome (4.1%; n=6/146); however, none were related to treatment. Fatal events among participants in FIGHT-202 included failure to thrive in two participants, and bile duct obstruction, cholangitis, sepsis, and pleural effusion in a single participant each.[60]

Serious TEAEs with a fatal outcome occurred in 4.3% of the Cholangiocarcinoma population (n=7/161) and in 7.7% of the All Cancer population (n=36/466).[60] Across all three populations, only one fatal event was considered related to pemigatinib by the investigator: cerebrovascular accident in a participant in the All Cancer Population. However, causality assessment for the event was confounded by a concurrent cardiovascular condition (patent foramen ovale), obesity, and hypothyroidism.[60]

B.2.10.8 Adverse events associated with permanent treatment discontinuation

Discontinuations in FIGHT-202 due to TEAEs were low (9%; n=13/146). The AEs most frequently leading to discontinuation were intestinal obstruction and acute kidney injury (1.4%; n=2/146 each).[5,84] Overall the TEAEs leading to discontinuation of pemigatinib administration in FIGHT-202, the Cholangiocarcinoma Population, and the All Cancer Population were generally consistent with the diseases under study (Table 28).

Table 28. TEAEs leading to study drug discontinuation in ≥2 participants in FIGHT-202, the Cholangiocarcinoma Population, or the All Cancer Population

MedDRA System Organ Class preferred term, n (%)	FIGHT-202 (N = 146)	Cholangiocarcinoma Population (N = 161)	All Cancer Population (N = 466)
Any TEAE leading to study drug discontinuation	13 (8.9)	13 (8.1)	45 (9.7)
Gastrointestinal disorders	3 (2.1)	3 (1.9)	9 (1.9)
Intestinal obstruction	2 (1.4)	2 (1.2)	2 (0.4)
Small intestinal obstruction	0	0	2 (0.4)
General disorders and administration site conditions	1 (0.7)	1 (0.6)	6 (1.3)
Disease progression	0	0	2 (0.4)
General physical health deterioration	0	0	2 (0.4)
Infections and infestations	0	0	2 (0.4)
Pneumonia	0	0	2 (0.4)
Metabolism and nutrition disorders	0	1 (0.6)	4 (0.9)
Dehydration	0	1 (0.6)	2 (0.4)
Renal and urinary disorders	2 (1.4)	2 (1.2)	4 (0.9)
Acute kidney injury	2 (1.4)	2 (1.2)	4 (0.9)

TEAE, treatment-emergent adverse event.
Source: Abou-Alfa et al, 2020;[29] Incyte, data on file.[60]

B.2.10.9 Adverse events associated with dose reductions

Dose interruptions and reductions due to TEAEs occurred in 42% (n=62/146 and 14% (n=20/146) of participants in FIGHT-202 (see Table 29).[29] The most common events leading to dose interruption were stomatitis (7.5%), palmar-plantar erythrodysesthesia syndrome (5.5%), and arthralgia (4.8%), and these events, which were consistent with FGFR inhibition and/or the disease under study, led to a pemigatinib dose reduction in 3.4% of patients for each TEAE. It is notable that dose interruptions or reductions due to hyperphosphataemia were infrequent, suggesting that dietary phosphate restriction and/or administration of phosphate-lowering therapy along with the one-week dose holiday for participants receiving pemigatinib on an intermittent schedule were effective strategies for managing this on-target effect of pemigatinib.

Table 29. TEAEs leading to study drug interruption or dose reduction in ≥1% of patients in FIGHT-202

MedDRA System Organ Class preferred term, n (%)	Pemigatinib 13.5 mg Intermittent Dose[1] (N=146)	
	TEAE Leading to Study Drug Interruption	TEAE Leading to Dose Reduction
Any TEAE leading to pemigatinib dose modification	62 (42.5)	20 (13.7)
Gastrointestinal disorders	24 (16.4)	5 (3.4)
Abdominal pain	4 (2.7)	0
Diarrhoea	2 (1.4)	0
Small intestinal obstruction	3 (2.1)	0
Stomatitis	11 (7.5)	5 (3.4)
General disorders and administration site conditions	11 (7.5)	2 (1.4)
Asthenia	3 (2.1)	2 (1.4)
Fatigue	6 (4.1)	0
Pyrexia	3 (2.1)	0
Hepatobiliary disorders	6 (4.1)	1 (0.7)
Cholangitis	3 (2.1)	0
Hyperbilirubinemia	2 (1.4)	0
Investigations	8 (5.5)	1 (0.7)
Alanine aminotransferase increased	3 (2.1)	1 (0.7)
Aspartate aminotransferase increased	3 (2.1)	1 (0.7)
Blood alkaline phosphatase increased	3 (2.1)	0
Electrocardiogram QT prolonged	2 (1.4)	0
Metabolism and nutrition disorders	8 (5.5)	2 (1.4)
Decreased appetite	2 (1.4)	1 (0.7)
Dehydration	2 (1.4)	0
Hypercalcaemia	2 (1.4)	0
Hyperphosphataemia	2 (1.4)	1 (0.7)
Hypophosphataemia	2 (1.4)	0
Musculoskeletal and connective tissue disorders	12 (8.2)	5 (3.4)
Arthralgia	7 (4.8)	5 (3.4)
Back pain	2 (1.4)	0
Pain in extremity	2 (1.4)	0
Nervous system disorders	4 (2.7)	0
Syncope	2 (1.4)	0
Renal and urinary disorders	3 (2.1)	0

MedDRA System Organ Class preferred term, n (%)	Pemigatinib 13.5 mg Intermittent Dose[(1)] (N=146)	
	TEAE Leading to Study Drug Interruption	TEAE Leading to Dose Reduction
Acute kidney injury	2 (1.4)	0
Skin and subcutaneous tissue disorders	14 (9.6)	9 (6.2)
Onychomadesis	2 (1.4)	2 (1.4)
Palmar-plantar erythrodysaesthesia syndrome	8 (5.5)	5 (3.4)
Vascular disorders	3 (2.1)	0
Hypotension	2 (1.4)	0

TEAE, treatment-emergent adverse event.
Source: Incyte, data on file.[59]

The overall incidences of TEAEs leading to dose interruption or reduction among participants in the Cholangiocarcinoma Population (42.2% and 14.3%, respectively) were similar to those in FIGHT-202, and the most common TEAEs, including stomatitis, palmar-plantar erythrodysesthesia syndrome, and arthralgia, associated with these actions for the Cholangiocarcinoma Population were also congruent with those in FIGHT-202.[60]

Pemigatinib dose interruptions and reductions due to TEAEs occurred in 43.3% and 15.0% of participants, respectively, in the All Cancer Population. The events leading to these dose modifications were similar to those seen in FIGHT-202, with stomatitis (4.9% and 3.2%, respectively) and palmar-plantar erythrodysesthesia syndrome (3.4% and 1.5%, respectively) being among the most frequently occurring events leading to pemigatinib interruption or dose reduction. Other events leading to pemigatinib interruption in ≥3.0% of participants included hyperphosphatemia (3.6%) and fatigue (3.0%).[60]

B.2.10.10 Clinically notable adverse events

The most common AEs reported in patients treated with pemigatinib were those associated with a “class effect” common to all FGFR inhibitors.[14] Clinically notable AEs included hyperphosphataemia, hypophosphataemia, serous retinal detachment, and nail toxicity.[29]

The TEAEs of hyperphosphatemia and increased blood phosphorus were grouped and occurred in 60% (n=88/146) of patients in FIGHT-202; however, all were grade 1 or 2.[29,60] The majority of patients were managed with a low phosphate diet, phosphate binders, and diuretics. Very few patients (2.1%; n=3/146) required dose reductions or interruptions, suggesting that dietary phosphate restriction and/or administration of phosphate-lowering

therapy, along with the one-week dose holiday for participants receiving pemigatinib on an intermittent schedule, were effective strategies for managing this treatment-related effect of pemigatinib.[60]

Hypophosphataemia was the most common grade ≥3 AE (n=18/146, 12.3%; all grades: n=32/146, 21.9%); however, no cases were clinically significant or serious, and none led to pemigatinib discontinuation or dose reduction.[60]

Serous retinal detachment occurred in 4.1% (n=6/146) of patients. Most cases were grade 1/2 and 0.7% (n=1/146) of cases were grade ≥3; none resulted in clinical sequelae.[60]

Nail toxicity events of grade 1/2 were frequently reported as events of nail discolouration, onychomadesis, and onycholysis in patients (42.5%; n=62/146). No nail toxicity event was serious or led to pemigatinib discontinuation.[60]

B.2.10.11 Safety conclusions

Safety and exposure data from FIGHT-202 and the pooled populations demonstrate that the safety profile of pemigatinib administered according to the proposed dose regimen of 13.5 mg QD on a 14 days-on/7 days-off schedule in patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements, is acceptable, with no meaningful differences in safety based on intrinsic or extrinsic factors.[59,60] Furthermore, the evaluation of the safety data from the pooled populations (Cholangiocarcinoma Population and All Cancer Population) did not uncover potentially important safety concerns that were not evident based on the safety data from FIGHT-202.[59,60]

Analyses from the pooled populations showed that common TEAEs, including hyperphosphatemia, alopecia, diarrhoea, fatigue, dysgeusia, nausea, constipation, stomatitis, dry mouth, decreased appetite, and nail toxicities, were consistent with FGFR inhibition and/or the disease under study and are considered acceptable in the context of an oncology population.[60] The majority of these common events were grade 1 or 2 in severity, non-serious, and did not lead to pemigatinib dose modification.[60] In the context of the diseases under study, and the common TEAEs that were observed, no additional safety concerns were identified based on serious TEAEs. Hyperphosphataemia and hypophosphataemia were found to be manageable, as evidenced by the absence of important clinical sequelae and events leading to pemigatinib discontinuation. Serous

retinal detachments were generally grade 1 or 2 in severity, self-limiting, or manageable with dose modification.[60]

No treatment-related deaths were reported for pemigatinib in FIGHT-202.[59] In the All Cancer population, one death was considered related to pemigatinib; however, causality assessment for the event was confounded by a concurrent cardiovascular condition (patent foramen ovale), obesity, and hypothyroidism.[60]

B.2.11. Ongoing studies

Clinical evidence from the ongoing, pivotal, phase 2 trial FIGHT-202 (NCT02924376), assessing the efficacy of pemigatinib in patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements (Cohort A, n=107) was presented in this submission.[29] The final data cut for FIGHT-202 is scheduled to align with the date the last patient comes off therapy with pemigatinib.

B.2.12. Innovation

There are no approved targeted therapies for patients with advanced or metastatic CCA who have progressed on at least one line of prior therapy in England.[38] Patients are limited to salvage chemotherapy regimens, which have shown variable efficacy and systemic toxicity.[34,39,48,67] Pemigatinib addresses the urgent unmet need in previously treated, unresectable, locally advanced or metastatic CCA patients harbouring an *FGFR2* fusion/rearrangement. As a targeted treatment, pemigatinib offers proven efficacy in this patient population with a manageable safety profile. As well, genetic testing in this patient population is likely to become part of the standard clinical pathway in England, allowing for the early identification of patients who are likely to benefit from treatment with pemigatinib.

B.2.12.1 Pemigatinib is recognised as innovative at the regulatory level

In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) awarded pemigatinib a Promising Innovative Medicine (PIM) designation in April 2020.[68] Pemigatinib also received Breakthrough Therapy designation in February 2019 and Priority Review in November 2019 by the US Food and Drug Administration (FDA). On 18 April 2020, the FDA approved pemigatinib for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic CCA harbouring an *FGFR2* fusion or rearrangement, as detected by an FDA-approved test.[69]

B.2.13. Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Interim findings from the clinical evidence

Treatment options for the target population of this submission—patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements—are limited to older chemotherapy regimens that yield suboptimal benefit, with low response rates and rapid progression.[14,39] Furthermore, AEs related to systemic chemotherapy are burdensome to patients and have a detrimental effect on HRQoL.[41-47] Patients who present with advanced disease may have substantial comorbidities including advanced age, intercurrent sepsis, and poor performance status score.[40] Many patients who progress after 1L systematic chemotherapy move directly to ASC, including biliary drainage, antibiotics, and analgesia, to relieve symptoms.[14] A significant unmet need exists for a targeted therapy that is effective in this patient group where there have previously been limited efficacious treatment options.

In FIGHT-202, pemigatinib demonstrated a clinically meaningful benefit in patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements. The study achieved the predetermined threshold for a positive outcome (lower limit of the 95% CI for ORR exceeded 15%; ORR for Cohort A: 35.5%; 95% CI: 26.5%, 45.4%). As well, the study demonstrated a persistence of efficacy of treatment with pemigatinib by the duration of the IRC-assessed, confirmed tumour responses (median DOR in Cohort A was 7.5 months; 95% CI: 5.7 months, 14.5 months) with a median follow-up of 15.44 months.[29] Analyses from the pooled safety populations showed that common TEAEs were consistent with a “class effect” common to all FGFR inhibitors, and were mild (grade 1 or 2), non-serious, and did not lead to pemigatinib dose modification.[29]

The indirect treatment comparison results showed that in comparison to mFOLFOX+ASC or ASC alone, patients receiving pemigatinib demonstrated:

- Significantly greater improvements in OS compared with patients receiving mFOLFOX+ASC (unweighted HR: [redacted]; 95% CI: [redacted]; weighted HR: [redacted]; 95% CI: [redacted]).

- Significantly greater improvements in PFS compared with patients receiving mFOLFOX+ASC (unweighted HR: [redacted]; 95% CI: [redacted]; weighted HR: [redacted]; 95% CI: [redacted]).

- Significantly greater improvements in OS compared with patients receiving ASC alone (unweighted HR: [redacted]; 95% CI: [redacted]; weighted HR: [redacted]; 95% CI: [redacted]).

In summary, the efficacy and safety results from FIGHT-202 and the pooled safety population, along with the indirect treatment analysis comparison with mFOLFOX+ASC and ASC alone show that pemigatinib is a highly effective and well-tolerated targeted treatment for patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements.

B.2.13.2 Strengths and limitations of the clinical evidence base

Overall, the clinical data for pemigatinib provide an appropriate base for assessment of its clinical and cost-effectiveness in patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements. The strengths of the clinical evidence base are as follows:

- FIGHT-202 is a large international clinical trial in patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements; therefore, the results can be considered widely applicable to the population in England and Wales.

- The trial primary endpoint of ORR and key secondary endpoints of DOR, DCR, PFS, and OS are widely regarded as appropriate endpoints to assess the efficacy of anti-cancer therapy and/or are relevant to routine clinical practice.

The evidence base has some limitations.

- The study design of FIGHT-202 excludes a comparative assessment of the contribution of the *FGFR2* fusions/rearrangements to the survival results.

- FIGHT-202 is a single-arm study; however, single-arm trials are common for rare diseases with a limited patient pool and acute unmet need and allow for quicker patient access to new treatments.

B.2.13.3 End-of-life criteria

Pemigatinib meets the NICE end-of-life criteria as summarised in Table 30.

Table 30. End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• The median OS for patients treated with systemic chemotherapy (mFOLFOX+ASC) was 6.2 months.[34]	Section B.1.3.2 Pages 18
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• Median OS differences between pemigatinib and the source used for OS exceeds 3 months (21.1 months[29] vs 6.2 months; unadjusted).[34] • Results of a MAIC analysis are presented in Section B.2.9.	Section B.2.9.3–B.2.9.5 Pages 53–58

MAIC, matching-adjusted indirect comparison; NE, not estimated; NHS, National Health Service; OS, overall survival.
Sources: Abou-Alfa et al. 2020;[29] Lamarca, 2019.[34]

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

In 2018, a comprehensive SLR was carried out to identify studies assessing the cost effectiveness of interventions for the treatment of CCA patients with *FGFR2* alterations who have failed one or more previous treatments. A total of 1,750 articles were identified in the original searches, but no evidence was found in the population of interest. Subsequently the inclusion criteria were revised, and searches were updated on 22 April 2020 to identify studies in adults (≥18 years) with advanced, metastatic or surgically unresectable CCA, irrespective of previous treatment and/or the presence of *FGFR2* alterations. An additional 769 articles were identified in the updated searches. The original and expansion/update search results are presented in Figure 16 and Figure 17, respectively, and the eight included studies are summarised in Table 31.

The paucity of cost-effectiveness studies identified in the original searches corroborates finding that there are no reimbursed therapies for patients who have failed one or more previous systemic therapies and, therefore, no corresponding economic evaluations. The evidence identified in the updated searches is of limited relevance to this appraisal

because the studies primarily considered treatment of patients earlier in the disease pathway (1L).

Interventions evaluated included hepatic resections, biliary drainage and various forms of stent. In addition, Cillo et al. (2015) also evaluated whether adjuvant chemotherapy was more cost effective when used before or after hepatic resection.[70] Modelling approaches included primarily Markov model frameworks, although Harwood et al. 2002 implemented a decision tree structure.[71] Health states were consistent with the early stages of cholangiocarcinoma, including resection, curative resection, progression and death.

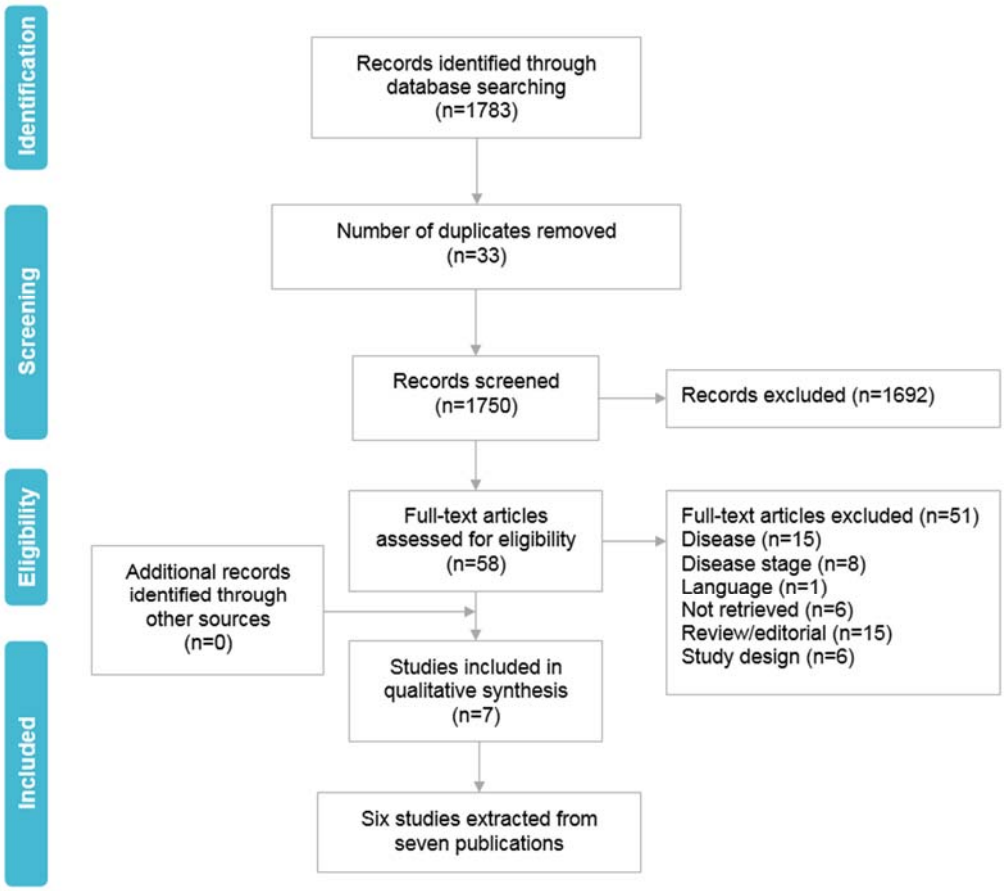


Figure 16. PRISMA diagram for economic modelling SLR – original 2018 SLR

BTC, biliary tract cancer; CCA, cholangiocarcinoma; FGFR2+, fibroblast growth factor receptor 2 positive; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

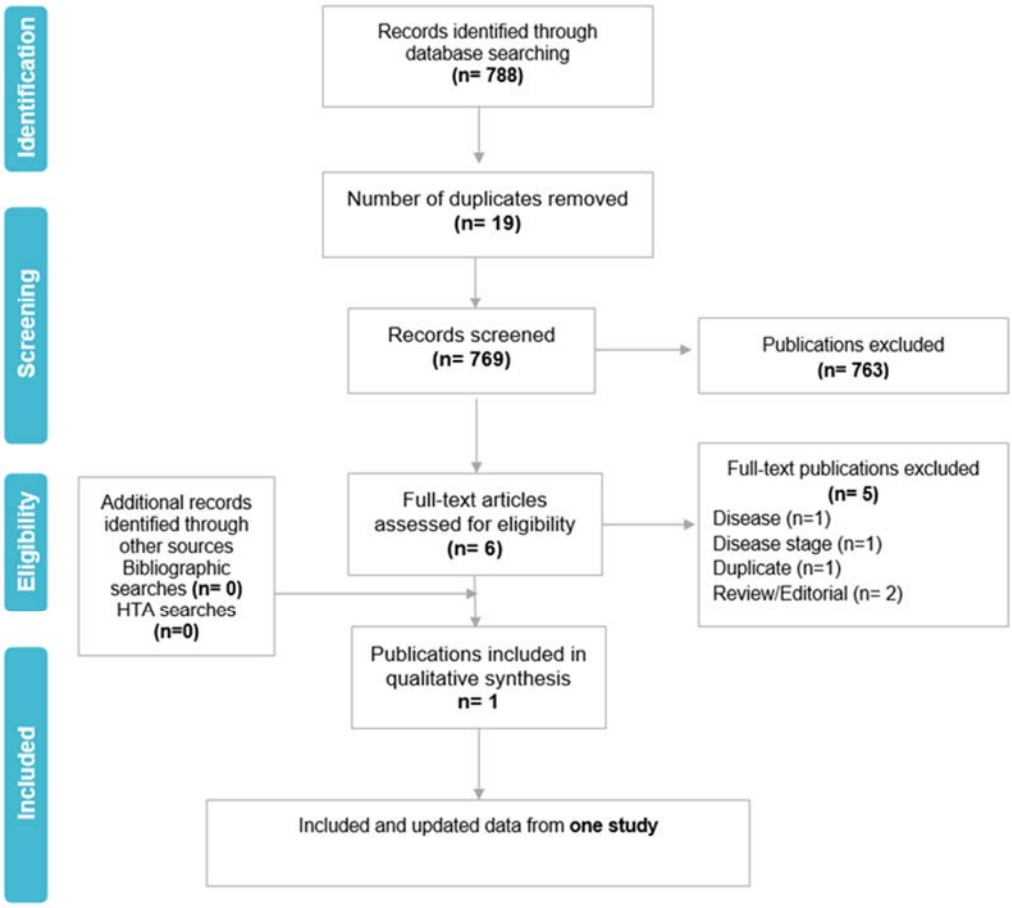


Figure 17. PRISMA diagram for economic modelling SLR – April 2020 expansion and update SLR

BTC, biliary tract cancer; CCA, cholangiocarcinoma; FGFR2+, fibroblast growth factor receptor 2 positive; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Table 31: Summary list of published cost-effectiveness studies

Study, year	Treatment	Summary of model (model structure, health states)	Patient population	Time horizon, cycle length	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY/LY gained)
Borntrakulpipat, 2016[72]	• Palliative care • ERCP with metal stent • PTBD	NR, NR	Unresectable hCCA	NR, NR	**Mean QALYs** PTBD: 0.18 ERCP: 0.25 Palliative care: 0.05	**Mean total cost (Thai baht)** PTBD: 68,293 ERCP: 91,422 Palliative care: 3,521	**Thai Baht/QALY vs palliative care** PTBD: 490,577 ERCP: 422,822
Suttichaimongkol, 2018[73,74]	• Palliative care • EBD using metal stent • PTBD	Direct calculation method, health states: • NR	Unresectable hCCA	NR, 2 weeks	**Mean QALYs** EBD: 0.25 PTBD: 0.18 Palliative: 0.05 **Average life expectancy (days)** EBD: 218 PTBD: 197 Palliative: 89	**Total lifetime cost (baht):** EBD: 91,422 PTBD: 68,294 Palliative: 3,521	**Thai Baht/QALY vs palliative care** EBD: 422,822 (US$12,622) PTBD: 490,578 (US$14,644)
		Markov model, health states: • NR			**Mean QALYs** EBD: 0.21 PTBD: 0.07 Palliative: 0.07 **Average life expectancy (days)** EBD: 153 PTBD: 66 Palliative: 62	**Total lifetime cost (baht):** EBD: 99,582 PTBD: 29,758 Palliative: 6,287	**Thai Baht/QALY vs palliative care** EBD: 655,520 (US$19,976) PTBD: 6,548,398 (US$199,549)
Sangchan, 2014[75,76]	• SEMS • Plastic stent	Markov model, health states:	Unresectable hCCA	Lifetime, 2 weeks	**Average QALY/ patient** SEMS: 0.29	**Total lifetime cost/patient;**	**SEMS vs PS** Thai baht/QALY: 192,650

		• EBD, PTBD, post-EBD, post-PTBD, no drainage, death			PS: 0.10 **Average life expectancy/ patient** SEMS: 0.56 PS: 0.27	**Thai baht (US dollar)** SEMS: 98, 841 (3,242) PS: 62981 (1,066)	Thai Baht/LYG: 124,508 US dollar/QALY: 6,318
Cillo, 2015[70]	• Hepatic resection followed by adjuvant sCT (A) • sCT with cisplatin + gemcitabine[a] followed by hepatic resection (B)	Markov model, health states: • Resection, sCT, no sCT, downstaging, no downstaging, progression, curative resection, death	Advanced iCCA	Lifetime, NR	**QALMs** • iCCA > 6 cm Strategy A: 19.7 Strategy B: 17.1 NHB; A vs B: 1.4 • iCCA with vascular invasion Strategy A:16.5 Strategy B: 14.2 NHB; A vs B: 1.3 • Multi-focal iCCA Strategy A: 12.0 Strategy B: 11.6 NHB, A vs B: -0.3	**Lifetime cost (US$):** • iCCA >6 cm Strategy A: 41,532 Strategy B: 36,586 • iCCA with vascular invasion Strategy A: 39,640 Strategy B: 35,617 • Multi-focal iCCA Strategy A: 37,028 Strategy B: 34,244	**US$/QALY (A vs B)** iCCA >6 cm: 22,482 iCCA with vascular invasion: 20,953 Multi-focal iCCA: 83,604
Harewood, 2002[71]	• MRCP • Double stent placement	Decision tree, health states: • Success, surgery, PTC failure. Relief, complications	Unresectable hCCA	NR	**Survival (days)** MRCP: 115 Double stent placement: 160	**Overall cost (US$)** MRCP: 3,806 Double stent placement: 4,275	**Cost-effectiveness ratio** MRCP: $11,866/LY Double stent placement: $10,348/LY **ICER; US$/LY** Double stent placement vs MRCP: 3,908
Martin, 2002[77]	• Endoscopic stent • Surgical biliary enteric bypass	Retrospective review, health states: NR	Unresectable CCA	NR	**Median/mean survival (months range)**	**Median cost (range)**	Endoscopic stenting was suggested to be the most cost-effective intervention when compared to surgical therapy along with its

	with/without resection				Endoscopic therapy: 15 (10–30)/19Surgical therapy: 13 (9–28)/16.5	Endoscopic therapy: $24,251 (10,362-58,536) Surgical therapy: $60,986 (18,895-115,646)	minimally invasive approach.

CCA, cholangiocarcinoma; EBD, endoscopic biliary drainage; ERCP, endoscopic retrograde cholangiopancreatography; hCCA, hilar cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; ICER, incremental cost-effectiveness ratio; LY, life year; LYG, life years gained; MRCP, magnetic resonance cholangiopancreatography; NHB, net health benefit; NR, not reported; PS, plastic stent; PTBD, percutaneous biliary drainage; PTC, plasma thromboplastin component; QALM, quality-adjusted life month; QALY, quality-adjusted life year; sCT, systemic chemotherapy; SEMS, self-expandable metal stent; USD, United States Dollar.

Notes: a followed by curative hepatic resection in those patients who respond to sCT.

B.3.2. Economic analysis

Due to the disparities between studies included in the SLR and the economic evaluation required to inform this appraisal, none of the included studies were considered relevant for evaluating pemigatinib for the treatment of patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements. Therefore, a de novo economic model was constructed to evaluate pemigatinib in this setting.

B.3.2.1 Patient population

The relevant patient population for the cost-effectiveness analysis is adult patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements. The term 'translocation' may also be used, although the updated terminology of 'fusions/rearrangements' more precisely describes these genetic alterations. The presence of *FGFR2* fusions/rearrangement status is confirmed by genomic testing.

This population is consistent with patients included in Cohort A of the prospective, open-label FIGHT 202 phase 2 study and is also in line with the expected licensed indication (Table 2). The molecularly selected population reflects demonstrated clinical activity and efficacy for patients with these specific genetic alterations treated with pemigatinib.

The current SOC for the 1L treatment of patients with advanced/metastatic surgically unresectable CCA is chemotherapy with gemcitabine and cisplatin.[38,78] Currently, ESMO guidelines state that 'there is no established second-line systemic therapy following progression after 1L treatment, although fluoropyrimidine-based therapy (either in monotherapy or in combination with other cytotoxics) is sometimes used.[38]

B.3.2.2 Model structure

The chosen model structure provides a framework that suitably captures the experience of patients with CCA, both in terms of the current treatment pathway as well as disease progression. Utilising the best available data, the model calculates relevant outcomes for patients treated with pemigatinib and its relevant comparators, and outputs cost-effectiveness results to support health technology assessment (HTA) decision makers.

The model applies a partitioned survival approach, using parametric survival models to predict outcomes including time-on-treatment (ToT), PFS and OS. Typically, partitioned survival models may include only PFS and OS outcomes, with patients moving between three mutually exclusive health states: PFS, post-progression survival and death. As patients receiving treatment for CCA can discontinue therapy while remaining progression-free, ToT was also included and as a result the chosen model structure includes five health states, with patients in both the PFS and post-progression survival health states either being on or off treatment (Figure 18).

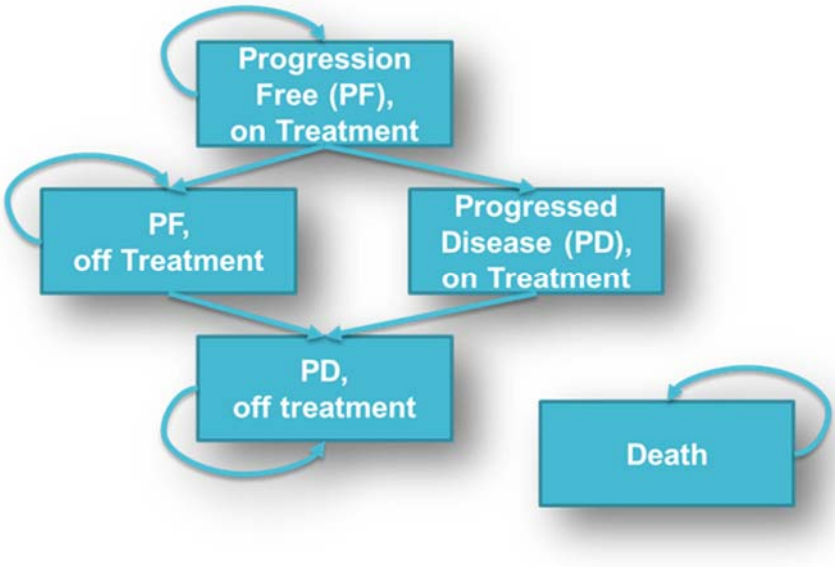


Figure 18: Markov Model health states

Note: The progressed disease on treatment state was not included in the base case analysis due to treatment scheduling rules for both the intervention and comparators.

The health states descriptions reflect patients enter the model in the progression-free health state, despite having already received at least one line of prior therapy. Therefore, progression refers to disease progression during or after receiving pemigatinib or a comparator. Furthermore, although it is correct that within this model framework patients may progress yet remain on treatment, treatment scheduling rules (see Table 2) and clinical expert opinion suggests that this was not appropriate, so the model assumes that patients do not remain on treatment after disease progression (Figure 19).

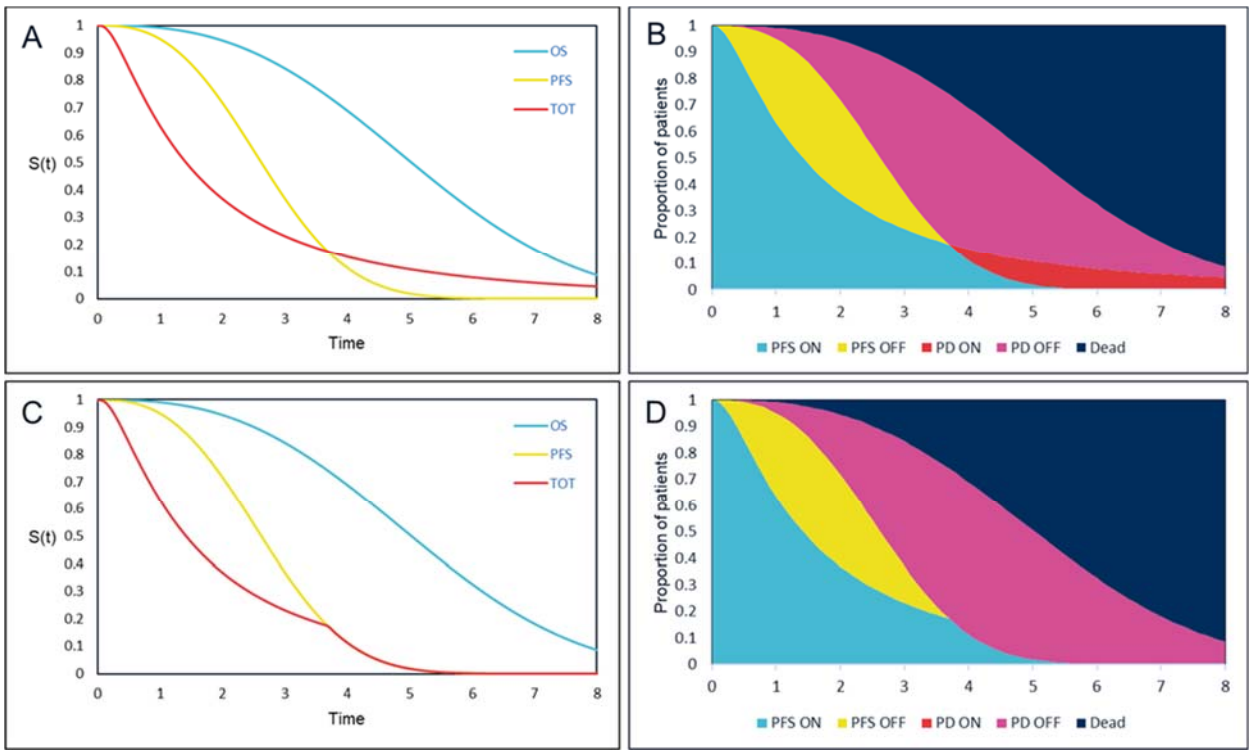


Figure 19: Example parametric survival models and Markov trace to demonstrate partitioned survival analysis approach and ToT assumptions

Key: (A) Example parametric survival distributions fitted to OS, PFS and ToT, where ToT is permitted to exceed PFS. (B) Corresponding Markov trace for A with patients permitted to enter the 'PD ON' health state. (C) Duplicate parametric survival distributions, while applying the assumption that all patients must discontinue treatment upon disease progression. (D) Corresponding Markov trace for C with no patients entering the "PD ON" health state.

PFS, progression-free survival; OFF, off-treatment; ON, on treatment; OS, overall survival; PD, progressive disease; St, survival function; ToT, time-on-treatment.

In a cohort level model, the cycle length determines the time points at which the distribution of patients across health states may change. A cycle length of one week is used to ensure short-term changes in disease progression are accurately captured. This relatively short cycle length is considered appropriate due to the poor prognosis of patients with advanced/metastatic CCA, frequently resulting in rapid disease progression. Due to the short cycle length, half-cycle correction is not required.[79]

The model's base case captures a lifetime time horizon, in line with the NICE reference case. This is estimated to be 40 years, at which point more than 99% of patients have died, whether receiving pemigatinib or a relevant comparator. A discount rate of 3.5% per annum is also applied to costs and effects, in line with the NICE reference case.[80] A summary of the features of the economic analysis is provided in Table 32.

Table 32: Features of the economic analysis

	Current appraisal	
Factor	Chosen values	Justification
Perspective	NHS and PSS perspective	Consistent with NICE reference case.[80]
Indication	Adults with locally advanced or metastatic cholangiocarcinoma with a *FGFR2* fusion or rearrangement that is relapsed or refractory after at least one line of systemic therapy	Aligned to anticipated licensed indication and consistent with final NICE scope (Section B.1.1).[59]
Model type	Cohort level partitioned survival approach	Informed by NICE TSD 19 and reflective of the disease progression pathway.[81] Model structure validated by health economics and clinical experts.[66]
Health states	• PF on-treatment • PF off-treatment • PD on-treatment • PD off-treatment • Death	Consistent with disease and treatment pathway.
Time horizon	Lifetime, 40 years	Consistent with NICE reference case[80]
Cycle length	1 week	Sensitive to short-term changes in disease and treatment status
Source of utilities	EORTC QLC C30 mapped to EQ-5D utilities. FIGHT-202 PLD analysis	Best available evidence. Consistent with NICE reference case[80]
Outcomes	QALYs, life years, costs, incremental results	Consistent with NICE reference case[80]
Discounting of outcome	The same annual discount rate (3.5%) is used for both costs and benefits	Consistent with NICE reference case[80]

EORTC QLQ C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FGFR2, fibroblast growth factor receptor 2; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PD, progressed disease; PF, progression free; PSS, Personal Social Services; QALY, quality-adjusted life year; TSD, technical support document.

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention

The intervention considered here is pemigatinib. Pemigatinib is a protein kinase inhibitor self-administered as a 13.5 mg once daily dose on a 14 days-on/7 days-off treatment schedule.[59] Treatment with pemigatinib may continue until documented disease progression or unacceptable toxicity related to pemigatinib. Dose interruptions and reductions are also permitted to manage any treatment related toxicity not thought to warrant permanent treatment discontinuation.[59]

B.3.2.3.2 Comparators

There are no approved targeted therapies for patients with advanced or metastatic CCA who have progressed on at least one line of prior therapy in the UK.[38,59]

Clinical expert opinion suggests that oxaliplatin, mFOLFOX+ASC are now considered SOC therapy for previously treated CCA patients.[66] This is based on results from the phase 3 ABC-06 study, which demonstrated a significant improvement in OS for patients treated with mFOLFOX+ASC when compared with ASC alone.[34] Based on these results and the findings of the clinical SLR, ABC-06 was considered the only relevant source of comparator data. Therefore, the two arms of the ABC-06 study form the relevant comparators considered in the economic model with ASC alone treated as 'best-supportive care'.

ABC-06 was a randomised, phase 3, multicentre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin/5-FU chemotherapy for patients with locally advanced/metastatic BTCs previously treated with cisplatin/gemcitabine chemotherapy. This trial had a UK population and although this related disease area does not exactly match the patient population of interest for the cost-effectiveness model (ABC-06 investigates all BTCs, whereas Cohort A of FIGHT-202 only included those who have *FGFR2* fusions/rearrangements and mainly consisted of iCCA patients), the ABC-06 study provides the strongest and most relevant available data for comparison.

Patients receiving mFOLFOX+ASC received a biweekly chemotherapy administration of oxaliplatin (85 mg/m^2), L-folinic acid (175 mg) and 5 fluorouracil (FU; 400 mg/m^2 bolus) in addition to a 46-hour continuous infusion of 5 FU (2,400 mg/m^2).

Patients receiving ASC alone may have received biliary drainage, antibiotics, analgesia, steroids and anti-emetics as well as palliative radiotherapy and blood transfusions. The costs for these drugs and procedures are not explicitly included in the model, as they would be expected to apply to both arms equally and are thus not expected to significantly impact the outcomes. Clinical interviews have further confirmed that although this may be the case in clinical trials, radiotherapy is not routinely commissioned by the NHS[66] and is thus not appropriate for consideration in this cost-effectiveness model.

Finally, although use of biliary stents was included in the final scope for this appraisal, this has not been explicitly considered within the cost-effectiveness model. Biliary stents are mostly used for patients presenting with hilar or extrahepatic CCAs,[38] primarily as a treatment option in the earlier stages of the disease; while maintenance or replacement of stents may be required, insertion of a new stent is unlikely to be considered after failure of previous lines of chemotherapy.[3] This is confirmed by the findings of the economic SLR,

which found various studies evaluating the use of stenting in early stages of disease progression (Table 31). Data from the FIGHT-202 study also show no patients in Cohort A receiving a bile duct stent during the trial, suggesting stents would not be used in standard clinical practice for this indication.[59] Its exclusion is therefore considered appropriate for this economic evaluation.

B.3.3. Clinical parameters and variables

A key challenge for deriving robust clinical inputs for both the intervention and relevant comparators was that the FIGHT-202 study was a single-arm trial. In the absence of a direct treatment comparison or a common comparator to support methods of estimating a relevant treatment effect, an unanchored MAIC was conducted to generate outcomes data adjusted for prognostic variables observed for both pemigatinib and the relevant comparators.

Separately, the evidence for the comparators was only available in molecularly unselected patients with CCA, rather than for patients with *FGFR2* fusions or, as considered in this appraisal. Furthermore, studies reporting outcomes data for relevant comparators did not report data on the proportion of patients with *FGFR2* mutations. In the absence of any robust data to the contrary, patients with and without *FGFR2* fusions or rearrangements are assumed to have the same prognosis. A detailed summary of the available evidence investigating this important topic is provided in Section B.1.3.1. The model includes an approach to test this assumption (described in Section B.3.3.3).

In the base case, standard parametric survival functions recommended by NICE DSU TSD 14 were fitted to survival outcomes observed in the FIGHT-202 study.[82] The most appropriate curve was then selected based on visual and statistical fit within the trial period and the clinical plausibility of the extrapolated curves beyond the trial period. Statistical fit was assessed using the Akaike information criterion (AIC) and Bayesian information criterion (BIC) measures. Relative treatment effects in the form of HRs estimated for each of the relevant comparators were applied, informed by the MAIC analysis (Section B.2.9).

To address the considerable structural uncertainty of modelled survival outcomes, additional functionality of the model used estimates of relative treatment effect estimated by naïve comparisons (Cox proportional hazards models) as well as independently fitted PSMs to observed unadjusted survival data.

In this section, clinical parameters and variables have been outlined for the population and for each treatment considered. Several approaches have been investigated to best address the challenges described and are outlined in detail below.

B.3.3.1 Population parameters

Baseline patient characteristics were informed by the planned subgroup 'Cohort A' of the FIGHT 202 study.[59] Mean age and the gender distribution were used to adjust general population mortality data sourced from the Office for National Statistics (ONS) to match the demographics of Cohort A.[83] Mean body surface area was calculated using height and weight data for patients in Cohort A using the Mostellar formula.[84] Body surface area was used to calculate accurate weight-based dosing for relevant comparator treatments.

Cohort A of the FIGHT-202 study consists of a molecularly selected population with 100% of patients having *FGFR2* fusions or rearrangements confirmed by genetic testing. As the prevalence of *FGFR2* mutations in the ABC-06 study is unknown, prevalence observed during screening of the FIGHT-202 study was considered the most suitable alternative proxy. In FIGHT-202, patients with *FGFR2* fusions/rearrangements were identified by screening, as well as enrolling patients with pre-existing 'reports in-hand' with already confirmed *FGFR2* fusion/rearrangement status.[29] Of those who were identified by pre-screening, Hollebecque et al. (2019) reported a comprehensive genomic profiling assessment of patients, presenting *FGFR2* fusion/rearrangement prevalence by country of origin. Data from patients enrolled from the UK are used for the prevalence estimate in the base case (8.6%).[85] However, *FGFR2* fusion/rearrangement prevalence was shown to vary considerably by country of origin in the FIGHT-202 study and alternative literature sources provide an even wider range of plausible estimates. Therefore, alternative estimates using all European patients from FIGHT-202 and data from Jain et al. (2018) are tested in scenario analyses (Table 33).[28,85] This *FGFR2* fusion/rearrangement prevalence only informs any testing costs or efficacy adjustments in the cost-effectiveness model.

Table 33: Summary of population inputs

Parameter	Value (SD)	Source
Mean age	55.3 (12.02)	Cohort A, FIGHT-202 Study[29]
Percentage male (%)	39.3	Cohort A, FIGHT-202 Study[29]
Body surface area (m^2)	1.88 (0.30)	Cohort A, FIGHT-202 Study[29]. Calculated using Mostellar equation.[84]
FGFR2+ prevalence (%)	8.6% (base case)	Hollebecque et al. 2019[85]
	19.6%	Jain et al. 2018 Table A1 frequency of FGFR2 genetic aberrations as a proportion of total study patient number (74/377).[28]
	7.4%	Hollebecque et al. 2019[85]

FGFR, fibroblast growth factor receptor; FGFR2, fibroblast growth factor receptor 2-positive; SD, standard deviation.

B.3.3.2 Background mortality

General population mortality was estimated from the most recent version of the national life tables for England and Wales, published by the ONS in 2019.[83] General population mortality was included to ensure that the modelled mortality risk did not fall below the general population mortality risk at any given age. To do so, the hazards of PFS and OS events were always equal to or exceeded the general population mortality hazard. In most cases, general population mortality does not influence model results, especially when the prognosis of patients is poor. However, it can help to adjust outcomes accordingly where parametric models with 'long tails' would otherwise result in implausible survival estimates.

B.3.3.3 FGFR2+/iCCA prognostic effect

There are no prospective high-quality studies investigating the prognostic and predictive impact of FGFR2 genetic aberrations. However, several other retrospective studies have evaluated this important question. Clinical experts identified a study by Jain et al. (2018) as the most robust evidence to support the potential prognostic effect of FGFR.[28,66]

The study by Jain et al. reported survival outcomes for CCA patients by FGFR genetic aberration status and showed that patients these patients had greater OS than those without the mutation. Patients with FGFR genetic aberrations were younger, more likely to be women, presented at an earlier stage of the disease (TNM I/II vs III/IV 35.8% vs 22%, respectively), and had more intrahepatic disease 87.4% vs 67%, respectively). In addition, these patients had a range of prior lines of therapy across different stages of disease. This makes it challenging to discern whether patients confer a survival advantage due to presenting at an earlier stage of disease, thus being more likely to be successfully

resected and receive adjuvant therapy; 43% of patients had been resected and received adjuvant therapy.[28] When consulted on this issue, clinical experts agreed that it is unknown whether the prognostic effect is due to the genetic aberration itself or other associated characteristics of this molecularly selected population such as intrahepatic disease.

While acknowledging the considerable limitations of the study described above (and in Section B.1.3.1) an approach is investigated in scenario analyses to re-weight comparator OS based on the estimated prognostic effect of, and the estimated proportion of, patients with *FGFR2* fusions/rearrangements in the ABC-06 study. As the proportion of patients with *FGFR2* fusions/rearrangements within the key comparator study (ABC-06) was not reported, this was therefore estimated based on the published literature ([Section B.3.3.1], 8.6%).[85]

The FGFR2 prognostic effect was calculated as a HR informed by a Cox-proportional hazards model fitted to pseudo-PLD derived from digitised KM curves for the whole population of the Jain et al. (2018) study.[28] Patients of all stages of the study were included as it represents the only analysis that reported outcomes excluding patients treated with FGFR-targeted therapies (Table 34). Using analyses from the advanced population may overestimate any true effect of the *FGFR2* genetic alteration by also including the added benefit of treatment of this cohort with a targeted therapy.

The inputs described above and tested in scenario analyses are considered exploratory, but are presented to inform decision makers of the potential impact on results of an unobserved prognostic effect. Base case settings including no adjustment for FGFR2 status are described in detail throughout the rest of Section B.3.3.

Table 34: Estimates of FGFR2+ prognostic effect used in the economic model

Population	OS (months)	HR using naïve medians	HR using Cox PH model
All stages of CCA without FGFR GA	20.0		
All stages with FGFR GA	30.0	0.67	0.65
Advanced CCA without FGFR GA	17.0		
Advanced CCA with FGFR GA	24.0	0.71	0.57

CCA, cholangiocarcinoma; FGFR, fibroblast growth factor receptor; GA, genetic aberration; HR, hazard ratio; OS, overall survival; PH, proportional hazards.
Notes: HRs presented as without FGFR GA as reference level. HR indicative of prognostic effect
Source: Jain et al., 2018[28]

B.3.3.4 Overall survival

In the base case for pemigatinib, PSMs were fitted to unadjusted OS observed from Cohort A of the FIGHT-202 study. Comparator survival is informed by relative treatment effects estimated by the MAIC analysis, described in detail in Section B.2.9. All survival outcomes were adjusted for background mortality, as mentioned in Section B.3.3.2.

B.3.3.4.1 Pemigatinib

OS for patients treated with pemigatinib was informed by parametric survival models fitted to the FIGHT-202 OS KM data for Cohort A patients (participants with *FGFR2* fusions/rearrangements; Table 34). Fitted models extrapolated beyond the observed follow-up period of the trial and predicted survival for the duration of the model time horizon (Figure 20; Table 35).

All models showed acceptable visual and statistical fit to the observed KM data, although the Weibull, Gompertz and log-logistic curves had marginally better statistical fit. Given the immaturity of the observed data greater weight was given to the clinical plausibility of extrapolations, to determine which curve should be used for the base case. When validating the extrapolations of pemigatinib OS, both interviewed clinicians struggled to choose the most feasible curve but suggested that they may expect to observe 5% of patients alive at 5 years.[66] Literature sources also report that approximately 70% of patients are diagnosed late with unresectable, locally advanced, or metastatic disease – these patients have an estimated 5-year survival rate of ≤ 10%.[14,30-33]

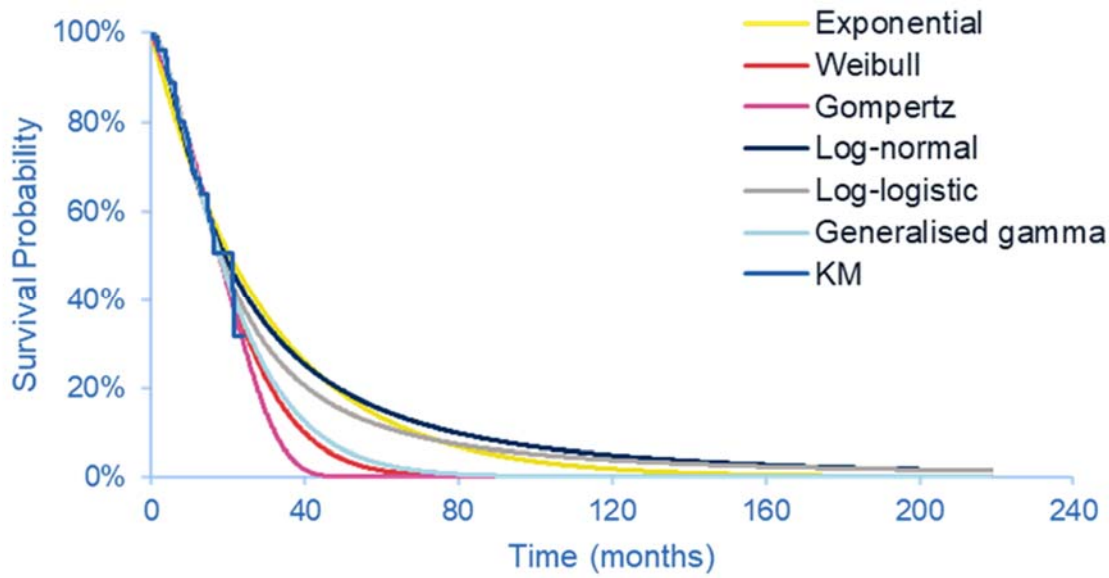


Figure 20: Pemigatinib OS KM data and fitted PSM models

KM, Kaplan–Meier; OS, overall survival.

Neither the log-logistic (11%), the Weibull (1%) or the Gompertz (0%) curves had 5-year survival estimates close enough to the clinicians' estimates to be considered better than the other. However, the log-logistic curve was selected for the base case, due to the selection of Weibull causing crossing of OS and PFS extrapolations when selecting best fitting PFS curves. The use of a Weibull model was explored in scenario analyses.

Table 35: Pemigatinib OS – AIC, BIC and 5-year survival estimates

Model	AIC	BIC	5-year survival estimate
Exponential	353.28	355.95	13%
Generalised gamma	349.91	357.93	3%
Gompertz	**349.92**	**355.27**	**0%**
Log-logistic	**348.17**	**353.51**	**11%**
Log-normal	349.99	355.33	15%
Weibull	**347.98**	**353.32**	**1%**

AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

B.3.3.4.2 Active symptom control

Overall survival for patients treated with ASC was informed by the relative treatment effect derived from the MAIC analysis using digitised pseudo-PLD from the ABC-06 study.[34] The MAIC-adjusted relative treatment effect considered the prognostic factors age, gender, ECOG performance status score and serum albumin concentration (Figure 21). The HR derived from the MAIC was applied to the base case PSM fitted for pemigatinib.

Assessment of the log-cumulative hazards plot shows that the hazards remained parallel for most of the follow-up period despite crossing initially (Appendix L, Figure 11). Therefore, it is considered that the proportional hazards assumption holds for OS when comparing pemigatinib versus ASC.

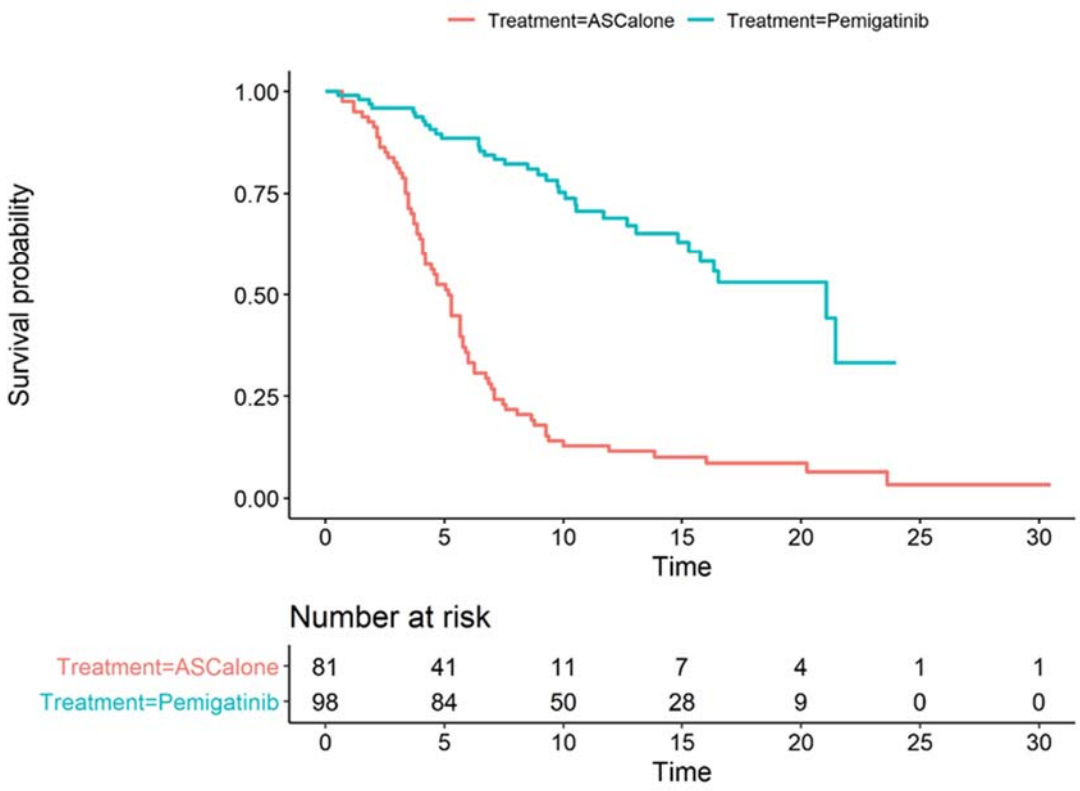


Figure 21: Unadjusted OS KM – Pemigatinib versus ASC (ABC-06)

ASC, active symptom control; KM, Kaplan-Meier; OS, overall survival.

The resulting base case comparator OS curve is shown in Figure 22. Alternative options for modelling comparator OS included using relative treatment effects derived by a naïve comparison using a Cox proportional hazards model, as well as extrapolating using independently fitted PSMs to observed KM data. These options are presented in the scenario analysis (Table 61). OS including an adjustment for FGFR2 status was also tested in scenario analyses and reported in Appendix L.

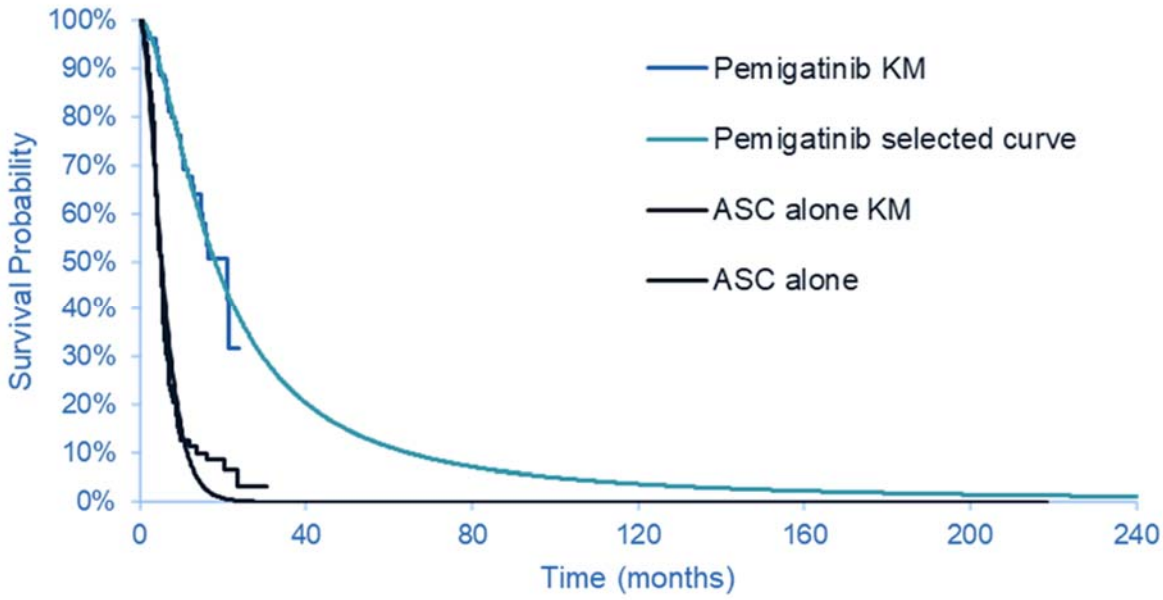


Figure 22: ASC alone OS informed by MAIC HR, compared with pemigatinib OS

ASC, active symptom control; KM, Kaplan–Meier; OS, overall survival.

Table 36: Relative treatment effects for ASC OS, derived by Cox proportional hazards model and MAIC

	Unadjusted		MAIC adjusted	
OS	HR (95% CI)	SE (Ln[HR])	HR (95% CI)	SE (Ln[HR])
ASC (ABC-06)	[redacted]	[redacted]	[redacted]	[redacted]

ASC, active symptom control; CI, confidence interval; HR, hazard ratio; OS, overall survival, MAIC, matching-adjusted indirect comparison; SE, standard error.

B.3.3.4.3 mFOLFOX+ASC

Overall survival for patients treated with mFOLFOX+ASC was informed by a relative treatment effect derived from the MAIC analysis using digitised pseudo-PLD from the ABC-06 study.[34] The MAIC-adjusted relative treatment effect considered the prognostic factors of age, gender, ECOG score and serum albumin concentration (Figure 23). The HR derived from the MAIC was applied to the base case PSM fitted for pemigatinib. The log-cumulative hazards plot for pemigatinib versus mFOLFOX+ASC was consistent with ASC alone. The proportional hazards assumption was considered to hold (Appendix L, Figure 12).

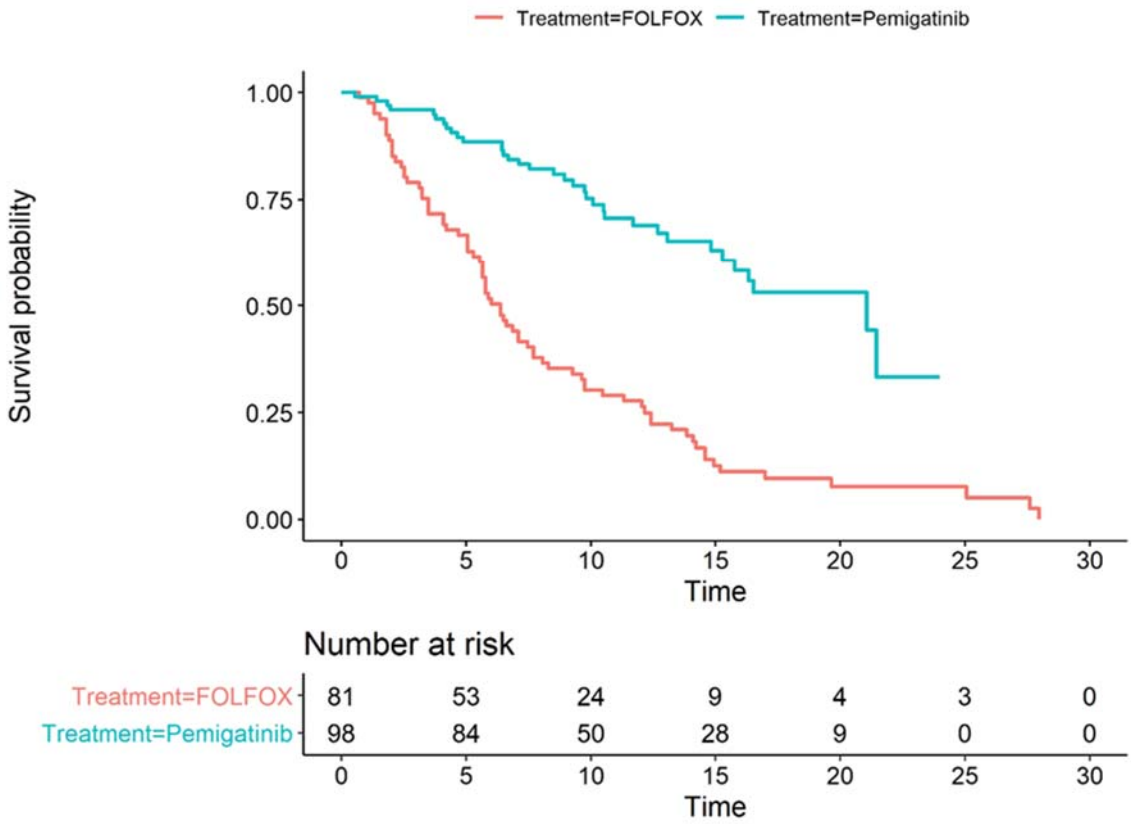


Figure 23: Unadjusted OS KM – Pemigatinib versus mFOLFOX+ASC (ABC 06)

ASC, active symptom control; KM, Kaplan-Meier; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; OS, overall survival.

As with ASC alone, the results reported below show the mFOLFOX+ASC OS modelled using the MAIC HR (Table 37) without an adjustment for FGFR2 status (Figure 22). Notwithstanding the differences in population between FIGHT-202 and ABC-06, OS data for both ASC alone and mFOLFOX+ASC were mature with survival less than 3% in both arms at the maximum follow-up of 30 months.

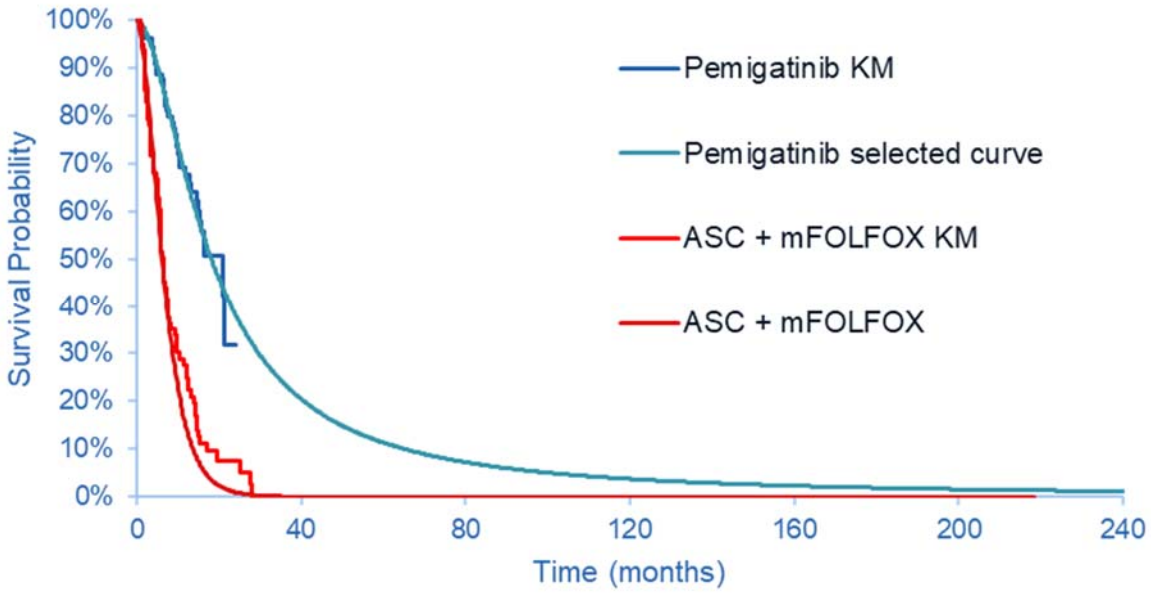


Figure 24: mFOLFOX+ASC OS informed by MAIC HR, compared with pemigatinib OS

ASC, active symptom control; KM, Kaplan–Meier; mFOLFOX+ASC, oxaliplatin, L-folinic acid and fluorouracil; OS, overall survival.

Table 37: Relative treatment effects for mFOLFOX+ASC OS, derived by Cox proportional hazards model and MAIC

	Unadjusted		MAIC adjusted	
OS	**HR (95% CI)**	**SE (Ln[HR])**	**HR (95% CI)**	**SE (Ln[HR])**
mFOLFOX (ABC-06)	[redacted]	[redacted]	[redacted]	[redacted]

ASC, active symptom control; CI, confidence interval; HR, hazard ratio; OS, overall survival, MAIC, matching adjusted indirect comparison; mFOLFOX; oxaliplatin, L-folinic acid and fluorouracil; SE, standard error.

B.3.3.5 Progression-free survival

For modelling PFS, the same approach was used as for OS in the base case. PSMs were fitted to unadjusted PFS data observed from Cohort A of the FIGHT-202 study. Comparator survival was informed by relative treatment effects estimated by the MAIC analysis (Section B.2.9). PFS as per the independent review committee analysis was used in the base case, as this was a key secondary outcome of the FIGHT-202 study and also matched the analysis used in the ABC-06 study.[34]

B.3.3.5.1 Pemigatinib

PFS for patients treated with pemigatinib was informed by parametric survival models fitted to the FIGHT-202 PFS KM data for Cohort A patients (Figure 25). Assessment of the statistical fit showed only marginal differences between models, with Weibull and log-

normal performing the best. Some models, demonstrated good visual fit for the initial follow-up period but provided an overly optimistic extrapolation and relatively poor fit to the tail of the KM data (Table 38). Although one of the clinicians interviewed for model validation could not choose between any of the PFS curves of patients treated with pemigatinib, the other suggested that they would expect approximately 10% of patients to be progression-free at 2 years.[66] Therefore, the log-normal distribution was chosen as it has the better statistical fit and is closely aligned with clinical expert opinion.

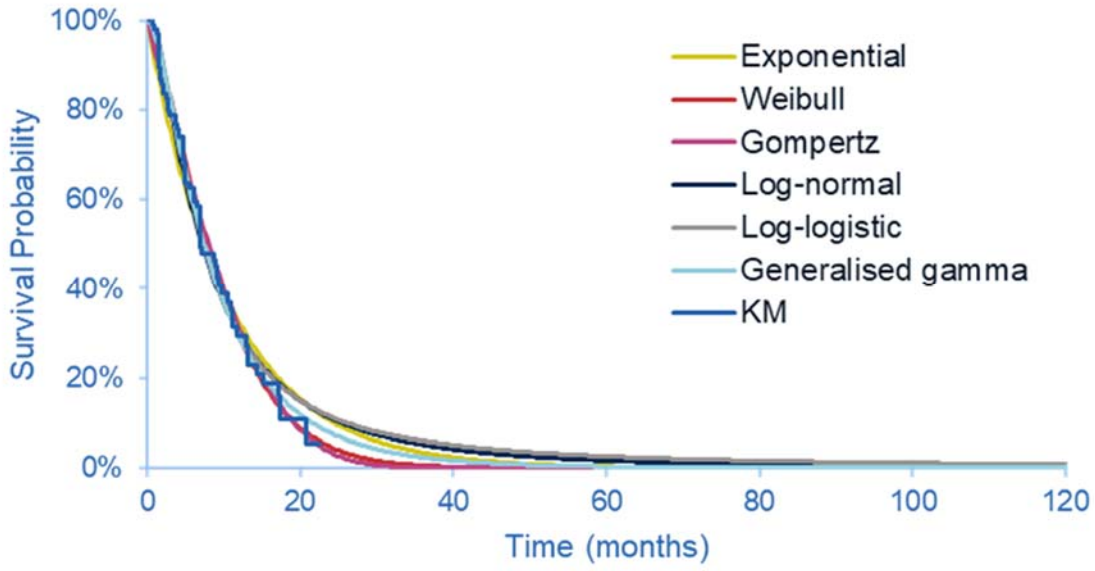


Figure 25: Pemigatinib PFS KM data and fitted PSM models

KM, Kaplan–Meier; PFS, progression-free survival.

Table 38: Pemigatinib PFS - AIC, BIC and 2-year survival estimates

Model	AIC	BIC	2-year PFS estimates
Exponential	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]

AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

B.3.3.5.2 Active symptom control

In the absence of any PFS data reported for ASC alone in the ABC-06 publication, PFS for the ASC arm was assumed to be equal to that of the mFOLFOX+ASC arm.[34] This is considered a conservative assumption, as it is likely the OS benefit for mFOLFOX+ASC in the ABC-06 study would translate into a PFS benefit too.

B.3.3.5.3 mFOLFOX+ASC

PFS for patients treated with mFOLFOX+ASC was informed by a relative treatment effect derived from the MAIC analysis using digitised pseudo-PLD from the ABC-06 study (Figure 26).[34] The HR derived from the MAIC was applied to the base case PSM fitted for pemigatinib. Assessment of the log-cumulative hazards plot shows the hazards for the treatments coming together initially and then following a parallel path for the remainder of the follow-up period. The proportional hazards assumption is not clearly violated in this case but the subjective nature of the assessment is acknowledged.

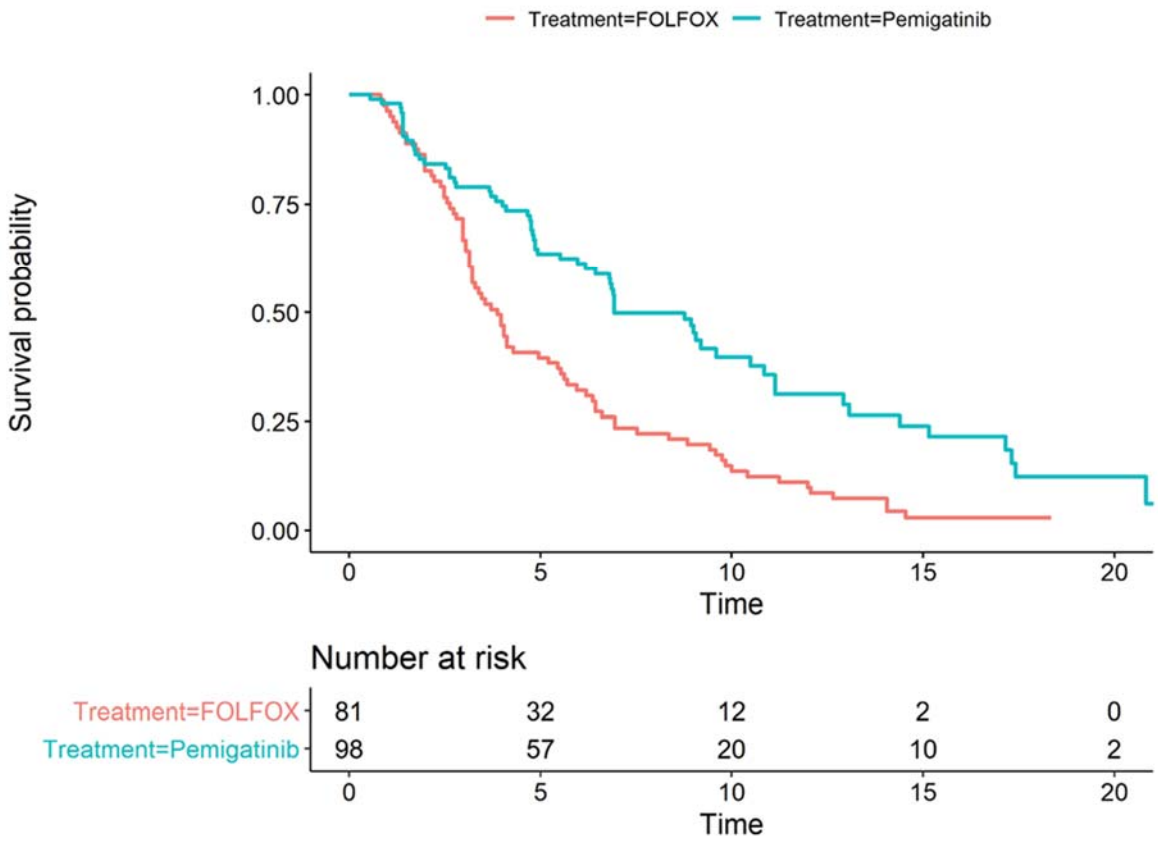


Figure 26: Unadjusted PFS KM – Pemigatinib versus mFOLFOX+ASC (ABC-06)

ASC, active symptom control; KM, Kaplan-Meier; mFOLFOX; oxaliplatin, L-folinic acid and fluorouracil; PFS, progression-free survival.

Results reported in Figure 27 show extrapolated PFS for pemigatinib compared with mFOLFOX+ASC informed by the MAIC adjusted HR. Alternative options for modelling comparator PFS include relative treatment effects derived by naïve comparison using a Cox proportional hazards model (Table 39) as well as independently fitted PSMs to observed KM data from the ABC-06 study.

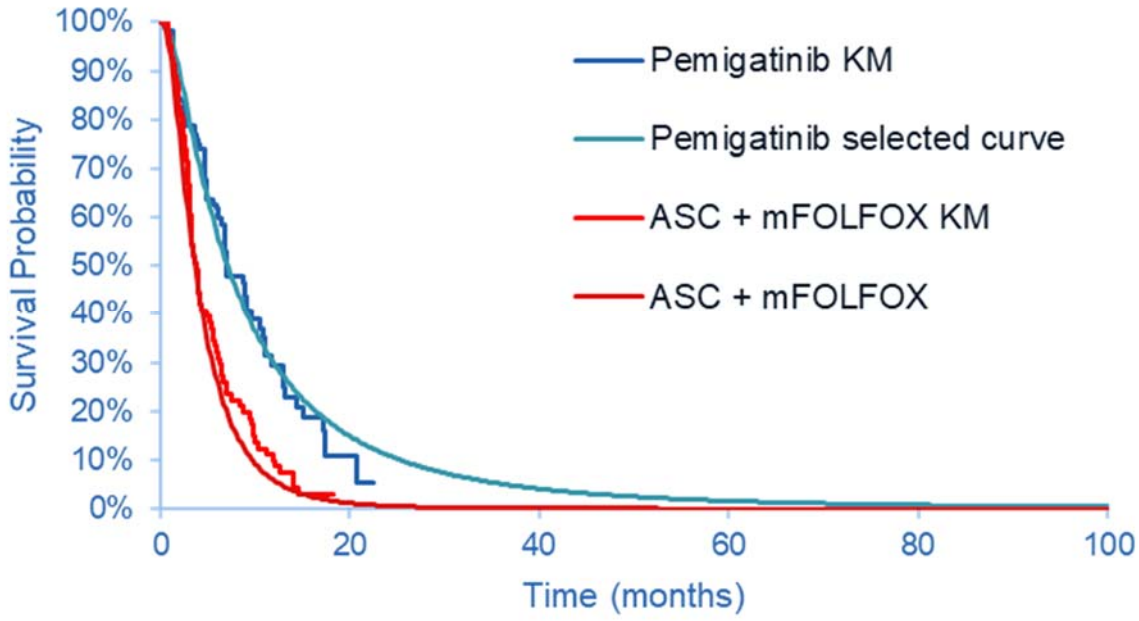


Figure 27: mFOLFOX+ASC PFS compared with pemigatinib PFS

ASC, active symptom control; KM, Kaplan–Meier; mFOLFOX+ASC, oxaliplatin, L-folinic acid and fluorouracil; PFS, progression-free survival.

Table 39: Relative treatment effects for mFOLFOX+ASC PFS, derived by Cox proportional hazards model and MAIC

	Unadjusted		MAIC adjusted	
OS	HR (95% CI)	SE (Ln[HR])	HR (95% CI)	SE (Ln[HR])
mFOLFOX (ABC-06)	[redacted]	[redacted]	[redacted]	[redacted]

ASC, active symptom control; CI, confidence interval; HR, hazard ratio; OS, overall survival, MAIC, matching-adjusted indirect comparison; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; PFS, progression-free survival; SE, standard error.

B.3.3.6 Time on treatment

In the base case for pemigatinib, ToT was modelled using PSMs fitted to observed data from Cohort A of the FIGHT-202 study. For ToT there was a lack of published data for the relevant comparators from any sources, including ABC-06. A simplifying assumption was therefore required that for ASC alone and mFOLFOX+ASC ToT would be equivalent to PFS; mFOLFOX was limited to a maximum of 24 weeks, consistent with its use in the ABC-06 study.[34]

Additional adjustments were made so that ToT could not exceed PFS for any modelled treatment arm. Therefore, all patients discontinued treatment prior to or at the point of disease progression. This is in line with UK clinical practice as well as the current anticipated license for pemigatinib (Appendix C).

B.3.3.6.1 Pemigatinib

ToT for the pemigatinib treatment arm was extrapolated from the FIGHT-202 KM data (Figure 28). Visual fit of the PSMs to the observed KM data was relatively good for all distributions. The same can be said for statistical fit, with the exponential and log-logistic models performing the best, although differences in AIC and BIC were small. The log-normal and log-logistic distributions had long-extended tails not thought to be appropriate for modelling ToT for CCA patients. [redacted] Therefore, the exponential model was used in the base case as it represents the simplest approach, has good visual and statistical fit and a close alignment with clinical expert estimates (Table 40).

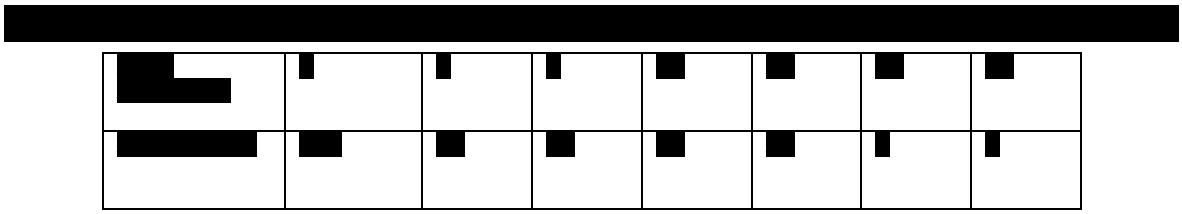


Figure 28: Pemigatinib unadjusted ToT KM data and models

KM, Kaplan–Meier; ToT, time on treatment.

Table 40: Pemigatinib unadjusted ToT AIC and BIC scores

Model	AIC	BIC	2-year ToT estimates
Exponential	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]

AIC, Akaike information criterion; BIC, Bayesian information criterion; ToT, time on treatment.

B.3.3.7 Adverse event probabilities

Adverse events (AEs) were included in the model if treatment-related grade ≥3 events occurred in ≥5% of patients for any relevant comparator in their respective clinical trial. If an AE was included based on these criteria, but AEs occurred in <5% of patients for another treatment, these events were still included where possible. For ASC and mFOLFOX+ASC, where AE incidence data were not publicly available, AE incidence was assumed to be zero as a conservative assumption. In addition, AEs were also included irrespective of these criteria, if clinical experts deemed them to have a known significant clinical impact (Table 41). For inclusion in the model, the frequency of each event was used to calculate an annual rate, adjusted for the number of patients treated [redacted].

Table 41: Adverse event annual rates

Adverse event	Pemigatinib[59]	ASC[34]	mFOLFOX+ASC[34]
Abdominal pain	[redacted]		
Alanine aminotransferase increased	[redacted]		
Anaemia	[redacted]	[redacted]	[redacted]
Anorexia	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]		
Aspartate aminotransferase increased	[redacted]		
Biliary event	[redacted]	[redacted]	[redacted]
Cholangitis	[redacted]		
Decreased serum albumin level	[redacted]		
Fatigue	[redacted]	[redacted]	[redacted]
Hypophosphataemia	[redacted]		
Infection (lung/urinary/fever/not specified)	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]		
Neutropenia	[redacted]		[redacted]
Palmar-plantar erythrodysaesthesia syndrome	[redacted]		
Thromboembolic events	[redacted]	[redacted]	
Hyperphosphataemia (Grade 2+)	[redacted]		

ASC, active symptom control; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil.

B.3.4. Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

Health related quality-of-life data collected from patients in Cohort A of the FIGHT 202 study are described in Section B.2.6. The study did not collect data using any preference-based patient reported outcome measures, such as the EuroQol five-dimension, three-level tool (EQ-5D-3L). Instead, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) data were mapped to EQ-5D-3L utilities using a published algorithm. These mapping analyses are described in Section B.3.4.2. A summary of the exploratory analyses and regression models fitted to the mapped utilities are provided below. Outputs of the regression models were used to inform the health state utilities for the cost-effectiveness analysis.

B.3.4.1.1 Methods

An exploratory analysis was carried out including all patients with at least one utility observation. Descriptive statistics were reviewed to assess the mapped EQ-5D-3L utilities derived from Cohort A EORTC-QLQ-C30 data and assess the impact of potential explanatory variables on utility. Observations with unknown accompanying progression status were removed for the fitting of mixed effects models due to the importance of progression status in informing the health states of the economic model.

A series of linear mixed effects regression models were fitted to the observed data. The model selection process explored simple models (including only baseline utility which is forced in all models) as well as more complex models including interaction terms between health state and treatment status. A random effect for patient was included to adjust for the correlation between multiple observations from the same patient. All statistical analyses were performed using R, and mixed effects regression models were performed using the 'lme' function from the package 'nlme'.[86,87]

The following linear mixed effects models were explored:

- Model 1: Utility = treatment + baseline utility
- Model 2: Utility = treatment + baseline utility + treatment state
- Model 3: Utility = treatment + baseline utility + health state
- Model 4: Utility = treatment + baseline utility + treatment state + health state

- Model 5: Utility = treatment + baseline utility + treatment state*health state (interaction) + treatment state + health state

The assumptions for the mixed effect regression models were that the random effects and the residual errors were normally distributed with mean 0 and were independent of the random effects. These assumptions were tested using a normal quantile–quantile (QQ)-plot with a reference line as a slope; that is, the variance of the random effects, where the points should be along the straight line. Model residuals versus the fitted values should result in a random scatter of points if the assumptions have been met.

B.3.4.1.2 Results

A total of 496 observations from 107 patients from Cohort A were available to inform these analyses. Of the post-screening observations, 282 (71%) were observed prior to disease progression, with 91 observations (19%) after disease progression. There were relatively few observations with unknown progression status, which were subsequently removed from the analysis. Descriptive statistics indicated lower utility for patients post-progression and off treatment compared with pre-progression and on-treatment respectively (Table 42). Furthermore, it appeared that the impact of treatment status on utility was independent of progression status.

Table 42: Summary of utility observations by progression and treatment status

	Category	Mean (SD)	Median (range)	N Subjects (N utility observations)
All observations	All	[redacted]	[redacted]	[redacted]
	Screening	[redacted]	[redacted]	[redacted]
	Post-screening	[redacted]	[redacted]	[redacted]
Progression-status	Pre-progression	[redacted]	[redacted]	[redacted]
	Post-progression	[redacted]	[redacted]	[redacted]
	Unknown	[redacted]	[redacted]	[redacted]
Treatment-status	On-treatment	[redacted]	[redacted]	[redacted]
	Off-treatment	[redacted]	[redacted]	[redacted]

	Category	Mean (SD)	Median (range)	N Subjects (N utility observations)
Pre-progression	On-treatment	[redacted]	[redacted]	[redacted]
	Off-treatment	[redacted]	[redacted]	[redacted]
Post-progression	On-treatment	[redacted]	[redacted]	[redacted]
	Off-treatment	[redacted]	[redacted]	[redacted]

SD, standard deviation.

Utility observations by visit also demonstrated that mean utilities increased over the follow-up period (Table 43). HRQoL observations were scheduled at screening and then every three cycles while patients remained on treatment. Upon treatment discontinuation, patients had one end of treatment observation. The increasing mean utility over time highlighted potential selection bias, as unhealthier patients discontinued treatment and stopped contributing HRQoL data. This was accounted for in regression analyses, using a random effect for patient. In addition, by only including a single observation post treatment discontinuation and with progression being so closely linked to treatment discontinuation, there is a significant risk that post-progression observations failed to capture the full impact of disease progression on CCA patients' HRQoL with the FIGHT-202 study.

Finally, observations in the FIGHT-202 study were scheduled every three cycles, with cycles lasting 21 days. With patients on average having 2 months between observations, it is unlikely that the data captured are sensitive to short-term changes in HRQoL, such as those observed because of an AE.

Table 43: Summary of utility observations by visit

Visit	Mean (SD)	Median (range)	N Subjects (N utility observations)
Screening	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]

Visit	Mean (SD)	Median (range)	N Subjects (N utility observations)
Cycle 13	[redacted]	[redacted]	[redacted]
Cycle 14	[redacted]	[redacted]	[redacted]
Cycle 15	[redacted]	[redacted]	[redacted]
Cycle 16	[redacted]	[redacted]	[redacted]
Cycle 17	[redacted]	[redacted]	[redacted]
Cycle 18	[redacted]	[redacted]	[redacted]
Cycle 21	[redacted]	[redacted]	[redacted]
Cycle 24	[redacted]	[redacted]	[redacted]
Cycle 27	[redacted]	[redacted]	[redacted]
Cycle 30	[redacted]	[redacted]	[redacted]
Cycle 33	[redacted]	[redacted]	[redacted]

Note: Cycle length is 21 days.

Utility regression coefficients are reported in Table 44. All models are shown to have similar statistical fit. Although the AIC for Model 5 was slightly higher than that of Model 1 and 2 (as models with more covariates were penalised more for the AIC criterion), the interaction effect between progression and treatment status was highly significant. When included in isolation, treatment status and disease progression were both associated with a utility decrement, whereas only the treatment status coefficient was shown to be statistically significant. When included in combination, the effect of treatment status remained significant, whereas the impact of progression independent of treatment status was negligible. Model 5 was shown to have significant coefficients for both treatment status and an interaction term for treatment and progression status. However, these results are highly uncertain, as there were only five observations available for patients who were pre-progression and off-treatment.

The choice of model for use in the base case was difficult. Model 5 was chosen due to its superior statistical fit to the data. Model 3 was tested in scenario analyses.

Table 44: Linear mixed effects regression model coefficients and statistical fit

Coefficient	Model 1 coef (p-value)	Model 2 coef (p-value)	Model 3 coef (p-value)	Model 4 coef (p-value)	Model 5 coef (p-value)
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Off-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interaction: post-progression *off-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fit statistic					
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIC; Akaike information criterion.

B.3.4.2 Mapping

As EQ-5D data were not available from the trial, a mapping algorithm was required to convert the collected EORTC data to the EQ-5D-3L measure. Four potential mapping algorithms were reviewed based on the use of the UK tariff for EQ-5D-3L and the type of cancer the mapping algorithm was derived from.[88-91] In addition, a review by Doble & Lorgelly et al. (2016) found that although most published algorithms were not fit for purpose, the Longworth algorithm was an exception and found it to accurately predict EQ-5D-3L utilities.[92] For this reason, the mapping algorithm by Longworth et al., 2014[90] was used in the base case from then on with the acknowledgement that no algorithms were found that were developed specifically for patients with BTC.

Visual validation of the Longworth algorithm was conducted using graphical methods, comparing results to an alternative algorithm published by Kontodimopoulos et al., 2009.[89] This basic validation exercise showed that both algorithms predicted similar utility values. However, the Kontodimopoulos et al., 2009 algorithm resulted in a high proportion of utilities predicted as >1, which can be a limitation of the ordinary least squares approach (Figure 29). Therefore, the Longworth algorithm was used in the economic model analyses as it is designed for use across a range of cancers, while the response mapping technique enables the application of alternative EQ-5D tariffs.

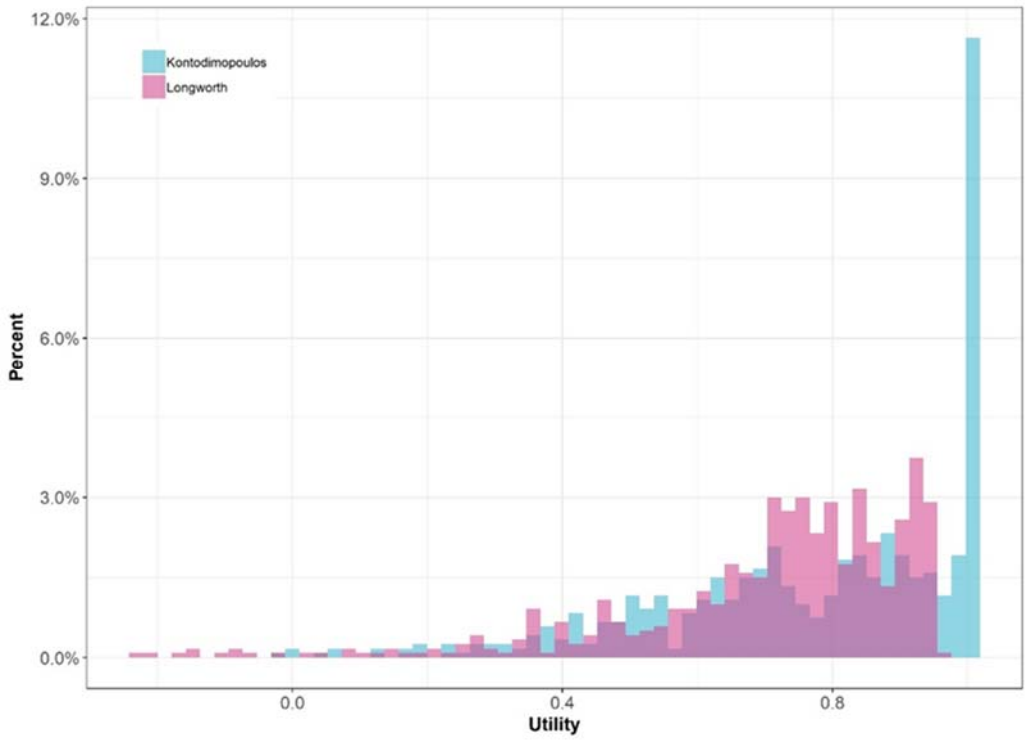


Figure 29: Comparison of mapped utilities using Longworth and Kontodimopoulos et al., 2009 algorithms

The Longworth algorithm uses a 'response mapping' technique that predicts the probability of a patient scoring 1, 2 or 3 for each of the five EQ-5D-3L dimensions using multinomial logistic regression models applied to the EORTC-QLQ-C30 responses from each patient.

The EQ-5D is a standardised measure of health status developed by the EuroQol group to provide a simple, generic measure of health for clinical and economic appraisal.[93] The EQ-5D-3L descriptive system is comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problems (1), some problems (2) and extreme problems (3). Each combination of dimensions and levels can be converted to an EQ-5D index score.

To estimate utility score in the observed EQ-5D data, the coefficients for each domain score from the standard UK utility tariff were multiplied by the corresponding probability derived by the Longworth algorithm, as shown in Equation 1.[94]

Equation 1: Calculation of EQ-5D index score (UK tariff)

$$\text{EQ} - \text{5D index} = 1 - 0.069\,\text{P}_{\text{MO2}} - 0.314\,\text{P}_{\text{MO3}} - 0.104\,\text{P}_{\text{SC2}} - 0.214\,\text{P}_{\text{SC3}} - 0.036\,\text{P}_{\text{UA2}} -$$

$$0.094\,\text{P}_{\text{UA3}} - 0.123\,\text{P}_{\text{PD2}} - 0.386\,\text{P}_{\text{PD3}} - 0.071\,\text{P}_{\text{AD2}} - 0.236\,\text{P}_{\text{AD3}} - 0.081\,\text{P}_{\text{N2}} - 0.269\,\text{P}_{\text{N3}}$$

Note: The number following the codes indicates a Level 2 or Level 3 response.
AD, anxiety/depression; MO, mobility; N2, one or more questions reported as a 2 or 3; N3, one or more questions answered as a 3; PD, pain/discomfort; SC, self-care; UA, usual activity.

B.3.4.3 Health-related quality-of-life studies

To conduct the SLR of HRQoL studies, the same approach was used as for the cost-effectiveness studies (Section B.3.1). No studies were identified in the original searches for HRQoL studies in patients consistent with the setting considered in this appraisal. Updated searches found a small number of studies in patients treated with earlier stages of disease, prior to the use of systemic therapies. Of the included utility estimates, the majority were from studies in patients from Thailand, using the country's corresponding EQ-5D value set (Appendix H).

Utility estimates identified from the SLR were therefore not considered appropriate for inclusion in the cost-effectiveness model. To investigate utilities from a source other than FIGHT 202, the utilities used in the NICE appraisal for sorafenib in advanced hepatocellular carcinoma were used in the model for scenario analysis [redacted] Figure 30 shows the PRISMA for the original SLR conducted in 2018. Figure 31 shows the PRISMA for the April 2020 expansion and update SLR.

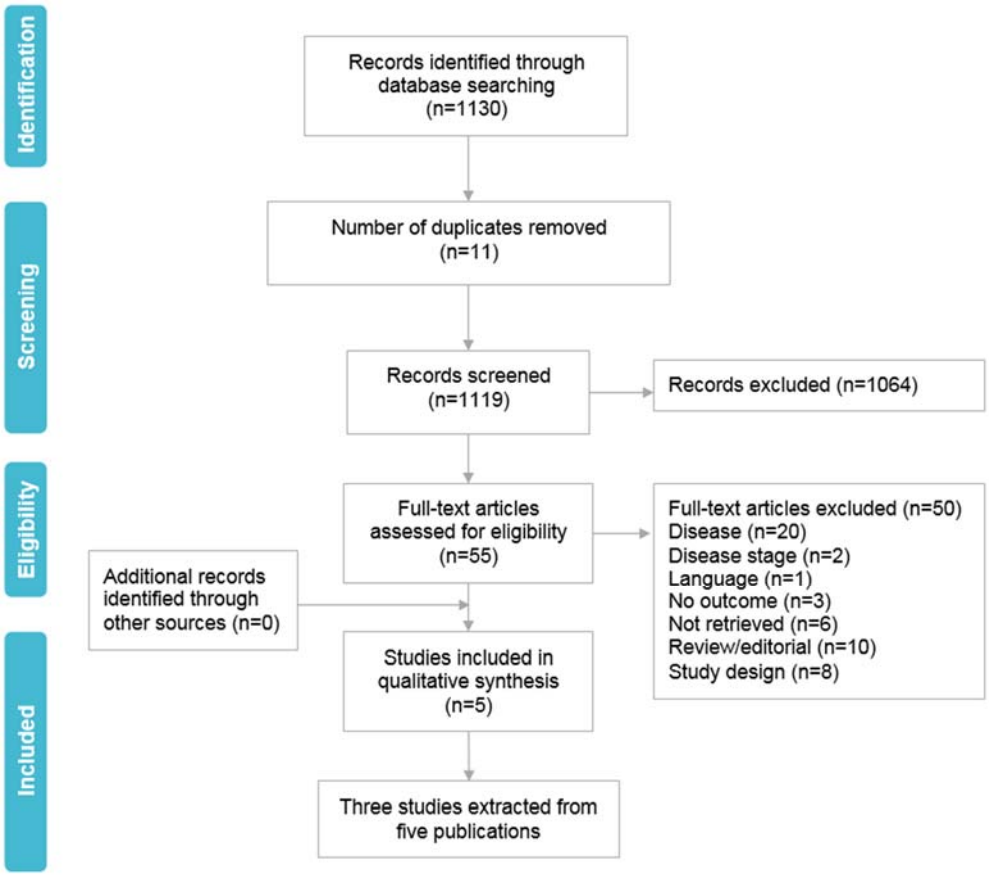


Figure 30. PRISMA diagram for HRQL SLR – original 2018 SLR

HTA, health technology appraisal; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

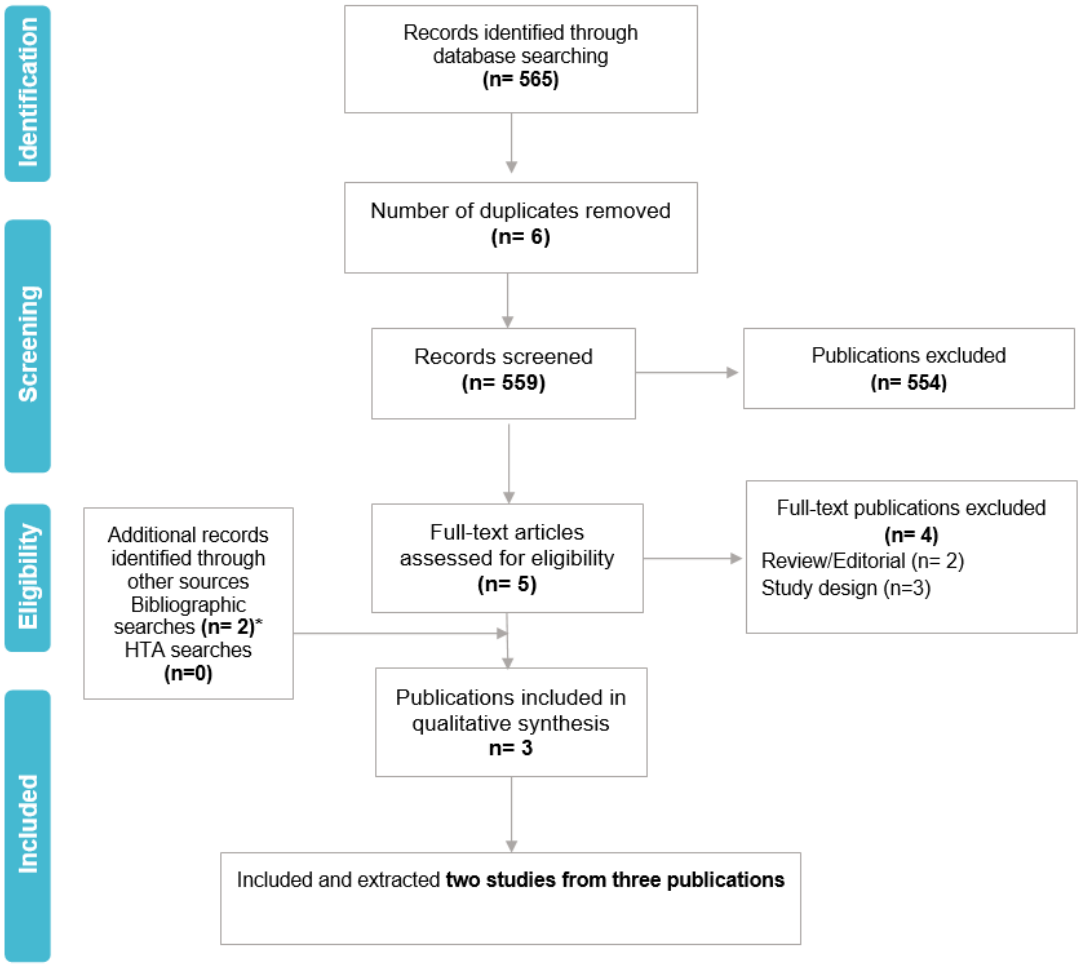


Figure 31. PRISMA diagram for HRQL SLR – April 2020 expansion and update SLR

HTA, health technology appraisal; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

B.3.4.4 Adverse reactions

The impact of treatment-related, grade ≥3 AEs on HRQoL was included in the economic model, considering these were expected to have the greatest impact on patients. Grade ≥2 AEs were considered for hyperphosphataemia due to their frequency in patients treated with FGFR inhibitors. Inclusion of AE disutilities was considered appropriate as the scheduled frequency of HRQoL observations in the FIGHT 202 study was unlikely to be sensitive to short-term changes in utility. AE disutilities and durations were sourced from the available literature and combined to estimate the quality-adjusted life year (QALY) decrement for each event (Table 45). In the absence of published data, assumptions were made based on clinical expert opinion. QALY decrements were applied to pemigatinib and the relevant comparators while patients remained on treatment, based on the frequency of AEs reported in Section B.3.3.7.

Table 45: Adverse event disutilities

Event	AE duration (days)	Disutility per AE	Source/assumption
Abdominal pain	11.8[59]	-0.069	Assumed same as arthralgia
Alanine aminotransferase increased	8.3[59]	0	Assumed to have limited impact on HRQoL[66]
Anaemia	9.9[59]	-0.085	TA439: cetuximab and panitumumab for previously untreated metastatic colorectal cancer[96]
Anorexia	17[97]	-0.069	Assumed same as for decreased appetite; TA307: aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy[98]
Arthralgia	18.7[59]	-0.069	Assumed same as SAE for bone pain; TA391: cabazitaxel for the second-line treatment of hormone-refractory metastatic prostate cancer[99]
Aspartate aminotransferase increased	6.8[59]	0	Assumed to have limited impact on HRQoL[66]
Biliary event	2.625	-0.085	Assumed same as anaemia
Cholangitis	4.7[59]	-0.085	Assumed same as anaemia
Decreased serum albumin level	7[59]	-0.085	Assumed same as anaemia
Fatigue	2.625	-0.085	Assumed same as anaemia
Hypophosphataemia	29.3[59]	0	Assumed to have limited impact on HRQoL[66]
Infection (lung/urinary/fever/not specified)	8.3[59]	-0.085	Assumed same as anaemia
Stomatitis	9.8[59]	-0.0375	TA439: cetuximab and panitumumab for previously untreated metastatic colorectal cancer[96]
Neutropenia	7	-0.0607	TA439: cetuximab and panitumumab for previously untreated metastatic colorectal cancer[96]
Palmar-plantar erythrodysaesthesia syndrome	17.3[59]	-0.085	Assumed same as anaemia
Thromboembolic events	14	-0.085	Assumed same as anaemia, with duration longer than seven days as per clinical opinion[66]
Hyperphosphataemia (Grade 2+)	15.5[59]	0	Assumed to have limited impact on HRQoL[66]

AE, adverse event; HRQoL, health-related quality of life; SAE, serious adverse event; TA, technology appraisal.

B.3.4.4.1 Treatment administration disutility

Due to the additional patient burden of intravenous (IV) treatment administration, the model included administration disutilities. Clinician interviews confirmed that treatment with the mFOLFOX regimen typically requires an implantable port, particularly given the 46 hours continuous infusion time with 5-FU.[66] Comparative HRQoL data that capture the differential administration disutility of an IV therapy versus an oral therapy such as pemigatinib in BTC are not currently available. However, administration disutilities have been considered and used in other oncology health technology appraisals.

NICE technology appraisal TA427 (pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib) used a disutility of 0.025 for patients receiving either subcutaneous or IV therapies.[100] In addition, a separate UK study used a time trade-off approach to derive disutilities for different modes of treatment administration, finding a disutility of 0.037 for an infusion at hospital every 4 weeks versus SC injection at home every 12 weeks.[101] Finally, an SLR in non-small cell lung cancer identified a paper reporting disutilities of 0.014 for oral therapy and 0.043 for IV therapy (a difference of 0.029).[102] Acknowledging the uncertainty of treatment administration disutilities for patients with advanced CCA, a value of 0.025 was used to estimate the administration disutility value of mFOLFOX+ASC in the model and applied while patients were on treatment. This is considered to be an estimate within the range reported by the studies listed above, and is included in one-way and probabilistic sensitivity analyses.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

A qualitative description of CCA is provided in Section B.1.3. HRQoL data are scarce for patients previously treated, unresectable, locally advanced, or metastatic CCA. This is primarily due to the rarity of the condition and lack of previously approved treatment options and corresponding clinical trial data. The same is true for the specific population of patients with an *FGFR2* fusion/rearrangement who are considered in this model, although there is no evidence to suggest that FGFR2 status is predictive of HRQoL.

The model structure includes five mutually exclusive health states. For the absorbing dead state, utility is zero. For each of the living states, a health state utility value that can vary between a value considered worse than death (negative utility) and perfect health (utility equal to 1) was assigned. In the base case, a linear mixed effects regression model including covariates: baseline utility and progression status was used.

The only available robust HRQoL evidence available is from the single-arm FIGHT 202 pemigatinib study. Published algorithms provided the necessary means to predict EQ-5D-3L utilities from the observed EORTC QLQ-C30 data. As discussed (Section B.3.4.2), mapped utilities are used in a regression analysis to predict health state utilities. In the base case, patients' baseline utility, treatment and progression status were considered. This model demonstrated the best statistical fit to the available data (Table 46). Health state utilities were applied consistently across all treatment arms, as there was no evidence to support an alternative assumption. However, treatment specific administration and AE disutilities were included, as described above.

Table 46: Summary of base case utility values for cost-effectiveness analysis

State	Utility value: mean	Reference in submission (section and page number)	Justification
Progression-free on treatment	[redacted]	Section B.3.4.1.2 (pages 101–104)	See Section B.3.4.1 and Section B.3.4.5
Progression-free off-treatment	[redacted]	Section B.3.4.1.2 (pages 101–104)	
Progressive disease on-treatment	[redacted]	Section B.3.4.1.2 (pages 101–104)	
Progressive disease off-treatment	[redacted]	Section B.3.4.1.2 (pages 101–104)	

CI, confidence interval; SE, standard error.

Acknowledging the uncertainty of these estimates, alternative inputs were tested in scenario analyses. These included an alternative specification of the FIGHT-202 regression analysis in addition to utility estimates from a clinically comparable indication, advanced hepatocellular carcinoma. Scenario 1 removed the impact on utility associated with treatment discontinuation, independent of progression. [redacted] However, they provided the best available comparison to utilities derived from FIGHT-202 and demonstrated that utilities from the two sources were comparable. Table 47 summarises the utilities for the two scenarios.

Table 47: Summary of utility values for cost-effectiveness analysis

Health state	Base case[59]	Scenario 1[59]	Scenario 2[95]
Progression-free, on treatment	[redacted]	[redacted]	[redacted]
Progression-free, off treatment	[redacted]	[redacted]	[redacted]
Progressed disease, on treatment	[redacted]	[redacted]	[redacted]
Progressed disease, off treatment	[redacted]	[redacted]	[redacted]

B.3.5. Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Intervention and comparators' costs and resource use

An SLR was conducted to identify studies assessing cost and healthcare resource use in patients with advanced cholangiocarcinoma that is relapsed or refractory after at least one prior systemic therapy. Due to the lack of evidence identified from the original searches, an updated search was conducted without the requirement for patients to have failed one or more previous treatments. Details of the original 2018 SLR are provided in Figure 32 and of the expanded and updated SLR (April 2020) in Figure 33, although no UK studies were identified. The full details of the methods used to conduct this review are presented in Appendix I.

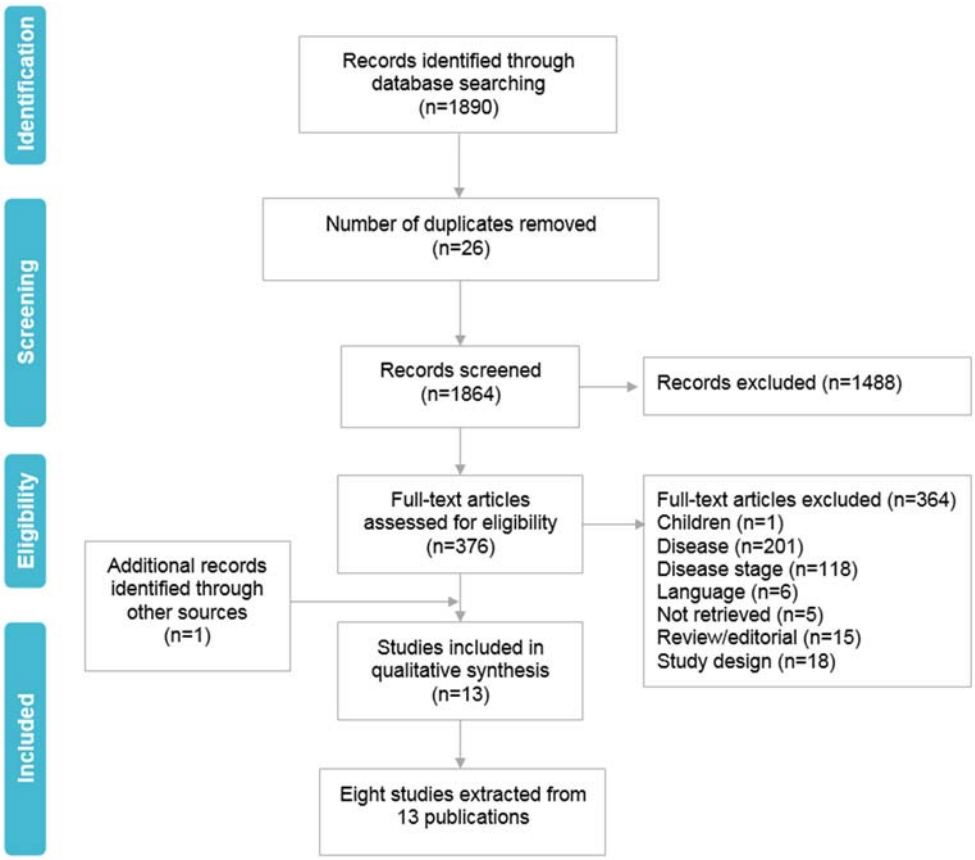


Figure 32. PRISMA diagram for cost and healthcare resource use SLR – original 2018 SLR

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

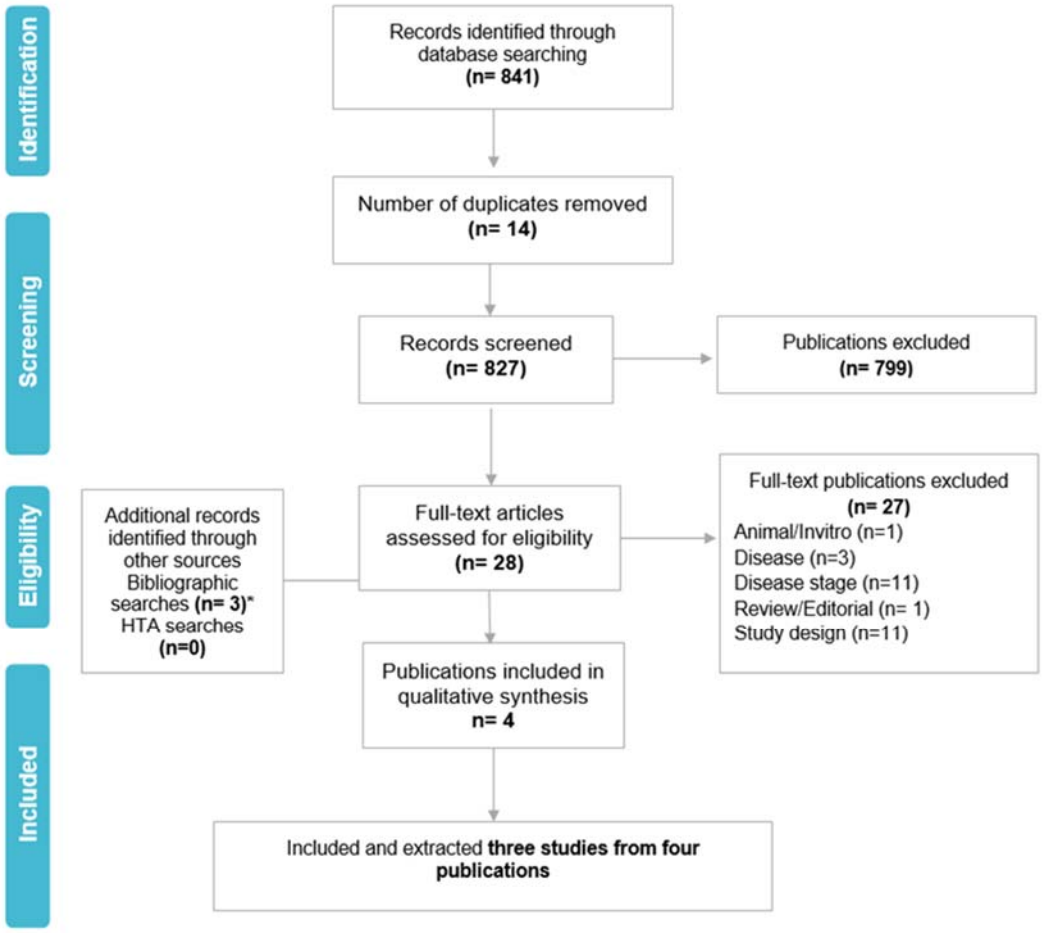


Figure 33. PRISMA diagram for cost and healthcare resource use SLR – April 2020 expanded and updated SLR

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

B.3.5.1.1 Drug costs

Drug costs were sourced from the most recent publication by the Electronic Medicines Compendium (eMC) 2020, where available.[103] The drug acquisition cost for pemigatinib is £37.88 per mg (£511.36 per 13.5 mg tablet). The pemigatinib list price is subject to a further simple discount of [redacted] Where multiple units of a single drug were available, costs per mg are weighted by real-world usage. The weighted costs were £0.001/mg for fluorouracil, £0.10/mg for oxaliplatin, £0.05/mg for calcium folinate. No acquisition costs were applied for ASC (Table 48).

Pemigatinib drug costs were adjusted for dose interruptions but not for dose reductions. This is appropriate given the flat dosing structure of pemigatinib, as 4.5 mg, 9 mg and 13.5 mg formulations all have the same cost. An adjustment for dose interruptions was made by calculating the percentage of doses received as a proportion of the expected number of doses without any interruptions ([redacted]). Where doses were reported per square metre,

the mean body surface area from the FIGHT-202 patient population was applied (Table 49).

No wastage was assumed in the model. This is because, for the comparators, the chemotherapy acquisition costs are minimal; therefore, the effect of any wastage assumptions is expected to be negligible. Given the assumed packaging for pemigatinib, it will include 14 tablets for a 21-day cycle; therefore, wastage is expected to be negligible.

Table 48: Drug acquisition costs

Drug	Pack size	Pack cost (£)	Cost per mg (£)	Source
Pemigatinib (list price)	1 x 13.5 mg	511.36	37.88	Incyte Corporation
Fluorouracil	1 x 1g	1.13	0.001	eMC[103]
	1 x 2.5 g (100 ml)	2.84	0.001	
	1 x 2.5 g (50 ml)	1.88	0.001	
	1 x 500 mg (10 ml)	0.96	0.002	
	10 x 500 mg (20 ml)	66.00	0.013	
	1 x 5 g	4.82	0.001	
Oxaliplatin	1 x 100 mg	8.67	0.087	
	1 x 200 mg	18.78	0.094	
	1 x 50 mg	7.19	0.144	
Calcium folinate	1 x 100 mg	2.23	0.022	
	10 x 100 mg	5.97	0.006	
	1 x 300 mg	9.97	0.033	
	1 x 350 mg	5.96	0.017	
	10 x 350 mg	54.96	0.016	
	1 x 50 mg	4.50	0.090	
	10 x 50 mg	14.66	0.029	
	1 x 10 mg	21.37	2.137	
	1 x 20 mg	39.94	1.997	
	1 x 40 mg	79.88	1.997	

eMC, Electronic Medicines Compendium

Table 49: Treatment regimens

Treatment	Drug	Administration route	Dosing schedule	Source
Pemigatinib		Oral	13.5 mg once daily,	FIGHT-202[59]
ASC				Lamarca et al.2019[34]
mFOLFOX +ASC	Fluorouracil	IV	Once every 14 days for up to 12 cycles, 400 mg/m^2 bolus injection + 2400 mg/m^2 continuous infusion over 46 hours	Lamarca et al.2019[34]
	Oxaliplatin	IV	Once every 14 days for up to 12 cycles, 85 mg/m^2	
	Calcium folinate	IV	Once every 14 days for up to 12 cycles, 350 mg	

ASC, active symptom control; IV, intravenous; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil.

B.3.5.1.2 Administration costs

A cost of £370.68 was applied for each intravenous infusion, representing the delivery of complex chemotherapy and including a prolonged infusional treatment at first attendance (healthcare resource group code - SB14Z).[104] As 5-FU is administered over 46 hours, an additional cost is incurred for patients returning to hospital to have their infusion removed by a nurse – this was costed as £147.38 per visit (WF01A)[104] and aligned with the methodology used to cost 46-hour 5-FU administrations in other NICE appraisals.[105] Patients treated with mFOLFOX+ASC receive an infusion once every 2 weeks for up to 12 cycles[34], with an average weekly infusion cost of £259.03.

As pemigatinib is administered orally, no administration cost was assumed. ASC was also assumed to incur no administration costs, as these costs are assumed to be equal across arms.

B.3.5.2 Health-state unit costs and resource use

According to the ESMO guidelines for biliary cancer follow-up, major centres currently employ a monitoring strategy using a combination of clinical examination, computed tomography (CT) scans and blood tests.[38] These were used in the cost-effectiveness model and, using NHS reference costs, were costed as £194.17 (WF01A), £105.37 (RD22Z) and £2.79 (DAPS05), respectively.[104] The guidelines suggest follow-up visits once every 3 months during the first 2 years after therapy[38] – this frequency was assumed for all patients in the model, with patients incurring each test cost once every 3 months, irrespective of progression status for clinical examinations and blood tests.

CT scans were assumed to be performed once every 12 months for progressed patients, as clinician feedback suggested these scans would be performed less frequently after progression.[66] As recommended at the clinical validation meeting, the model included the cost of pain medication for patients in the progressed state (daily morphine sulphate, £5.78[106]), which was costed in line with other oncology NICE appraisals.[107] This resulted in annual monitoring costs of £1,208.08 and £3,003.55 per patient for the progression-free and progressed status, respectively.

B.3.5.3 Adverse reaction unit costs and resource use

The cost associated with each treatment-related grade ≥3 AE included in the model was taken from the National Schedule of Reference Costs 2018–2019, where available.[104] These were considered to be the AEs with the greatest cost burden. AE grades ≥2 were considered for hyperphosphataemia due to their frequency in patients treated with FGFR inhibitors. A large number of AEs reported in FIGHT-202 and ABC-06 were not reported explicitly in the reference costs and were therefore assumed to have the same cost as a similar AE instead. For AEs, increased alanine aminotransferase increased and aspartate aminotransferase and watchful waiting with no additional costs were assumed. All modelled event costs are reported in Table 50. Annual AE costs per treated patient year were £4,334 for pemigatinib, £4,265 for ASC alone and £7,925 for mFOLFOX+ASC.

Table 50: Adverse event costs

Event	Unit cost (£)	Assumption/NHS code
Abdominal pain	990	Assumed same as arthralgia
Alanine aminotransferase increased	0	Watchful waiting (and thus no cost) assumed
Anaemia	691	Non-elective short stay weighted average SA04G-SA04L, Iron deficiency anaemia
Anorexia	1,256	Non-elective short stay weighted average FD04C-FD04E, Nutritional Disorders without Interventions
Arthralgia	990	Non-elective short stay average HD26D-HD26G, Musculoskeletal Signs or Symptoms
Aspartate aminotransferase increased	0	Watchful waiting (and thus no cost) assumed
Biliary event	1,256	Assumed equal to cholangitis
Cholangitis	1,256	Assumed equal to infection
Decreased serum albumin level	1,077	Non-elective short stay average SA08G-SA08J, Other Haematological or Splenic Disorders
Fatigue	1,256	Assumed equal to anorexia
Hypophosphataemia	19	One pack of oral phosphate supplements - Phosphate Sandoz effervescent tablet[108]
Infection (lung/urinary/fever/not specified)	1,256	Assumed equal to fatigue
Stomatitis	3,346	Non-elective short stay average FD10E-FD10H, Non-malignant Gastrointestinal Tract Disorders with Single Intervention
Neutropenia	1,077	Non-elective short stay average SA08G-SA08J, Other Haematological or Splenic Disorders
Palmar-plantar erythrodysaesthesia syndrome	1,256	Assumed equal to infection
Thromboembolic events	640	Non-elective short stay average SA12G-SA12JK Thrombocytopenia
Hyperphosphataemia (Grade 2+)	18	One pack of phosphate binders - Renacet 950 mg tablets[109]

NHS, National Health Service.
Source: National Schedule of Reference Costs 2017-2018[104]

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 FGFR testing costs

Until recently, genetic testing for CCA was not part of routine clinical practice, due in part to the incomplete understanding of different genetic phenotypes, in addition to the lack of any targeted therapies. However, with better evidence supporting the key role of FGFR2 and other genetic alterations in the disease biology of CCA, genetic testing is now considered best practice in patient management and treatment planning. The National Genomic Test Directory specifies which genomic tests are commissioned by the NHS in England, which technology is available and the patients eligible for tests. It is likely that FGFR2 for CCA will be included in the next iteration of the Test Directory thus allowing it to be incorporated into standard clinical practice. Therefore, FGFR testing costs were not included in the base case, as these costs apply to all treatment arms. Inclusion of testing costs were tested in scenario analyses and selected for each treatment arm (Table 51). NGS is the gold standard technique for genetic testing, using sequencing panels to detect abnormalities across a wide range of different genes simultaneously (including FGFR). Consultation with several providers including NHS laboratories indicated that the cost of a multi-gene NGS test which can detect FGFR2 fusions varied between £500 and £750. Taking into consideration factors specific to the processing of CCA samples, an approximate cost of £550 was used in scenario analyses. When FGFR testing costs were included, an adjustment was made for the prevalence of FGFR2 fusion positive patients, to effectively incorporate the cost of both positive and negative tests required to treat one additional patient.

Table 51: FGFR testing costs (scenario analysis)

Resource	Unit cost (£)	Source
Test cost	550.00	Clinical consultation
Total	6,395	Calculation, test unit cost divided by FGFR2+ prevalence (8.6%)

FGFR, fibroblast growth factor receptor.

B.3.5.4.2 End of life costs

End-of-life costs were also included in the base case, based on the healthcare and social care costs reported by Round et al.[110] Of the cancer types included in the study (breast, lung, prostate and colorectal), colorectal was deemed to be the most clinically comparable to CCA. Health care costs were inflated to 2019 costs using the Personal Social Services Research Unit inflation indices[111] and were applied to all patients upon entering the death state. These costs are presented in Table 52.

Table 52: End-of-life costs

Terminal care	Cost (£)
Healthcare	5,203
Social care	1,596
Total	6,799

B.3.6. Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Table 53 summarises the base-case analysis inputs used in the model.

Table 53. Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Population parameters			
Body surface area	1.88	1.83 to 1.94 (normal)	Section B.3.3.1
Starting age	55.30	53.02 to 57.58 (normal)	
Proportion male	39%	0.3 to 0.49 (beta)	
FGFR prevalence	8.60%	0.04 to 0.16 (beta)	
Parametric survival distribution parameters			
ToT exponential rate for pemigatinib	[redacted]	Exponential distribution	Section B.3.3.6
PFS log-normal mean log for pemigatinib	1.96	Multivariate distribution	Section B.3.3.5
PFS log-normal SD log for pemigatinib	-0.01	Multivariate distribution	
OS log-logistic shape for pemigatinib	0.54	Multivariate distribution	Section B.3.3.4
OS log-logistic scale for pemigatinib	2.90	Multivariate distribution	
Dosing, dosing costs and treatment regimens			
IV administration cost	£370.68	298.03 to 443.33 (normal)	Section B.3.2.3 and Section B.3.5.1
5-FU follow-up visit	£147.38	118.49 to 176.26 (normal)	
Oral administration cost	£0.00	0 to 0 (normal)	
Weekly administrations pemigatinib	4.67	Fixed	
Weekly administrations ASC	0.00	Fixed	
Weekly administrations 5-FU	1.00	Fixed	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Weekly administrations fluorouracil	0.50	Fixed	
Weekly administrations oxaliplatin	0.50	Fixed	
Weekly administrations calcium folinate	0.50	Fixed	
Administration dose for pemigatinib	13.5	Fixed	
Administration dose for ASC	0	Fixed	
Administration dose for fluorouracil	2800	Fixed	
Administration dose for oxaliplatin	85	Fixed	
Administration dose for calcium folinate	350	Fixed	
Drug acquisition costs	See Table 48	Pemigatinib fixed eMC costs varied using a normal distribution using SD and N for each unit	Section B.3.5.1
RDI for pemigatinib	[redacted]	Fixed value	
Adverse events and HCRU costs			
Adverse event costs	See Table 50	Normal, with SE assumed to be 10% of the mean value	Section B.3.5.3
Frequency of adverse events	See Table 41	Normal, with SE assumed to be 10% of the mean value	Section B.3.3.7
Cost per blood test	£2.79	2.24 to 3.33 (normal)	Section B.3.5.4

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Blood test; progression disease proportion	0.333	0.27 to 0.4 (normal)	
Blood test; progression-free proportion	0.333	0.27 to 0.4 (normal)	
Pain medication: cost per day	5.78	4.65 to 6.91 (normal)	
Pain medication: progression disease frequency	30.4375	24.47 to 36.4 (normal)	
Cost per CT scan	£105.37	84.71 to 126.02 (normal)	
CT scan; progression disease proportion	0.08	0.07 to 0.1 (normal)	
CT scan; progression-free proportion	0.33	0.27 to 0.4 (normal)	
Cost per examination	£194.17	156.11 to 232.23 (normal)	
Cost of palliative care per patient	£6,799.33	5466.69 to 8131.97 (normal)	
Clinical exam; progression disease proportion	0.33	0.27 to 0.4 (normal)	
Clinical exam; progression-free proportion	0.33	0.27 to 0.4 (normal)	
FGFR test; cost per test for biopsy	550	442.2 to 657.8 (normal)	Section B.3.5.4
Adverse event disutilities and duration	See Table 45	Disutilities and duration varied using a beta and normal distribution, respectively, with SE assumed to be 10% of the mean value	Section B.3.4.4

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Health state utilities and treatment administration disutilities			
Utility intercept	[redacted]	[redacted]	Section B.3.4.1
Baseline regression utility	[redacted]	[redacted]	
Utility decrement; post-progression	[redacted]	[redacted]	
Utility decrement; off-treatment	[redacted]	[redacted]	
Utility decrement; post-progression & off treatment	[redacted]	[redacted]	
Utility baseline	[redacted]	[redacted]	
Utility decrement, pemigatinib admin	[redacted]	[redacted]	Section B.3.4.4
Utility decrement, ASC admin	[redacted]	[redacted]	
Utility decrement, mFOLFOX+ASC admin	[redacted]	[redacted]	

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
MAIC adjusted relative treatment effects			
Pemigatinib hazard ratio for OS versus ASC	[redacted]	[redacted]	Section B.2.9 and Section B.3.3
Pemigatinib hazard ratio for OS versus mFOLFOX	[redacted]	[redacted]	
Pemigatinib hazard ratio for PFS versus ASC	[redacted]	[redacted]	
Pemigatinib hazard ratio for PFS versus mFOLFOX	[redacted]	[redacted]	

5-FU, 5-fluorouracil; ASC, active symptom control; CI, confidence interval; CT, computerized tomography; FGFR, fibroblast growth factor receptor; HCRU, healthcare resource use; IV, intravenous; MAIC, matched adjusted indirect comparison; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity; SD, standard deviation; SE, standard error; ToT, time on treatment.

B.3.6.2 Assumptions

A summary of all the model assumptions and justifications is provided in Table 54.

Table 54: Summary of base-case assumptions

Subject	Base-case assumption	Justification
Model settings		
Perspective	NHS and PPS	NICE reference case
Discounting of outcomes	3.5% per annum for costs and effects	NICE reference case
Time horizon	40 years	Lifetime time horizon consistent with NICE reference case.
Efficacy		
Survival hazard ratio for *FGFR2*+ alteration for OS	1 (no difference)	Model assumes no effect of FGFR2 status on OS, due to a lack of prospective, high-quality data. Alternative assumptions are tested in scenario analyses.
Survival hazard ratio for *FGFR2*+ alteration for PFS	1 (no difference)	No significant difference in PFS from Jain et al.[28]
Prevent ToT from exceeding PFS	Yes	As per licence (treatment should continue until disease progression or unacceptable toxicity)[112]
Comparator efficacy	MAIC adjusted relative treatment effects from ABC-06	Best available evidence adjusted for known observed prognostic factors
Pemigatinib survival		
Pemigatinib OS PSM	Log-logistic	See Section B.3.3.4. PSM chosen based on statistical and visual fit to the observed data and clinical plausibility of the extrapolated curve.[66]
Pemigatinib PFS PSM	Log-normal	See Section B.3.3.5. PSM chosen based on statistical and visual fit to the observed data and clinical plausibility of the extrapolated curve.[66]
Pemigatinib ToT PSM	Exponential	See Section B.3.3.6. PSM chosen based on statistical and visual fit to the observed data and clinical plausibility of the extrapolated curve.[66]
ASC survival		
OS	HR for MAIC adjusted relative treatment effects from ABC-06	Best available evidence adjusted for known observed prognostic factors. Log-cumulative hazards suggests proportional hazards assumption is met.
PFS	Assumed equivalent to mFOLFOX+ASC	Simplifying assumption due to lack of available data.
ToT	Assumed equal to ASC PFS	Simplifying assumption due to lack of available data.

Subject	Base-case assumption	Justification
mFOLFOX+ASC		
OS	HR for MAIC adjusted relative treatment effects from ABC-06	Best available evidence adjusted for known observed prognostic factors. Log-cumulative hazards suggests proportional hazards assumption is met.
PFS	HR for MAIC adjusted relative treatment effects from ABC-06	Best available evidence adjusted for known observed prognostic factors. Log-cumulative hazards suggests proportional hazards assumption is met.
ToT	Assumed equal to ASC PFS	Simplifying assumption due to lack of available data.
Utilities		
Apply AE disutilities	Yes	Frequency of data collection in FIGHT-202 unlikely to capture short-term changes in HRQoL. Lack of available HRQoL evidence for comparators requires adjustment for treatment specific toxicities using AE disutilities.
FIGHT-202 regression model specification.	Covariates: baseline utility, treatment status and progression status included	Regression model provided the best statistical fit to the data.
EORTC-QLQ C30 mapping algorithm	Longworth et al. 2014[90]	Identified in the literature as one of the most accurate algorithms and supported by comparisons made using the FIGHT-202 dataset.
Costs		
Apply FGFR testing	No	Considered part of standard clinical practice
Wastage	No wastage included	Comparator costs relatively small and thought to have negligible impact on results. No wastage for pemigatinib expected due to oral administration.

AE, adverse event; ASC, active symptom control; EORTC-QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FGFR, fibroblast growth factor receptor; FGFR2+, fibroblast growth factor receptor 2-positive; HRQoL, health-related quality of life; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; MAIC, matching-adjusted indirect comparison; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; PSM, parametric survival model; ToT, time on treatment.

B.3.7. Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The base case incremental deterministic results are presented Table 55 including a simple discount of [redacted] applied to the list price of £511.36 for pemigatinib. Results indicate that treatment with pemigatinib produces substantial health benefits when

compared to both ASC alone and mFOLFOX+ASC and is close to being considered cost effective when using the NICE willingness to pay threshold of £50,000 for treatments meeting the 'end-of-life' criteria. Results from the cost-effectiveness analysis validate the arguments made in Section B.2.13 that pemigatinib clearly meets the NICE 'end-of-life' criteria—patients on current standard of care are expected to have a life expectancy less than 2 years (0.51 and 0.60 years for ASC and mFOLFOX+ASC, respectively) and the intervention offers an extension to life of at least 3 months or 0.25 years (an incremental 1.82 and 1.73 LYs versus ASC and mFOLFOX+ASC, respectively). Table 56 summarises the base-case pairwise deterministic results vs mFOLFOX+ASC (PAS price).

When comparing mFOLFOX+ASC to ASC alone, mFOLFOX provides small incremental life-year gains (0.09) as a function of the OS HRs derived from the MAIC. In the absence of any published data, PFS was assumed equivalent for the two treatment arms, meaning health benefits were accumulated due to greater time spent in the post-progression health state as is shown in more detail in Section B.3.3.5.2.

Although mFOLFOX + ASC provides more LYs and QALYs than ASC alone, fully incremental analysis revealed that mFOLFOX+ASC is extendedly dominated by pemigatinib since it has a higher incremental cost-effectiveness ratio (ICER) and is less effective. Extended dominance is shown in Figure 34, in which mFOLFOX lies above and to the left of the cost-effectiveness frontier, representing the ICER for pemigatinib versus ASC alone. The fully incremental analysis therefore compared pemigatinib to ASC alone, resulting in an ICER of £61,084. These cost-effectiveness results are subject to parameter and structural uncertainty, which were investigated thoroughly in sensitivity analyses (Section B.3.8).

Figure 34: Cost-effectiveness frontier

ASC, active symptom control; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; QALY, quality-adjusted life year.

Table 55. Base-case fully incremental deterministic results – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ASC	[redacted]	0.51	[redacted]					
mFOLFOX+ASC	[redacted]	0.60	[redacted]	[redacted]	0.09	[redacted]	298,132	Extendedly dominated
Pemigatinib	[redacted]	2.34	[redacted]	[redacted]	1.82	[redacted]	61,084	61,084

ASC, active symptom control; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 56: Base-case pairwise deterministic results versus mFOLFOX+ASC – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
mFOLFOX+ASC	[redacted]	0.60	[redacted]					
Pemigatinib	[redacted]	2.34	[redacted]	[redacted]	1.73	[redacted]	NA	57,315

ASC, active symptom control**;** ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; PAS, patient access scheme; QALYs, quality-adjusted life years.

B.3.8. Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

The probabilistic sensitivity analysis (PSA) involved randomly sampling from the assigned probability distribution for each model parameter. Random samples were drawn simultaneously, and the cost-effectiveness results saved for each iteration. Probabilistic results represent the mean results for a set of iterations, capturing the parameter uncertainty inherent in the economic model. The PSA presented includes 1,000 iterations, at which point the ICER was sufficiently stable (Figure 38).

The model parameters used, their chosen distribution and associated uncertainty are shown in Table 53.

The probabilistic results confirmed the findings of the deterministic analysis, in that mFOLFOX+ASC remained extendedly dominated by pemigatinib, and the pemigatinib ICER, while being slightly reduced, was broadly consistent with that of the deterministic analysis, showing substantial incremental health benefits of [redacted] QALYs and 1.86 life-years gained (Table 57). All results presented include the simple discount of [redacted] applied to the pemigatinib list price with fully incremental (Table 57) and pairwise analysis versus mFOLFOX+ASC (Table 58) presented below.

Table 57: Base case probabilistic results – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ASC	[redacted]	0.51	[redacted]					
mFOLFOX+ASC	[redacted]	0.60	[redacted]	[redacted]	0.09	[redacted]	284,012	Extendedly dominated
Pemigatinib	[redacted]	2.38	[redacted]	[redacted]	1.86	[redacted]	58,856	58,856

ASC, active symptom control; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 58: Base-case pairwise probabilistic results versus mFOLFOX+ASC – PAS price

Technologies	Total costs (£)		Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
mFOLFOX+ASC	[redacted]		0.60	[redacted]					
Pemigatinib	[redacted]		2.38	[redacted]	[redacted]	1.77	[redacted]	NA	55,161

ASC, active symptom control; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; PAS, patient access scheme; QALYs, quality-adjusted life years.

Figure 35 and Figure 36 show PSA results for pemigatinib versus ASC alone and mFOLFOX+ASC, respectively. These figures correspond to the results presented in Table 57. For completeness, the PSA ICER for pemigatinib versus mFOLFOX+ASC is [redacted], although this is considered irrelevant due to extended dominance. Each PSA iteration is shown as a single point, with the mean ICER shown in yellow. The line presented on each scatterplot represents the NICE 'end of life' willingness-to-pay threshold of £50,000. As pemigatinib is close to being cost-effective, a large proportion of iterations fall below the line, indicating instances where pemigatinib would be considered cost-effective. The cost-effectiveness acceptability curve (Figure 37) provides a more quantitative representation of the likelihood of cost-effectiveness indicating that at a willingness-to-pay threshold of £50,000 pemigatinib would be cost-effective [redacted] of the time.

Figure 35: Probabilistic sensitivity analysis of pemigatinib vs ASC

ASC, active symptom control; QALY, quality-adjusted life year.

Figure 36: Probabilistic sensitivity analysis of pemigatinib vs mFOLFOX+ASC

ASC, active symptom control; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; QALY, quality-adjusted life year.

Figure 37: Cost-effectiveness acceptability curve – PAS price

ASC, active symptom control; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; PAS, patient access scheme.

Figure 38: PSA ICER stability

ASC, active symptom control; ICER, incremental cost-effectiveness ratio; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; PSA, probabilistic sensitivity analysis; QALY, quality-adjust life year.

B.3.8.2 Deterministic sensitivity analysis

To identify model parameter values for which cost-effectiveness results were most sensitive a one-way sensitivity analysis (OWSA) was conducted. This analysis took model inputs with known parameter uncertainty and varied them at their upper and lower plausible bounds, considered here to be the 95% CI. Each parameter was varied in isolation and model results recorded at both the upper and lower bound. Where the CI of a parameter was unknown, an estimate was used assuming a standard error of 10% of the mean value. The results of the OWSA are presented as a tornado plot (Figure 39) as well as a table showing the ICER associated with each model parameter (Table 59) evaluating pemigatinib versus ASC alone. The same results are presented for pemigatinib versus mFOLFOX+ASC in Figure 40 and Table 60.

The most influential parameter was the pemigatinib OS HR versus the comparator derived from the MAIC. The HR for PFS also had a noticeable but less significant impact. These parameters reflect the key area of uncertainty in the economic model, the relative treatment effect using the single-arm FIGHT-202 study, and the MAIC analysis informed by the ABC-06 trial. Utility at baseline was also shown to have a considerable impact on the ICER as a higher baseline utility value was associated with a lower ICER for pemigatinib due to a greater QALY gain ([redacted]).

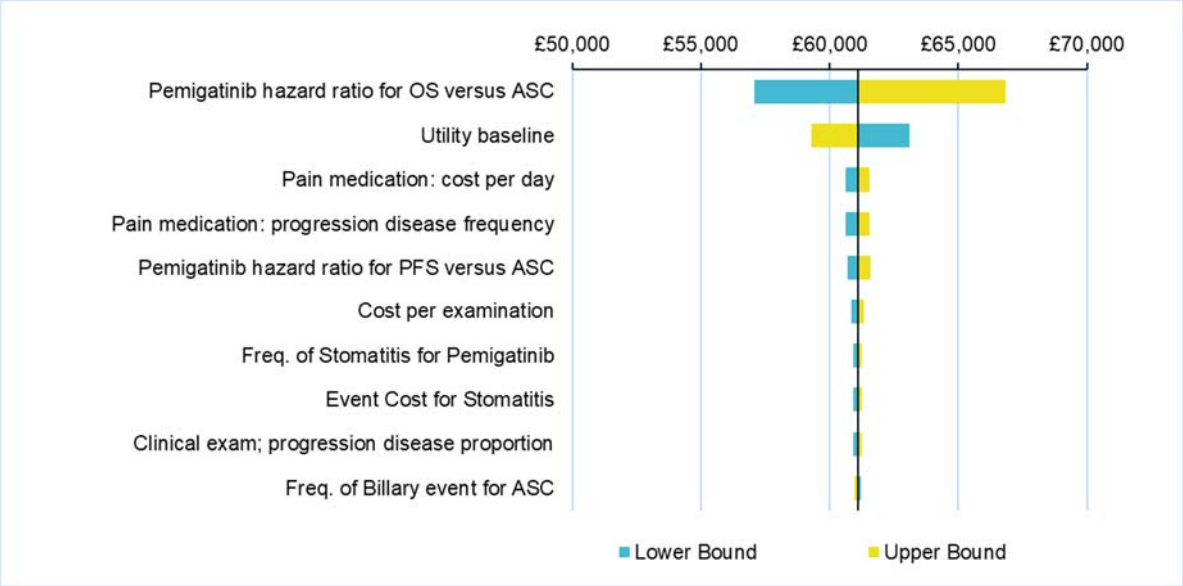


Figure 39: One-way sensitivity analysis tornado diagram, pemigatinib versus ASC alone

ASC, active symptom control; OS, overall survival; PFS, progression-free survival.

Table 59: One-way sensitivity analysis – pemigatinib versus ASC alone

Factor	Lower bound (£)	Upper bound (£)	Difference (£)
Pemigatinib hazard ratio for OS versus ASC	57,086	66,817	9,732
Utility baseline	63,090	59,277	3,812
Pain medication: cost per day	60,636	61,532	896
Pain medication: progression disease frequency	60,636	61,532	896
Pemigatinib hazard ratio for PFS versus ASC	60,703	61,573	870
Cost per examination	60,853	61,315	463
Frequency of stomatitis for pemigatinib	60,908	61,260	351
Event cost for stomatitis	60,912	61,256	345
Clinical exam; progression disease proportion	60,919	61,249	329
Frequency of biliary event for ASC	61,212	60,956	257

ASC, active symptom control; OS, overall survival; PFS, progression-free survival.

When comparing to mFOLFOX the same parameters were shown to affect the ICER the most. Differences included replacement of some costly resource use items that were influential when comparing to ASC alone, with parameters associated with

mFOLFOX treatment, such as the cost of IV administration and the 5-FU follow up visit.

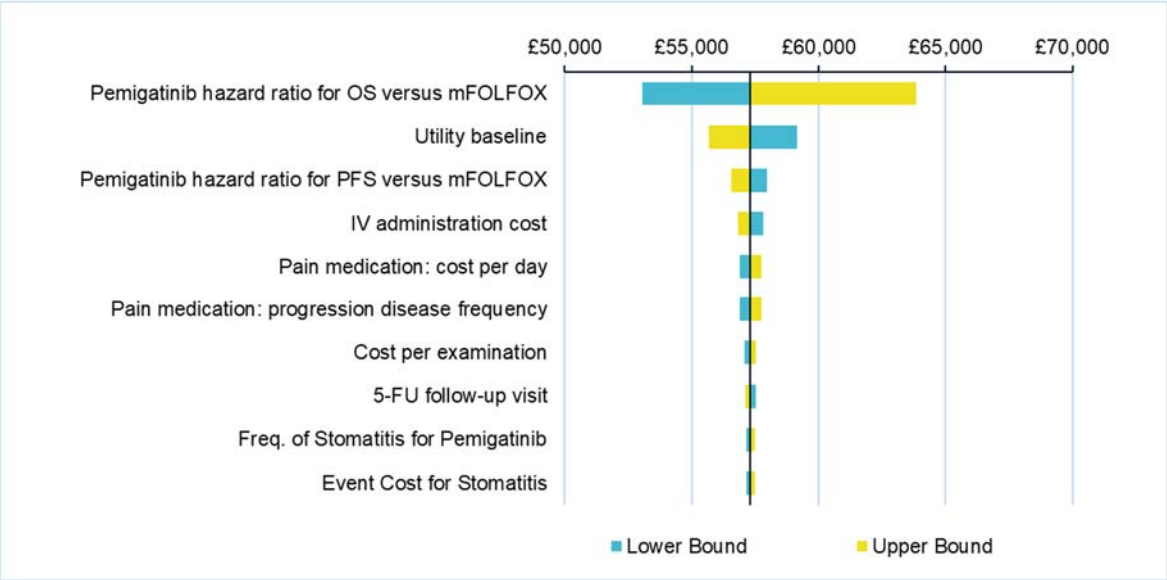


Figure 40: One-way sensitivity analysis tornado diagram, pemigatinib versus mFOLFOX+ASC

ASC, active symptom control; FU, fluorouracil; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; IV, intravenous; OS, overall survival; PFS, progression-free survival.

Table 60: One-way sensitivity analysis, pemigatinib versus mFOLFOX+ASC

Factor	Lower bound (£)	Upper bound (£)	Difference (£)
Pemigatinib hazard ratio for OS versus mFOLFOX	£53,057	£63,856	£10,799
Utility baseline	£59,130	£55,676	£3,454
Pemigatinib hazard ratio for PFS versus mFOLFOX	£57,975	£56,547	£1,427
IV administration cost	£57,823	£56,807	£1,016
Pain medication: cost per day	£56,889	£57,740	£851
Pain medication: progression disease frequency	£56,889	£57,740	£851
Cost per examination	£57,092	£57,538	£447
5-FU follow-up visit	£57,517	£57,113	£404
Frequency of stomatitis for pemigatinib	£57,137	£57,493	£356
Event cost for stomatitis	£57,140	£57,490	£350

ASC, active symptom control; FU, fluorouracil; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; IV, intravenous; OS, overall survival; PFS, progression-free survival.

B.3.8.3 Scenario analysis

To explore the structural assumptions used to inform the economic model, a series of exploratory scenarios were investigated to assess the impact of these assumptions on the cost-effectiveness results. Table 61 presents the scenario analysis results alongside a brief summary of the rationale for why the scenario was explored.

The scenarios with the greatest influence on the results related to the choice of methods used to model survival outcomes (OS, PFS) for both intervention and comparators. In the base case, MAIC adjusted HRs were applied to PSMs fitted to unadjusted pemigatinib survival. Scenario 17 used independent curves fitted to both intervention and comparator OS, using a Weibull distribution in all cases. Doing so increased the ICER by £39,311. A similar result was seen when continuing to use the MAIC HRs for comparator efficacy while switching to the Weibull extrapolation for pemigatinib OS (increase of [redacted]), acknowledging that this extrapolation was considered too pessimistic by clinical experts. Including an adjustment for the potential prognostic effect of FGFR2 also increased the ICER by £5,062. The magnitude of impact on the ICER for FGFR2 was dependent on the FGFR2 prevalence estimate used (Scenarios 9 and 10). Using Weibull independent curve fits for PFS in isolation reduced the ICER noticeably, as did using utilities based on the published literature. All other scenarios had a lesser impact on results.

Table 61: Scenario analysis results

Scenario		ICER of pemigatinib vs		Change from base case pemigatinib vs		Rationale
		ASC (£)	mFOLFOX +ASC (£)	ASC (£)	mFOLFOX +ASC (£)	
1	Base case	61,084	57,315	0	0	
2	A longer time horizon of 50 years	61,065	57,297	-19	-18	Exploration of the impact of longer model duration
3	Costs and benefits are not discounted	54,709	51,401	-6,375	-5,914	Undiscounted results
4	A higher discounting rate of 6% is assumed	64,869	60,810	3,785	3,495	Explore impact of alternative higher discount rate
5	Exclude adverse event utilities	60,891	57,125	-193	-190	Explore impact of AE disutilities
6	Use a utility model excluding treatment	59,598	57,495	-1,486	180	Explore model sensitivity to utility regression analyses used
7	Remove treatment admin disutilities	61,084	57,702	0	387	Explore impact of treatment administration disutility applied to mFOLFOX
8	Use literature values for progression-based utilities	57,172	55,223	-3,912	-2,092	Explore alternative source of health state utilities.
9	Assume FGFR2+ HR adjustment for comparators (all stages Cox model)	66,146	63,410	5,062	6,095	Explore structural assumptions relating to potential prognostic effect of FGFR2
10	Assume FGFR2+ HR adjustment for comparators (all stages Cox model) using prevalence from source (Jain et al)	65,261	62,305	4,177	4,990	Explore structural assumptions relating to potential prognostic effect of FGFR2, varying the prevalence of *FGFR2* genetic alteration
11	Comparator efficacy informed by naïve HRs	63,230	60,131	2,146	2,816	Test estimates of treatment effect unadjusted for prognostic effect
12	Comparator efficacy informed by MAIC HRs, using a Weibull extrapolation for pemigatinib OS	[redacted]	[redacted]	[redacted]	[redacted]	Explore impact on results of using MAIC HRs with alternative more pessimistic extrapolation of pemigatinib OS (Weibull)

13	Comparator efficacy informed by independent PSMs fitted to unadjusted KM	63,100	63,297	2,016	5,982	Explore impact on results of using independent curve fits to unadjusted comparator survival data
14	Survival informed by independent curve fits. Pemigatinib PSMs fitted to KM function adjusted to ASC population (ABC-06)	64,004	64,291	2,920	6,976	Same as Scenario 12, but using pemigatinib survival adjusted to match ASC arm of ABC-06 study
15	Survival informed by independent curve fits. Pemigatinib PSMs fitted to KM function adjusted to mFOLFOX+ASC population (ABC-06)	62,456	62,591	1,372	5,276	Same as Scenario 12, but using pemigatinib survival adjusted to match mFOLFOX arm of ABC-06 study
16	Extrapolate PFS for all treatments using Weibull (unadjusted KM)	55,385	54,852	-5,699	-2,463	Test alternative parameterisations of the PFS curves
17	Extrapolate OS for all treatments using Weibull (unadjusted KM)	100,395	97,124	39,311	39,809	Test alternative parameterisations of the OS curve
18	Extrapolate TOT for pemigatinib using log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	Test alternative parameterisations of the pemigatinib ToT curve
19	Include FGFR2+ testing costs only for pemigatinib	66,416	62,731	5,332	5,417	Explore impact of including FGFR testing costs only for patients treated with pemigatinib

AE, adverse event; ASC, active symptom control; FGFR2+, fibroblast growth factor receptor 2-positive; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; PSM, parametric survival model; ToT, time on treatment.

B.3.8.4 Summary of sensitivity analysis results

Results from the cost-effectiveness analysis demonstrate the substantial health benefits associated with pemigatinib treatment for patients with CCA presenting with FGFR2 fusions or rearrangements. ASC alone was the least effective treatment although mFOLFOX+ASC was extendedly dominated by pemigatinib (i.e., it had a higher ICER but was less effective.

PSA results were consistent with the deterministic analysis results and OWSA demonstrated that parameter uncertainty of model inputs did not drastically impact model results. Scenario analyses are perhaps the most useful to inform decision making, evaluating and exploring key structural assumptions made in the economic model. When using independent curve fits to predict intervention and comparator survival, the ICER was shown to be highly sensitive to the choice of parametric distribution. Incorporating an adjustment for the prognostic effect of FGFR2+ also increased the ICER.

The sensitivity analyses provided both optimistic and conservative alternatives to the base case values and assumptions. However, the base case results, representing what are believed to be the most plausible and robust inputs and assumptions, show that pemigatinib is close to being considered cost effective and that it produces substantial benefits representing a step-change in the management of CCA patients with *FGFR2* fusions or rearrangements.

B.3.9. Subgroup analysis

No subgroup analyses were investigated in the cost-effectiveness model.

B.3.10. Validation

B.3.10.1 Validation of cost-effectiveness analysis

To externally validate the model with clinical and health economic experts, validation meetings were conducted with two practising UK clinicians and two health economics experts. In these meetings, the experts were presented with the key model inputs and methods, and invited to comment on them. These meetings were conducted via teleconference and lasted approximately 2 hours for each expert. The

items validated included the model structure, current clinical practice, survival extrapolations for pemigatinib, relative treatment effect assumptions, the impact of *FGFR2* fusions or rearrangements, monitoring and resource use, safety assumptions and HRQoL inputs.[66]

Internal validation showed that the OS and PFS model results closely reflected the reported medians from the trial publications (Table 62 and Table 63). The underestimation of pemigatinib OS compared with published results is noted but thought to be due to the plateau in the KM function between 16.53 and 21.06 months. The modelled survival reflects a longer term view than the median OS and predicted OS based on the most plausible extrapolations supported by clinical experts.

Table 62: Internal validation – OS

Treatment	Median (months)		
	Literature	Source	Model
Pemigatinib	21.06	FIGHT-202[59]	17.94
mFOLFOX+ASC	6.2	ABC-06[34]	5.98
ASC	5.3		5.06

ASC, active symptom control; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; OS, overall survival.

Table 63: Internal validation – PFS

	Median (months)		
	Literature	Source	Model
Pemigatinib	6.93	FIGHT-202[59]	6.90
mFOLFOX+ASC	4	ABC-06[34]	3.68
ASC	NR		3.68

ASC, active symptom control; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; PFS, progression-free survival.

The cost-effectiveness model was quality-assured using the internal processes of the economists who built the model. As part of these processes, an independent economist reviewed the model for coding errors, inconsistencies and input and assumption plausibility. The model was also reviewed using a checklist of known modelling errors.

B.3.11. Interpretation and conclusions of the economic evidence

The results of the economic model highlight the considerable clinical and economic benefits associated with pemigatinib treatment. The model framework chosen for this economic evaluation is considered to accurately reflect the disease progression of patients with CCA and sufficiently capture the benefits of the improved treatment options. The model includes extensive functionality and supplementary analyses were carried out to investigate key structural assumptions and highlight areas where a large degree of clinical uncertainty remains. The results should be viewed with an acknowledgment of the features of CCA, notably its rarity and the dismal prognosis associated with currently available treatments.

Clinical outcomes for pemigatinib were informed by the single-arm FIGHT-202 study.[29] For the economic model it was important to compare pemigatinib with the most relevant comparators. A significant limitation of this analysis is the lack of published data for alternative treatment options in the population considered in this appraisal—those with *FGFR2* fusion/rearrangement. The ABC-06 study was identified as the best available evidence evaluating ASC alone versus mFOLFOX+ASC, but was in a broader population with clear differences in baseline demographics when compared with the FIGHT-202 study though it should be considered that some patients may have carried a FGFR2 fusion/rearrangement.

To allow estimation of a relative treatment effect, a MAIC analysis was conducted to adjust for observed prognostic factors. The relative treatment effects of pemigatinib compared with comparators for both OS and PFS increased after MAIC adjustments highlighting the differences in observed prognostic factors between the two populations. Use of HRs derived from the MAIC relied on the proportional hazards assumption which was shown to hold for both OS and PFS. HRs were applied to the log-logistic and log-normal PSMs for OS and PFS, respectively. These were considered the most plausible extrapolations by clinical experts.

The ABC-06 study reported robust results for both comparators but there were significant gaps in the available published results. PFS for patients on ASC alone has not been published and therefore was assumed to be equivalent to that of mFOLFOX+ASC. This assumption likely overestimates PFS for ASC and therefore

leads to an underestimation for the benefit of pemigatinib and mFOLFOX when compared to ASC alone.

In addition, no ToT data were reported. For ASC alone this is not considered to be an issue because there are no drug costs. For mFOLFOX, the adopted approach of assuming that the ToT is equivalent to PFS, likely overestimates mFOLFOX drug costs, as some patients like those treated with pemigatinib may discontinue treatment prior to disease progression.

Notwithstanding the limitations due to the trial design of FIGHT-202 and the observed differences between the ABC-06 and FIGHT-202 study populations, a key limitation was that the ABC-06 study investigated a population that was not genetically profiled. The trial did not report the prevalence of patients with *FGFR2* fusions/rearrangements treated with ASC or mFOLFOX+ASC. In Section B.3.3.3 as well as clinical Section B.1.3.1, justification is provided for why adjustment for the effect of FGFR2 on survival outcomes was not included in the base case. There remains substantial clinical uncertainty as to the impact of *FGFR2* alterations on survival outcomes, but with the available published evidence there is no robust support for the causal relationship between *FGFR2* genetic alterations and improved survival outcomes for patients treated with 2L therapies.[28,29] What is clear is that a patient population with *FGFR2* fusions/rearrangements benefit greatly from treatment with an FGFR2-targeted therapy such as pemigatinib when compared with currently available treatment options.

Other limitations of the economic analysis include the paucity of HRQoL data collected using generic preference-based methods such as the EQ-5D-3L. Utility estimates are subject to uncertainty involved in mapping EORTC-QLQ-C30 data to EQ-5D-3L utilities. Health state utilities were also assumed to be the same for all included treatments which given the known toxicities of mFOLFOX may be considered a conservative assumption. The full impact of disease progression on patient HRQoL is also likely underestimated because data were collected for a maximum of one month post-progression in the FIGHT-202 study (Section B.3.4).[59] While estimates from surrogate conditions available from the published literature

were consistent with mapped utilities derived from the FIGHT-202 study further research is required to understand the full impact of CCA on patient HRQoL.

Overall, the results of the cost-effectiveness analysis suggest that, when including the confidential simple discount, pemigatinib is close to being cost-effective and conveys substantial clinical benefits for patients that would otherwise have a particularly poor prognosis when treated with currently available treatment options. The model addresses the significant uncertainty inherent in the economic analysis as well as possible with the available evidence base in this small population, and highlights remaining uncertainty that warrants further investigation: the relative treatment effect of pemigatinib in a real world clinical setting, the role of FGFR2 in predicting survival outcomes in CCA, and the impact of CCA and treatments on patient HRQoL.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

September 2020

File name	Version	Contains confidential information	Date
ID3740 Pemigatinib ERG Clarification company responses_submitted_V2_redacted.docx	2	Yes - redacted	18.09.2020

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Literature searching and references

A1. Priority question – Please provide copies of all studies and other information sources which are cited in the submission, e.g. references 59, 60, 65, 67 (data on file) – In the reference pack provided, these documents contain only the statement 'available on request.' Please also provide copies of all articles listed in appendix D (results of the SLRs, Table 12).

Response: Copies of all studies and sources cited in the submission and all articles listed in Appendix D are provided in along with the company responses to the Clarification Questions.

A2. Please supply a corrected strategy for the search detailed in Table 1, Appendix D, lines #10-#14 appear incorrectly reported.

Response: Please see below for a corrected version of Table 1, Appendix D. A formatting issue affecting lines #10–#14 has now been corrected; the number of hits for each line is unchanged.

Table 1. MEDLINE and Embase search strategy (09 November 2018)

#	Query	Hits
	Disease facet	
1.	'bile duct carcinoma'/exp OR 'bile duct carcinoma'/syn OR 'bile duct carcinoma' OR 'bile duct cancer' OR cholangiocarcinoma OR 'biliary tract cancer'/syn OR 'biliary tract cancer'/exp OR 'biliary tract cancer' OR 'biliary tract carcinoma'	39,381
2.	cholangiocarcinom*	17,772
3.	('bile duct':ab,ti OR 'bile tract':ab,ti OR 'biliary tract':ab,ti) AND (cancer*:ab,ti OR carcinom*:ab,ti OR malignan*:ab,ti OR neoplasm*:ab,ti OR tumor*:ab,ti OR tumour*:ab,ti)	20,132
4.	(('bile duct' OR 'bile tract' OR 'biliary tract') NEAR/2 (cancer* OR carcinom* OR malignan* OR neoplasm* OR tumor* OR tumour*)):ab,ti	7,040
5.	#1 OR #2 OR #3 OR #4	49,375
6.	'stage 3':ab,ti OR 'stage iii':ab,ti OR 'stage 3a':ab,ti OR 'stage iiia':ab,ti OR 'stage 3b':ab,ti OR 'stage iiib':ab,ti OR 'stage3':ab,ti OR 'stageiii':ab,ti OR 'stage 4':ab,ti OR 'stage iv':ab,ti OR 'stage4':ab,ti OR 'stageiv':ab,ti OR metastatic OR metasta*:ab,ti OR advanced OR advanc*:ab,ti OR unresect*:ab,ti OR relap*:ab,ti OR resist*:ab,ti OR refract*:ab,ti OR ((late* NEAR/2 stag*):ab,ti) OR nonresect*:ab,ti OR ((non NEXT/1 resect*):ab,ti) OR inoperable:ab,ti OR 'locally advanced':ab,ti OR 'locally-advanced':ab,ti OR local*:ab,ti OR ((ineligible OR 'in eligible' OR unfit OR 'un fit' OR 'un-fit' OR unsuitable OR 'not amenable' OR unamenable OR inamenable OR unhealthy OR 'not healthy') NEAR/2 surgery)	4,470,185
7.	#5 AND #6	19,955
	Randomized controlled trials (RCTs) search terms	
8.	('clinical trial'/exp OR 'randomized controlled trial'/exp OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR ((randomi?ed NEAR/2 'controlled trial*'):ab,ti) OR rct:ab,ti OR 'random allocation':ab,ti OR 'randomly allocated':ab,ti OR 'allocated randomly':ab,ti OR ((allocated NEAR/2 random):ab,ti) OR ((single NEXT/1 blind*):ab,ti) OR ((double NEXT/1 blind*):ab,ti) OR (((treble OR triple) NEAR/3 blind*):ab,ti) OR placebo*:ab,ti OR 'prospective study'/de) NOT ('case study'/de OR 'case report':ab,ti OR 'abstract report'/de OR 'letter'/de)	2,041,012

Other study design search terms		
9.	'clinical study'/de OR 'case control study'/de OR 'clinical article'/de OR 'clinical trial'/de OR 'community trial'/de OR 'family study'/de OR 'intervention study'/de OR 'longitudinal study'/de OR 'major clinical study'/mj OR 'open study'/de OR 'postmarketing surveillance'/de OR 'prospective study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/exp) OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic* NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	4,657,738
10.	#8 OR #9	5,187,553
Exclusion terms		
11.	(review:it OR 'review literature as topic'/exp OR 'literature review':ti) NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti) OR 'case report*':ab,ti OR 'case series':ab,ti OR ('animal'/exp NOT ('animal'/exp AND 'human'/exp)) OR letter:it OR editorial:it	9,542,276
12.	#10 NOT #11	4,577,721
Combine		
13.	#7 AND #12	6,482

Clinical trials

A3. Priority question – Data provided from the FIGHT-202 study are for the 22nd March 2019 cut-off. Please provide all results for the most recent data cut. If relevant, please also provide an updated CE model based on these updated results.

Response: Incyte Biosciences requested clarification on this question during the clarification meeting on 7 September. At this time, the company was unable to provide data other than that provided from FIGHT-202 as of 22nd March 2019. During the discussion it was proposed that data from a more recent data cut would be provided later during the appraisal process. Timelines are in process of being shared with NICE.

A4. Priority question – Section B.1.3.3 of the submission (unmet need in the treatment of CCA) states that: 'There are no data on the efficacy of second-line (2L) systemic chemotherapy in previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements—the target population of this submission.' Please provide evidence to show that there are no studies which

provide efficacy data second-line (2L) systemic chemotherapy in previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements, i.e. that there are no studies which can provide comparator data for a population comparable to that of the FIGHT-202 study (the target population of this submission).

Response: This statement was meant to reflect that there are no prospective studies on the effect of second-line or above (≥2L) systemic chemotherapy specifically in patients with previous treated, unresectable, locally advanced or metastatic cholangiocarcinoma (CCA) with fibroblast growth factor receptor 2-positive (FGFR2) fusions/rearrangements. We suggest amending this statement to specify the term 'prospective', as two recent published abstracts describe retrospective analyses in patients with previously treated advanced/metastatic CCA with *FGFR2* fusions/rearrangements from clinical trials.[1,2] The relevance of these publications are limited as they were post-hoc, retrospective, analyses of patients within a clinical trial setting. All other published data were limited to retrospective literature reviews and analyses in the first-line (1L) setting with no published data on progression-free survival (PFS) or overall survival (OS) in CCA patients with *FGFR2* fusions/rearrangements in the ≥2L setting.

Overall, limitations of these retrospective studies relate to differing definitions of survival time, enrolment of patients outside CCA or, more specifically, intrahepatic CCA, and recruitment of patients in different stages of their disease journey, as well as data limited to reference centres that can have inherent selection bias.

A5. Priority question – Given that the comparator study used in the MAIC does not report the FGFR mutation status of participants, please provide evidence to demonstrate that the efficacy of second line systemic chemotherapy does not vary with FGFR mutation status.

Response: There are no published, prospective data to date that have assessed the efficacy of chemotherapy in *FGFR*-altered CCA, either in 1L or ≥2L settings. Published data are limited to retrospective literature reviews and analyses.

In the ≥ 2L setting, a retrospective study of 37 patients with *FGFR2* fusions treated with another FGFR inhibitor (NCT02150967), showed that outcomes from ≥2L

chemotherapy in patients with CCA and *FGFR2* fusions before entering the trial were similar to those reported in the literature for all patients with CCA regardless of genomic status and remain dismal. Median PFS with standard 2L chemotherapy was 4.63 months and best objective response was 5.4%.[2] These data align with the results reported in the ABC-06 study where median PFS was 4.0 months (95% CI 3.2-5.0) and the best response (complete response and partial response) rate was 5%.[3]

A6. Priority question – The only reference provided for trial ABC-06, the comparator study used in the MAIC, is a conference presentation (reference 34 in the CS). Please confirm that this presentation was the only source of data for this study or provide copies of all data sources used.

Response: We confirm this presentation was the only published and/or available source of data for the ABC-06 trial[3] and was the only source of data used in the matching-adjusted indirect comparison (MAIC). Incyte understands that this status has not changed at the time of clarification

A7. Please confirm the number of participants in FIGHT-202 who were from the UK? Information in the CSR suggests six.

Response: A total of six patients (n=6/145; 4.1%) in FIGHT-202 were from the UK. All six patients were in Cohort A (n=6/107; 5.6%).[4]

A8. Regarding the results of the original SLR (Appendix D 1.3.1): Please confirm that you are not aware of any comparative studies assessing the clinical efficacy of pemigatinib (or any other FGFR2 inhibitor) vs. chemotherapy or best supportive care, for second or later-line treatment of advanced or metastatic FGFR2+ CCA.

Response: We confirm that the SLRs conducted for the NICE submission did not reveal any comparative studies assessing the clinical efficacy of pemigatinib (or any other FGFR2 inhibitor) vs chemotherapy or best supportive care for ≥2L treatment of advanced of metastatic *FGFR2*+ CCA.

A9. Of the studies listed in Appendix D of the submission (Table 12 Citations included in the final evidence base reporting rrCCA data, updated SLR), at least two appear to concern the efficacy of second-line (2L) systemic chemotherapy in

previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements (the target population of this submission):

- Bibeau et al. 2020. Progression-free survival in patients with cholangiocarcinoma with FGFR2 fusions or rearrangements: An exploration of response to systemic therapy.

- Milind et al. 2020. A retrospective analysis of post second-line chemotherapy treatment outcomes for patients with advanced or metastatic cholangiocarcinoma and FGFR2 fusions.

Please explain why these, and any similar studies, were not used to provide comparator data for the submission.

Response: Please note that the entry 'Milind et al. 2020' refers to Javle et al. 2020.[2] We have corrected this entry in Table 12 on page 39 of the appendices to the NICE submission. Relevant comparator data and clinical evidence for the submission were identified by SLR. To avoid duplication, multiple publications of a single trial have been grouped as one complete study. As such, data from Bibeau et al. 2020[1] is included with Abou-alfa et al. 2020,[5] while data from Javle al. 2020[2] is included with Javle et al. 2018.[6] The relevant extracted data from these studies in the 2L+ treatment of *FGFR2*+ CCA can be found in Tables 15 (Response rate of non-randomised controlled trials [RCT] and observational studies) and 16 (Survival outcomes of non-RCT and observational studies) of the SLR.

Bibeau et al. 2020 and Javle et al. 2020 are both retrospective analyses of single-arm studies and therefore, lack the robustness of an RCT such as ABC-06. Inadequate data were reported from these abstracts, and they represent a limited risk as they are broadly in line with ABC-06.

Data from these studies were not included in the NICE appendices, which only included studies relevant from a MAIC perspective.

A10. Please provide details of the method used to determine FGF/FGFR mutation status in the FIGHT-202 study: e.g. specify which mutations were included in each cohort; what was the limit of detection (i.e. the minimum percentage of mutation in tumour cells required to produce a positive result). Please also provide an indication

of whether or not the test used in FIGHT-202 is currently available/used in the UK NHS, and whether any alternative tests used in the UK NHS share the same operating characteristics.

Response: Archival, formalin-fixed, paraffin-embedded tumour samples from all pre-screened or enrolled patients in FIGHT-202 were analysed for genomic alterations using the FoundationOne® targeted next-generation DNA sequencing assay (Foundation Medicine Inc.), which uses hybrid capture–based DNA target enrichment to identify somatic genomic alterations in the coding regions of 315 cancer-related genes and introns from 28 genes often rearranged in cancer. The sensitivity of this assay for the detection on gene rearrangements was >90% for samples with ≥20% tumour content.

In FIGHT-202 patients were assigned to one of three cohorts based on their *FGFR* alteration status. Cohort A included patients with *FGFR2* fusions or rearrangements only, cohort B included patients with other *FGF/FGFR* pathway alterations (such as *FGF/FGFR* or *FRS2* amplification or *FGFR2* mutations) and cohort C included patients with no *FGF/FGFR* pathway alterations.[5]

Whilst the FoundationOne® assay itself is not available/used in the UK NHS, genomic testing with next-generation sequencing (using similar assays) is commonplace and used extensively throughout the NHS as a diagnostic tool in cancer. Testing for genetic alterations such as EGFR, ALK, BRAF, RET and ROS1 and others is commonplace in diseases such as non-small cell lung cancer and melanoma. In addition to the FoundationOne® assay, there are a variety of commercially available assays that can detect *FGFR2* fusions (e.g. Illumina TSO500, ArcherDX FusionPlex, and other locally developed tests), thus the detection of FGFR2 fusions for CCA may use the same technology as is current standard of care for these cancers.

A11. Please provide the median (range) duration of treatment with pemigatinib for each of the cohorts studied in FIGHT-202.

Response: The range and duration of treatment with pemigatinib for each cohort studied in the FIGHT-202 study are provided in Table 2.

Table 2. Summary of pemigatinib exposure (Safety Population)

Variable	Pemigatinib 13.5 mg once daily (QD) on a 14 days-on/7 days-off schedule				
	Cohort A (n=107)	Cohort B (n=20)	Cohort C (n=18)	Undetermined (n=1)	Total (n=146)
Duration of exposure (days)					
Mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	219.0	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	7, 730	[redacted]	[redacted]	[redacted]	[redacted]

NA, not applicable.
Source: FIGHT-202 CSR (page 42).[4]

A12. Section B.2.7 of the submission states: 'There were no pre-specified subgroup analyses based on baseline demographics and characteristics.' However, Figure 10 provides the results of subgroup analyses for the primary outcome ORR. Please clarify whether any further subgroup analyses were undertaken (secondary outcomes) and provide results for all such analyses.

Response: This was reported in error. The following subgroup-analyses were specified as exploratory:

Exploratory subgroup analyses of objective response rate (ORR; Figure 1) and PFS ([redacted]), both based on IRC assessment, and of duration of response (DOR; assessed by baseline renal impairment grade and baseline hepatic impairment grade) for participants in Cohort A were performed to assess the consistency of the pemigatinib treatment effect.

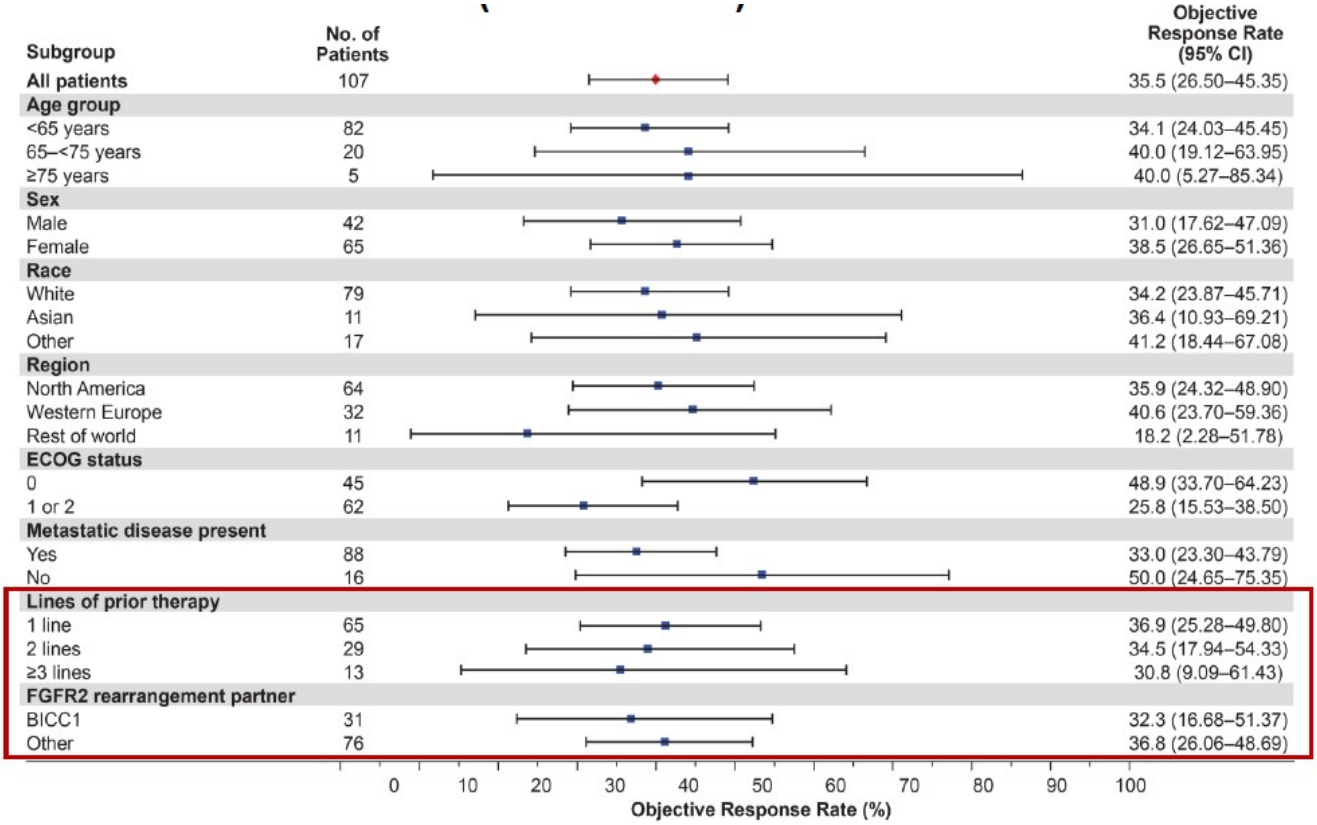

Figure 1. ORR by subgroup (Cohort A)

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FGFR2, fibroblast growth factor receptors 2.

Note: Cohort assignment is based on tumour FGF/FGFR status from the central genomics laboratory laboratory: Cohort A: *FGFR2* fusions/rearrangements

Note: Other races include Black or African American, Hispanic, Latino, or Spanish, not reported, or missing. Rest of World includes Israel, Japan, South Korea, Taiwan, and Thailand.

Source: Abou-Alfa et al. 2020[5]

[redacted]

Figure 2. PFS by subgroup (Cohort A)

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FGFR2, fibroblast growth factor receptors 2; PFS, progression-free survival.

Note: Cohort assignment is based on tumour FGF/FGFR status from the central genomics laboratory laboratory: Cohort A: *FGFR2* fusions/rearrangements

Note: Other races include Black or African American, Hispanic, Latino, or Spanish, not reported, or missing. Rest of World includes Israel, Japan, South Korea, Taiwan, and Thailand.

Source: FIGHT-202 CSR, page 55.[7]

In Cohort A, median DOR was consistent across baseline renal and hepatic impairment subgroups. The 95% CIs of DORs of the participant groups within the subgroups overlapped the 95% CI for all Cohort A participants (see [redacted] and [redacted]). Within each subgroup, the 95% CIs of complementary participant groups overlapped.

Table 3. Summary of DOR by baseline renal impairment grade based on IRC assessment according to RECIST v1.1 (Cohort A, Efficacy Evaluable Population)

Variable	Pemigatinib 13.5 mg once daily (QD) on a 14 days-on/7 days-off schedule		
	Renal Impairment Grade		
	[redacted]	[redacted]	[redacted]
Number (%) of participants with confirmed objective responses	[redacted]	[redacted]	[redacted]
Number (%) of participants with events	[redacted]	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Number (%) of participants censored	[redacted]	[redacted]	[redacted]
Median duration of response (months) (95% CI)[a]	[redacted]	[redacted]	[redacted]
Kaplan-Meier estimates of duration of response (95% CI)			
3 months	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]

CI, confidence interval; NE, not estimable.

Note: Cohort assignment is based on tumour FGF/FGFR status from the central genomics laboratory laboratory:

Cohort A: *FGFR2* fusions/rearrangements.

Note: Data are from IRC per RECIST v1.1, and complete and partial responses are confirmed.

[a]The 95% CI was calculated using the Brookmeyer and Crowley's method (1982)

Source: FIGHT-202 CSR, page 56.[4]

Table 4. Summary of DOR by baseline hepatic impairment grade based on IRC assessment according to RECIST v1.1 (Cohort A, Efficacy Evaluable Population)

	Pemigatinib 13.5 mg once daily (QD) on a 14 days-on/7 days-off schedule		
	Hepatic Impairment Grade		
Variable	[redacted]	[redacted]	[redacted]
Number (%) of participants with confirmed objective responses	[redacted]	[redacted]	[redacted]
Number (%) of participants with events	[redacted]	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Number (%) of participants censored	[redacted]	[redacted]	[redacted]
Median duration of response (months) (95% CI)[a]	[redacted]	[redacted]	[redacted]
Kaplan-Meier estimates of duration of response (95% CI)			
3 months	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]

CI, confidence interval; NE, not estimable.

Note: Cohort assignment is based on tumour FGF/FGFR status from the central genomics laboratory laboratory:

Cohort A: *FGFR2* fusions/rearrangements.

Note: Data are from IRC per RECIST v1.1, and complete and partial responses are confirmed.

[a]The 95% CI was calculated using the Brookmeyer and Crowley's method (1982)
Source: FIGHT-202 CSR, page 56.[4]

A13. The adverse reactions section of the submission (section B.2.10) includes a number of citations of 'data on file'. Please provide copies of the source information for all adverse events data reported in the submission**.**

Response: Copies of all studies and sources cited in the submission are provided in along with the company responses to the Clarification Questions.

A14. The safety population (described in section B.2.4.1 of the submission) appear to be derived from a number of studies, in addition to FIGHT-202, i.e. FIGHT-101, FIGHT-102, FIGHT-201 and FIGHT-203, which are not listed as relevant studies and for which no CSRs are provided. Please provide study details and CSRs for all studies which have contributed data to the submission.

Response: Copies of these CSRs are provided in along with the company responses to the Clarification Questions. The All Cholangiocarcinoma population comprises.

Exposure and safety results for two pooled populations are described:

- The Cholangiocarcinoma Population (n=161) includes participants in the modified safety population with cholangiocarcinoma, regardless of FGF/FGFR molecular alteration status, who were treated with pemigatinib as monotherapy.
- The All Cancer Population (n=466) includes participants in the modified safety population with advanced malignancies who were treated with pemigatinib as monotherapy.

Treatment groups summarised for each of these populations are detailed in Table 5.

Table 5.Treatment Groups for Pooled Analyses

Pooled Population	Studies	Treatment Groups (Columns in Tables)	Notes
Cholangiocarcinoma Population	INCB 54828-101 INCB 54828-102 INCB 54828-202	13.5 mg ID Other doses Total	Other doses = 9 mg ID, 20 mg ID, 13.5 mg CD, and 20 mg CD
All Cancer Population	INCB 54828-101 INCB 54828-102 INCB 54828-201 INCB 54828-202 INCB 54828-203	<13.5 mg ID 13.5 mg ID >13.5 mg ID Subtotal ID <13.5 mg CD 13.5 mg CD >13.5 mg CD Subtotal CD Total	<13.5 mg ID = 1, 2, 4, 6, and 9 mg ID >13.5 mg ID = 20 mg ID <13.5 mg CD = 9 mg CD >13.5 mg CD = 20 mg CD

ID, intermittent dose (once daily [QD] on a 14 days-on/7 days-off schedule); CD, continuous dose (QD).

Analyses of safety data for the Cholangiocarcinoma Population are primarily intended to support the results for Study FIGHT-202. Evaluation of the safety data for this slightly larger pool of participants with CCA increases the likelihood of identifying less common potentially important events while also accounting for exposure duration (i.e., excluding participants with inadequate exposure to meaningfully evaluate safety).

The All Cancer Population represents the largest pool of data from participants with advanced malignancies receiving pemigatinib monotherapy. Evaluation of safety data for this pool increases the likelihood of identifying less common potentially important events while also accounting for exposure duration and provides information about the safety profile of pemigatinib across all dose regimens and cancer diagnoses evaluated as of the data cutoff dates.

A15. Appendix D.1.6.1 The choice of trials for inclusion in the MAIC: How many studies identified in the SLR were excluded because of missing Kaplan-Meier data alone, i.e. studies which met all other listed criteria for inclusion in the MAIC.

Response: Of the 108 studies identified in the SLR, 77 were excluded as they did not report a Kaplan–Meier (KM) plot for both OS and PFS (Figure 3, Appendix D in CS). Of these 77 studies, eight reported an OS curve only and four reported a PFS curve only (these 12 studies are discussed further in question A18). The remaining 65

studies did not report KM data for either OS or PFS, and are deemed not useable for MAIC purposes since the KM is required to generate pseudo patient level data.

- 37/65 of these studies did not have a sample size >20. They were excluded as they did not meet the original criteria, leaving 28 studies for consideration
- 14/28 of these studies reported no descriptive summary of OS or PFS (eg, mean or median). They were excluded as they provide no informative efficacy information, leaving 14 studies
- 8/14 of these studies did not include a standard of care treatment, leaving six studies that met the initial criteria for the MAIC (Table 6).

Table 6. Studies that do not report an OS or PFS KM curve but met all other listed criteria for inclusion in the MAIC

Study	N	Intervention	FGFR2+ %	Age, median (range)	Men %	Intra-hepatic %	ECOG 0–1 %
Sebbagh 2014[8]	34	FOLFIRI	NR	NR	55.9	NR	NR
Poggi 2009[9]	20	Oxaliplatin eluting microsphere TACE (OEM-TACE) + ChT (oxaliplatin + gemcitabine)	NR	NR	33.3	100	NR
Sinn 2013[10]	37	Hepatic Arterial Infusion with Oxaliplatin and 5-FU/Folinic Acid	NR	NR	NR	NR	NR
Larsen 2018[11]	48	Capecitabine + Irinotecan + Gemcitabine + Bevacizumab	NR	66 (34–83)	45.8	60.4	100
Brandi 2011[12]	49	Gemcitabine ± (platinum compound / capecitabine / irinotecan)	NR	NR	NR	51.02	NR
Buyuksimsek 2020[13]	53	Gemcitabine + Oxaliplatin	NR	66 (35–81)	60.2	43.4	79.3

Evidence synthesis and meta-analysis

A16. Please provide evidence of the adverse event rates for the comparator(s) considered in the MAIC.

Response: MAICs for adverse events (AEs) were not conducted. Instead, the MAICs focussed on the clinical outcomes of OS and PFS.

A17. Section B.2.9 of the submission includes a list of key differences in baseline participant characteristics between FIGHT-202 and ABC-06:

- FIGHT-202 was a phase 2, single-arm clinical trial, whereas ABC-06 was a randomised phase 3, multicentre, open-label study
- FIGHT-202 was a multinational study, whereas ABC-06 was based in the UK
- ABC-06 investigated all BTCs, whereas the population of FIGHT-202 investigated patients with advanced/metastatic or surgically unresectable CCA who had progressed on at least one line of prior systemic therapy and included a majority of patients with iCCA
- Cohort A of FIGHT-202 included only patients with FGFR2 fusions or rearrangements; the proportion of patients with these mutations was not reported in ABC-06

Given point 2, above, please provide a justification for the selection of the ABC-06 study for use in MAIC based on its inclusion of only UK patients (as indicated in appendix D of the submission, page 54).

Response: An SLR was performed to identify comparator studies. For the efficacy of pemigatinib in patients with advanced CCA with *FGFR2* fusions or rearrangement that is relapsed or refractory after at least one prior systemic therapy, FIGHT-202 is the only relevant study. Acknowledging that there is no comparator study identified in the SLR that perfectly matches the pemigatinib target population, ABC-06 was deemed by clinicians as the most appropriate study for reflecting standard of care for these patients in England and for MAICs.[14] Since the treatment and patient population in ABC-06 is most likely to match the standard of care and patient profile in the UK compared to the other six originally identified studies (Table 14, Appendix D in CS), this was deemed the most suitable comparator study for this decision problem. In addition, ABC-06 was an RCT, whereas four of the other six studies were retrospective studies. As such, ABC-06 is likely to provide a higher quality of evidence. One of the differences between FIGHT-202 and ABC-06 (as well as the other final six studies that met the initial inclusion criteria) was that it included patients from a single country, whereas FIGHT-202 was a multinational study.

Overall, it is considered that ABC-06 is the most suitable study to perform MAICs for this decision problem. However, additional MAICs have been performed on other sources of evidence and used as sensitivity analyses within the CE model (see questions A18 and A19).

A18. Priority question – Appendix D.1.6.1 The choice of trials for inclusion in the MAIC , lists the criterion: 'Availability of Kaplan–Meier plots for OS and PFS (must have both as they are needed to derive the PLD needed for MAICs)'. Were any studies excluded because they only provided Kaplan–Meier plots for either OS or PFS or only reported response rates? If yes, please provide a revised MAIC, using separate data sources for PFS and OS, so that data from all relevant studies are utilised.

Response: From the SLR, there were eight studies that reported an OS curve only and four studies reported a PFS curve only. These were previously excluded from consideration of the MAIC since a hazard ratio (HR) for both OS and PFS is required in the model, and it was considered appropriate to use the same data source to inform both model inputs. Of the 12 studies only reporting a KM curve for one of either OS or PFS:

- 4/12 of these studies did not have a sample size >20 and were excluded as they did not meet the original criteria, leaving eight studies for consideration
- 4/8 of these studies did not include a standard of care treatment, leaving four studies for consideration
- 1 study (Moik 2019)[15] had a very low number of patients with intrahepatic CCA (34%), whereas FIGHT-202 has 98%, so this study was not considered sufficiently comparable to FIGHT-202
- 1 study (Kang et al 2014)[16] had a very low number of patients with ECOG 0–1 performance status (66%), whereas FIGHT-202 had 95%, so this study was not considered comparable to FIGHT-202

The remaining two studies (Lowery 2019[17] and Schweitzer 2019),[18] each have one treatment arm investigating chemotherapy. Both reported a KM for OS only and were deemed suitable to perform MAICs for sensitivity analyses. However, differences in

the two studies that made them a less appropriate comparison than that between FIGHT-202 and ABC-06, should be acknowledged. Both were retrospective studies which may indicate the studies are subject to incomplete data and possible biases (as discussed in Schweitzer 2019).[18] Lowery 2019[17] only included patients from the US and Schweitzer 2019[18] only included patients from Germany so are less likely to represent UK patients, than ABC-06.

The same matching covariates were used to ensure consistency between this analysis and the analyses presented in the CS, but neither study reported albumin and Lowery 2019[17] did not report ECOG, so the matching covariates used were age, sex, and ECOG (Schweitzer 2019 only).[18] Table 7 presents the baseline characteristics of the pemigatinib arm from FIGHT-202 (unadjusted and weighted) and the resulting effective sample size (ESS) of the comparisons.

Table 7. Comparison of baseline characteristics – pemigatinib (FIGHT-202) unadjusted and weighted

Treatment (study)	N/ESS	Mean age (years)	Male (%)	ECOG PS 0–1 (%)
Pemigatinib unadjusted (FIGHT-202)	107.0	55.3	39.3	95.3
Pemigatinib weighted to SoC (chemotherapy, Lowery 2019)	79.0	62.0	43.4	NR
Pemigatinib weighted to SoC (chemotherapy, Schweitzer 2019)	68.0	59.6	56.9	83.6

Table 8 presents the results of the unadjusted and weighted hazard ratios for OS for all comparators, including ABC-06.

Table 8. Hazard ratios for OS – pemigatinib (FIGHT-202) vs all comparators

Comparison	Study	Endpoint	Unadjusted hazard ratio (95% CI)	Weighted hazard ratio (95% CI)
Pemigatinib vs mFOLFOX+ASC	ABC-06	[redacted]	[redacted]	[redacted]
Pemigatinib vs ASC	ABC-06	[redacted]	[redacted]	[redacted]
SoC (chemotherapy)	Lowery 2019	[redacted]	[redacted]	[redacted]
SoC (chemotherapy)	Schweitzer 2019	[redacted]	[redacted]	[redacted]

A19. Priority question – Appendix D of the submission (Table 14) lists seven studies which met the inclusion criteria specified for the MAIC (D.1.6.1). Each of these studies evaluated a different chemotherapy regimen. Given that section B.1.3.3 of the submission argues (with supporting evidence) that there is currently no SOC for second line chemotherapy for patients with advanced CCA, please provide a revised MAIC, including all studies which met the inclusion criteria specified for the MAIC (D.1.6.1). With reference to question A18, such studies might not have been conducted solely in the UK.

Please also provide an updated version of the model that allows for the selection of revised or alternative MAIC results to be incorporated into the CE analysis.

Response: As discussed in question A17, we believe that ABC-06 is the most suitable study to perform MAICs for this decision problem, but we have assessed the suitability of the other six studies (Table 14, Appendix D in CS) and performed some additional MAICs (in addition to those presented in A18).

Upon further investigation of the publications, the following studies were not considered appropriate for the MAIC:

- The retrospective study by Croitoru et al 2012 focused on first-line patents and reported baseline characteristics at first line, rather than second line (but reported KMs for second line OS and PFS).[19] As KMs were reported for second line OS and PFS, it would not be possible to match to the previously-treated population

- The Rogers et al. 2014 study was made up of four arms, each of which had low patient numbers (11, 16, 21, and 8).[20] As such, criteria for sample size, one of the initial MAIC inclusion criteria, were not met. Additionally, the baseline characteristics were only reported for the overall population and not per arm

- The Belkouz et al. 2020 study had a very low number of patients with intrahepatic CCA (16.7%),[21] whereas FIGHT-202 had 98%.[5] This study was not considered sufficiently comparable to FIGHT-202

- The Westin et al. 2017 study had a very low number of patients with ECOG 0–1 performance status (64%),[22] whereas FIGHT-202 had 95%.[5] This study was also considered not sufficiently comparable to FIGHT-202

The remaining two studies (Kim et al. 2017[23] and Zheng et al. 2018)[24], each with two treatment arms, were deemed suitable to perform MAICs for sensitivity analyses (acknowledging the differences highlighted in the CS; Kim et al. 2017 was a retrospective study and included patients from Korea only, and Zheng et al. 2018 included patients from China only. Both are less likely to represent UK patients and their treatment than ABC-06).

The same matching covariates were used to ensure consistency between this analysis and the analyses presented in the CS, but neither study reported albumin, so the matching covariates used were age, sex, and ECOG. Table 9 presents the baseline characteristics of the pemigatinib arm from FIGHT-202 (unadjusted and weighted) and the resulting ESS of the comparisons.

Table 9. Comparison of baseline characteristics – pemigatinib (FIGHT-202) unadjusted and weighted

Treatment (study)	N/ESS	Mean age (years)	Male (%)	ECOG PS 0–1 (%)
Pemigatinib unadjusted (FIGHT-202)[5]	107.0	55.3	39.3	95.3
Pemigatinib weighted to SoC (fluoro mono, Kim 2017)[23]	82.8	60.0	57.3	91.3
Pemigatinib weighted to SoC (fluoro+platinum, Kim 2017)[23]	82.8	60.0	57.3	91.3
Pemigatinib weighted to SoC (IRI, Zheng 2018)[24]	81.2	55.0	63.3	100.0
Pemigatinib weighted to SoC (XELIRI, Zheng 2018)[24]	92.4	54.0	53.0	100.0

Table 10 presents the results of the unadjusted and weighted hazard ratios for OS and PFS for all comparators, including ABC-06. These HRs (along with those reported in response to A18) have been implemented as scenarios in the updated cost-effectiveness model, under switches C150, C152, C154, and C156 in the Controls tab. The cost-effectiveness results of these scenarios are presented in Table 22.

Table 10. Hazard ratios for OS and PFS – pemigatinib (FIGHT-202) vs all comparators

Comparison	Study	Endpoint	Unadjusted hazard ratio (95% CI)	Weighted hazard ratio (95% CI)
Pemigatinib vs mFOLFOX+ASC	**ABC-06[3] (n=81)**	[redacted]	[redacted]	[redacted]
Pemigatinib vs ASC	**ABC-06[3] (n=81)**	[redacted]	[redacted]	[redacted]
Pemigatinib vs SoC (fluoro mono)	**Kim 2017[23] (n=255)**	[redacted]	[redacted]	[redacted]
SoC (fluoro+ platinum)	**Kim 2017[23] (n=66)**	[redacted]	[redacted]	[redacted]
SoC (IRI)	Zheng 2018[24] (n=30)	[redacted]	[redacted]	[redacted]
SoC (XELIRI)	Zheng 2018[24] (n=30)	[redacted]	[redacted]	[redacted]
Pemigatinib vs mFOLFOX+ASC	**ABC-06[3] (n=81)**	[redacted]	[redacted]	[redacted]
Pemigatinib vs ASC	**ABC-06[3] (n=81)**	[redacted]	[redacted]	[redacted]
Pemigatinib vs SoC (fluoro mono)	**Kim 2017[23] (n=255)**	[redacted]	[redacted]	[redacted]
SoC (fluoro+ platinum)	**Kim 2017[23] (n=66)**	[redacted]	[redacted]	[redacted]
SoC (IRI)	Zheng 2018[24] (n=30)	[redacted]	[redacted]	[redacted]
SoC (XELIRI)	Zheng 2018[24] (n=30)	[redacted]	[redacted]	[redacted]

A20. Priority question – Section B.1.3.1 of the submission includes a section on the prognostic role of FGFR alterations. A study is described (Jain et al. 2018) in which 74/377 (19.6%) participants had FGFR2 alterations. This is consistent with the rate of FGFR mutations (20%) in CCA given on page 16, section B.1.3.1 of the submission. Participants in Jain et al.2018 with FGFR mutations had longer overall survival times, even after exclusion of those treated with FGFR inhibitors, than those with wild type CCA (30 months vs. 20 months). In the FIGHT-202 study, 107/146 (73.3%) of participants had FGFR2 alterations. The comparator study, selected for use in the MAIC, (Lamarca 2019) does not report the proportion of participants with FGFR2 alterations, however, as there were no inclusion criteria relating to FGFR mutation status or testing it may be reasonable to assume that the prevalence of FGFR2 alterations in this study would be similar to that expected for the CCA

population. Given the apparent increased OS in patients with FGFR mutations, irrespective of treatment, could the company please confirm that survival in the comparator study is likely to be an underestimate of what would be observe in clinical practice for the index population i.e. only those with FGFR2 alterations.

Response: There are no published prospective data to date that have assessed the efficacy of chemotherapy in *FGFR*-altered CCA, either in the 1L or ≥2L setting. The natural history of CCA with *FGFR* alterations and the prognostic role of such alterations are not fully characterised. To date, there are no published prospective studies that have assessed the prognostic role or the predictive impact of those alterations to chemotherapy. Published data are limited to retrospective literature reviews and analyses in the first-line setting with no published data on PFS or OS in patients with *FGFR2*-rearranged CCA in the ≥2L setting.

These retrospective studies have suggested that *FGFR* alterations (predominantly *FGFR2* fusions/rearrangements), contrary to the general CCA population, appear to occur more frequently in younger women and seem to confer a more indolent but chemo-insensitive disease status.[25-27] Limitations of these retrospective studies relate to differing definitions of survival time, enrolment of patients outside CCA or, more specifically, intrahepatic CCA, and recruitment of patients in different stages of their disease journey, as well as data limited to reference centres that can have inherent selection bias.

Jain et al (2018)[26] conducted a retrospective analysis of 377 patients with CCA, including 95 patients with *FGFR* molecular alterations (63 of whom had *FGFR2* fusions), and showed that patients with *FGFR* molecular alterations not treated with an FGFR inhibitor had a longer median OS from the time of initial diagnosis than patients without FGFR molecular alterations (30 versus 20 months, respectively; p<0.003). Median PFS for the subset of patients who received 1L chemotherapy for disease (31 patients with *FGFR* molecular alterations and 146 patients without *FGFR* molecular alterations) showed a non-significant result of 7.8 and 5.8 months, respectively (p=0.074). Furthermore, in a related updated analysis, differences between PFS in patients with tumours harbouring *FGFR2* fusions and those without *FGFR2* fusions were not statistically significant (6.0 vs 6.0 months, hazard ratio [HR] 1.19, p=0.36).[28] Although cross-trial comparisons are not recommended, compared

to historical data in the 1L setting, it seems that CCA patients with *FGFR2* fusions may respond similarly to chemotherapy or even worse than unselected biliary tract cancer (BTC) population, supporting the notion that these patients may benefit from a targeted treatment, based on the data from FIGHT-202.[5]

The hypothesis that *FGFR2*-rearranged CCA may benefit similarly or less from chemotherapy compared to non-*FGFR2* rearranged CCA was replicated in another retrospective study conducted by Boileve et al (2019).[29] They showed a median PFS duration of 4.7 months (95% CI: 2.1, 6.0) for 30 patients with *FGFR2* fusions on 1L gemcitabine and platinum therapy. These results were updated recently at ASCO 2020 and confirmed the previous mPFS result of 4.7 months.[29] In a related retrospective analysis that included 135 patients, Goyal et al (2020)[30] showed that for the 55 patients with *FGFR2* fusions who received gemcitabine/cisplatin as 1L palliative systemic therapy, the median time on treatment was 6.2 months and the median OS from time of initial diagnosis was 36.1 months.[30]

In summary, the above retrospective studies suggest that, compared to historical data, CCA patients with *FGFR2* fusions may respond similarly or even worse to chemotherapy than unselected BTC population, supporting the notion that survival in the comparator study ABC-06 is unlikely to underestimate what would be observed in clinical practice for the index population (i.e., only those with FGFR2 fusions/rearrangements).

A21. Priority question – Please provide all the R code and associated datasets to enable the ERG to rerun the MAIC for checking purposes.

Response: The R code and associated files are provided along with the responses to the Clarification Questions.

A22. Priority question – Please justify the choice of outcomes analysed in the MAIC and choice of covariates. Were the outcomes known to be effect-modifiers included?

Response: The outcomes analyses in the MAIC (OS and PFS) were chosen to align with the modelling strategy, the outcomes listed in the final NICE scope, and the primary trial outcomes in FIGHT-202 and comparator trials. It was not considered necessary to adjust the population for any other endpoint.

The covariates included in the MAIC were chosen based on the baseline characteristics reported in the ABC-06 study. This study has not yet been published. Therefore, the selection of covariates was limited to the data available in the conference presentation.

Section B: Clarification on cost-effectiveness data

Survival analysis

B1. Priority question – In the CS it is stated that the log-logistic curve was selected for the base case OS with pemigatinib, despite providing a less clinically plausible 5-year survival rate, due to the selection of Weibull causing crossing of OS and PFS extrapolations when selecting best fitting PFS curves. Please explain if this is indeed the only justification for the choice of the log-logistic distribution, and if so, why this is deemed more important than clinical plausibility.

Response: As stated in the CS, due to the immaturity of the observed OS data from FIGHT-202, greater weight was placed on clinical plausibility when selecting the base case parametric distribution. The challenge was that none of the curves exactly matched clinical expert opinion. When consulted, clinical experts were unsure of the expected long-term survival for the target population and stated that this would be dependent on several factors including secondary interventions and possibility of tumour resection.[14] Nevertheless, an estimate of 5% survival at 5 years was provided by both clinicians.

From the available extrapolations, the log-logistic (11%) and Weibull (1%) curves were the closest matches to clinical expert estimates, both providing good visual and statistical fit, but providing greater or lower estimates than the clinicians, respectively. With log-normal chosen as the base case PFS extrapolation (based on visual and statistical fit and clinical expectation of 24-month PFS), selecting Weibull for OS caused the PFS and OS extrapolations on the pemigatinib arm to cross at approximately 5 years (where 2% of patients would still be alive and progression-free), suggesting Weibull was too pessimistic for extrapolation in the base case. Although this crossing of PFS and OS extrapolations could be limited within the CE model, it suggests that after 5 years, the survival model for OS predicts that the probability of death would be lower than the probability of death or progression

predicted from the PFS model. The same was true for the ASC+mFOLFOX arm, although to a lesser extent. No further justification was available at the time of submission.

In an attempt to provide further evidence to support decision making on this topic, smoothed hazards plots of FIGHT-202 OS data have been provided, overlayed with the extrapolations included in the CE model. Initially, the hazards of the FIGHT-202 OS data increase slowly in the first year, before showing some evidence of slowing and decreasing, before increasing again after 400 days. The increase in hazards after 400 days is likely due to the high level of censoring and smaller numbers at risk at this time in the trial. From these plots, it is clear that both log-logistic and Weibull distributions estimate a hazard function with a reasonable fit to the observed hazards in the first year, although the Weibull extrapolation does not allow for the small decrease in hazards seen before 400 days (Figure 3).

The anticipated additional follow up from upcoming FIGHT-202 data cuts may provide further validation for the choice of OS curves.

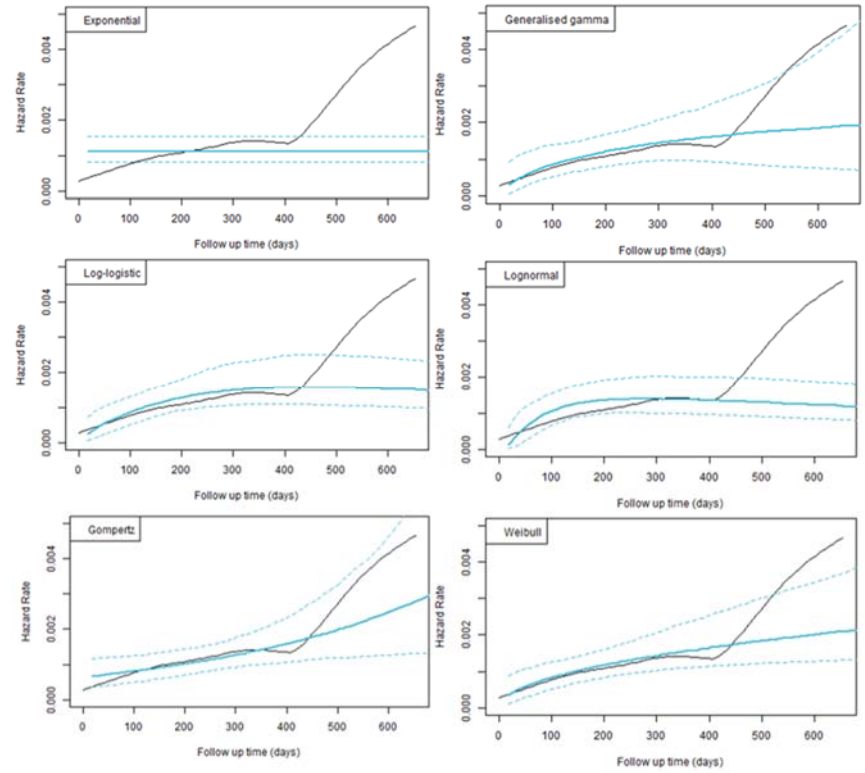

Figure 3. Overall survival smoothed hazard plots vs empirical hazards

Adverse events

B2. In calculating the yearly event rate for the adverse events, the number of observed events is defined by the number of patient-years. This number of patient-years is derived from the model by estimating the area under the ToT-curve for pemigatinib and the area under the PFS-curve for the comparators.

a) Why is the area under the extrapolated curve used for the number of patient-years rather than the area under the KM curve, given that the later represents the observed number of patient-years

b) There appears to be an error in the calculation of the annual AE rate, due to confusion between patient-months (worksheet 'TTE Tx1') and patient-weeks (worksheet 'Efficacy'). Please explain if indeed an error was made and if so, please provide a corrected version of the model.

Response: In response to B2a, the company agrees that it is more appropriate to use the area under the KM curve to calculate the observed AE rates. This has been amended in the economic model with the area under the time to treatment discontinuation KM used for pemigatinib and the area under the PFS KM ABC-06 mFOLFOX+ASC arm used for mFOLFOX+ASC and ASC alone, due to the absence of comparator data on time to treatment discontinuation.

In response to B2b, the company has corrected the error identified. Along with corrections to B2a, the company ICER vs ASC alone was reduced by £1,370 to £59,714 (Table 11). These changes are under the control of a switch in cell C140 of the Controls tab in the updated cost-effectiveness model.

Table 11. AE corrections – ICER impact

Technologies	ICER (£)	Change in ICER (£)
Company original base case	61,084	NA
AE corrections	59,714	-1,370

B3. Both for the AE-related disutilities and the costs associated with AEs, please explain the basis for the assumptions made about the near-equivalence of AEs, both in the context of disutilities and in the context of costs.

Response: In the absence of prior appraisals or published economic models in this indication, costs and health-related quality of life (HRQL) decrements associated with AEs were sourced from the available literature. This included other oncology appraisals and NHS reference costs. The initial inputs were validated by health economists and clinical experts, which provided an understanding of the face validity of these inputs.

In the absence of other inputs for costs, assumptions of equivalence were made between AEs that were judged to be similar, eg biliary event, cholangitis, and infection.

For utilities, a similar approach was followed. Because the specific expert clinical input was that biliary events, cholangitis, infection, stomatitis, palmar–plantar erythrodysaesthesia syndrome, and anorexia would be the worst AEs experienced by patients,[14] if no other sources for any of these AE inputs were identified, they were assumed to be equal to the AE with the highest disutility, which was anaemia.

HRQL

B4. Priority question – Please amend the model to account for the fact that utility declines with age.

Response: The company model has been amended to include adjustments for health state utilities to account for the decline in HRQL associated with age. Estimates of age-related decline in utility were sourced from Ara & Brazier 2010 and applied to the economic model.[31] Applying age-related decline in health state utilities had a negligible impact on results—the ICER increased by £1,120 for pemigatinib vs ASC alone (Table 12). The switch for this change can be found in cell C142 of the updated cost-effectiveness model.

Table 12. Age-adjusted utilities – ICER impact

Technologies	ICER (£)	Change in ICER (£)
Company original base case	61,084	NA
Age adjusted utilities (correction 2)	62,204	+1,120

B5. Priority question – Table 42 of the CS shows that 56 patients provided 91 utility observations post-progression. Please provide the following information:

a) A breakdown of the number of patients who provided 1, 2, etc. utility observations

b) The mean length of time between progression and the 1st and 2nd etc. utility observations.

c) Mean progressed utility value at 1st and 2nd etc observation.

Response: Please see below for the answers to the above questions.

a) Table 13 presents a breakdown of the number of patients who provided 1, 2, etc. utility observations.

Table 13. Number of patients by the number of post-progression utility observations

Number of utility observations	Number of patients	Number of observations
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
Total	[redacted]	**91**

b) Table 14 presents the mean length of time between progression and the 1st, 2nd, etc. utility observations.

Table 14. Mean number of days between progression and observation

Observation number post- progression	Mean number of days between progression and observation
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]

c) Table 15 presents the mean progressed utility value at 1st, 2nd, etc. observation.

Table 15. Mean utility by observation number post-progression

Observation number post- progression	Mean utility
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]

B6. Priority question – Please explain why utility model 4 was not also considered as either the base-case model or as a scenario, given that it has a lower AIC than both Models 3 and 5. Please include the option to use this utility model in the electronic model. Please provide a table with the resulting utility values per state for Models 3-5.

Response: The company confirmed during the ERG clarification call that model 4 does not have a lower AIC than model 3 and 5 (Table 44, CS) but rather has the worst statistical fit of the 3 models. Nevertheless, model 4 has been added to the economic model to aid decision making. It should be acknowledged that this is a statistically inferior model, not accounting for the statistically significant interaction between the progression and treatment status variables. The switch for this scenario can be found in cell C148 in the Controls sheet of the updated CE model.

Table 16. Utility model 4 – ICER impact

Technologies	ICER (£)	Change in ICER (£)
Company original base case	61,084	NA
Utility model 4 (scenario 1)	62,249	+1,165

B7. Priority question – In relation to the utility estimate for the PFS off treatment state, please provide:

a) The number of patients who discontinued treatment in Cohort 2 and the number of patients who provided a utility observation upon treatment discontinuation for the PFS without treatment state

b) The reason for discontinuation of the 4 patients that provided utility values for the PFS off treatment state?

c) The CS states that "upon treatment discontinuation, patients had one end of treatment observation". Please therefore clarify why there are more observations than patients for the PFS off treatment in Table 42 of the CS.

Response: Please see below for the answers to the above questions.

a) In Cohort 2, 79/107 patients discontinued treatment. Fifty patients provided a utility observation in the off-treatment state and four patients reported an observation pre-progression.

b) Table 17 presents the reason for discontinuation of the four patients that provided utility values for the PFS off-treatment state.

Table 17. Reason for discontinuation of the four patients that provided utility values for the PFS off-treatment state

Reason for discontinuation	Number of patients
Clinical progressive disease	[redacted]
Physician decision	[redacted]
Withdrawal by subject	[redacted]

c) One patient had two observations in the PFS off-treatment state. The date of treatment discontinuation is slightly later than the last dose of treatment (the date used to calculate on/off treatment). Therefore, they had one unscheduled observation just before formal treatment discontinuation and one just after treatment discontinuation (but both after the last dose of treatment).

B8. Please discuss the plausibility that utility in the PFS off treatment state is substantially lower than the utility in the progressed state off treatment.

Response: The plausibility and face validity of the PFS off treatment health state utility derived from model 5 is unclear. Clinical experts suggested that the substantial decrease seen could be explained if the HRQL questionnaire was completed while experiencing the AEs that led to treatment discontinuation.[14] Otherwise, the HRQL of patients in the PFS off-treatment state would be expected to improve rather than decline.[14] Consequently, model 3 was investigated in scenario analyses as an appropriate alternative and model 5 was used in the base case as it was shown to have the best statistical fit.

B9. Please provide 2 additional tables, similar to Table 43 of the CS, where utilities over time are separated according to: Table a) progression status and Table b) treatment status.

Response: Table 18 and Table 19 show the summary of utility observations by progression status and treatment status, respectively.

Table 18. Summary of utility observations by visit and progression status

	Pre-progression			Post progression		
Visit	**Time since screening (months)**	**Mean (SD)**	**N Subjects (N utility observations)**	**Time since screening (months)**	**Mean (SD)**	**N Subjects (N utility observations)**
Screening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Early termination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unscheduled visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 19. Summary of utility observations by visit and treatment status

	On-treatment			Off-treatment		
Visit	**Time since screening (months)**	**Mean (SD)**	**N Subjects (N utility observations)**	**Time since screening (months)**	**Mean (SD)**	**N Subjects (N utility observations)**
Screening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Early termination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unscheduled visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cost and healthcare resource use

B10. The CS states on p. 83 that the costs of drugs and procedures in ASC are "expected to apply to both arms equally". Please provide justification for this expectation, and include a report of clinical expert opinion on this matter if it was consulted.

Response: Limited data have been reported from the ABC-06 study but when compared with data collected from the FIGHT-202 study, differing reporting of adverse events did not permit adequate analysis to support application of costs of drugs and procedures for ASC. Given the advanced disease stage of the target patient population, the costs associated with ASC are expected to remain relatively unchanged despite treatment. Thus it is has been assessed that applying ASC

equally to both arms is the most appropriate and robust approach to adopt in the CE analysis. No additional clinical opinion was available at the time of this submission.

B11. No wastage costs are included in the analysis, neither for chemotherapy nor for pemigatinib. Although the ERG agrees that this assumption is justifiable for chemotherapy given their low acquisition costs, this is not the case for pemigatinib. This is particularly relevant given that dose reductions may occur, and that packaging of pemigatinib is assumed to correspond exactly to a single treatment cycle consisting of 14 tablets. Please provide detailed justification on how the implementation of dose reductions cannot lead to wastage as well as the packaging assumptions, or include wastage costs into the analysis. The ERG prefers that the latter is done using patient data on doses received, and by making alternative assumptions for packaging of pemigatinib.

Response: It is unclear what processes exist in clinical practice to minimise wastage of orally administered medicines. In response to the ERG's question, the company has implemented functionality to include pemigatinib wastage. A scenario is presented where patients are costed to receive a single pack of 14 tablets every three weeks, rather than accruing the average weekly cost of treatment. This scenario is extremely conservative as it is likely that clinicians would act to minimise wastage of valuable therapeutic treatments. The scenario results in an increase in the ICER of £1,241 when including the observed RDI percentage and £2,603 when assuming an RDI of 100%. The switches for the alternative costing method, and RDI application can be found in cells C144 and C146, respectively, in the Controls sheet of the updated cost-effectiveness model. Table 20 shows the impact on the ICER for the two wastage scenarios.

Table 20. Pemigatinib wastage scenarios – ICER impact

Technologies	ICER (£)	Change in ICER (£)
Company original base case	61,084	NA
Pemigatinib wastage including RDI (scenario 2a)	62,325	+1,241
Pemigatinib wastage excluding RDI (scenario 2b)	63,687	+2,603

B12. The CS states on p. 118 that “CT scans were assumed to be performed once every 12 months for progressed patients, as clinician feedback suggested these scans would be performed less frequently after progression.” A reference is then made to a document (Ref 65 in the CS) that is “available on request”. The ERG indeed requests that the document is made available. In addition, please make clear where in this document the information is provided on which the assumptions regarding CT scan frequency after progression are based.

Response: The requested document has been made available. Page 10 describes clinical expert opinion related to the frequency of CT scans following progression. The relevant excerpt is quoted below:

“Clinician #1 noted that few patients would be scanned following progression. Clinician #2 clarified post-meeting that following progression, patients on treatment for advanced disease would likely have CT scans every 3 months but for patients receiving best supportive care alone, scanning would not be performed.”

Section C: Textual clarification and additional points

C1. Given that the weekly price of treatment is marked as confidential, should the price per cycle also be marked?

Response: Yes.

Summary of impact on cost-effectiveness model results for company corrections and requested scenarios

In response to the ERG’s clarification questions, the company has made the suggested changes to the economic model where appropriate to do so. The updated company base case includes corrections for the calculation of AE rates and inclusion of age-adjusted utilities (Table 21). The updated company base case is believed to be the most robust cost-effectiveness estimate and shows the ICER is reduced by £278. Separately, scenarios applying alternative assumptions suggested by the ERG have also been investigated and are reported below. Each alternative assumption is applied independently to demonstrate the impact on results (Table 22).

Table 21: Company corrections and ERG requested scenarios – ICER impact

Technologies	ICER (£)	Change in ICER (£)
Company original base case	**61,084**	**NA**
AE correction (correction 1)	59,714	-1,370
Age adjusted utilities (correction 2)	62,204	+1,120
Company updated base case (correction 1 & 2)	**60,806**	**-278**
Utility model 4 (scenario 1)	61,956	+1,150
Pemigatinib wastage including RDI (scenario 2a)	62,067	+1,261
Pemigatinib wastage excluding RDI (scenario 2b)	63,450	+2,644
Notes: Change in ICER for ERG requested scenarios vs. company updated base case for pemigatinib vs. ASC alone (mFOLFOX + ASC extendedly dominated). Change in ICER for corrections vs. company original base case.		

Table 22: ERG requested MAIC scenarios – ICER impact (pairwise results vs. mFOLFOX+ASC)

Technologies	**ICER (£)**	**Change in ICER (£)**
Company original base case	**57,315**	**NA**
Company updated base case (correction 1 & 2)	**57,467**	**+152**
OS: Kim 2017 - Fluoro mono	61,921	+4,454
OS: Kim 2017 - Fluoro + platinum	61,202	+3,735
OS: Zheng 2018 - IRI	58,777	+1,310
OS: Zheng 2018 - XELIRI	65,947	+8,480
OS: Lowery 2019 - Chemo	78,690	+21,224
OS: Schweitzer - Chemo	74,485	+17,018
PFS: Kim 2017 - Fluoro mono	58,328	+861
PFS: Kim 2017 - Fluoro + platinum	58,861	+1,394
PFS: Zheng 2018 - IRI	59,610	+2,143
PFS: Zheng 2018 - XELIRI	57,520	+53
Notes: Change in ICER vs. company updated base case for pemigatinib vs. mFOLFOX + ASC		

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NICE National Institute for Health and Care Excellence

Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

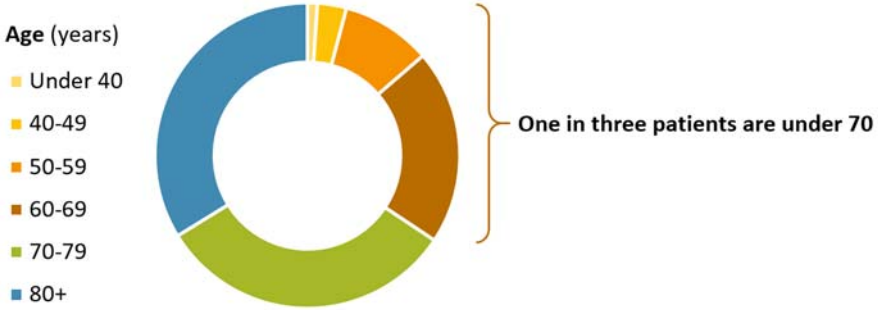
About you

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	AMMF – The Cholangiocarcinoma Charity
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	AMMF is a charity, registered with the Charity Commission for England and Wales, registration no 1091915. It is the UK's only charity dedicated solely to cholangiocarcinoma. Funding is received via donations from members of the public, and a small amount of industry funding is received by way of sponsorship of our annual conference. The charity does not have members.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	The charity received a small amount of sponsorship from Incyte for the AMMF Cholangiocarcinoma Conference 2019 (£1,500)

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	AMMF supports patients with cholangiocarcinoma and their caregivers, providing them with information on treatments and clinical trials. We communicate with patients and their loved ones on a one to one basis by email and telephone, and face to face at our annual conference, and some use AMMF's online discussion forum and social media platforms. www.ammf.org.uk
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The symptoms of cholangiocarcinoma (CCA) can be vague and easily attributed to a number of other causes and because of this, together with a lack of awareness at primary care level, this cancer is frequently diagnosed late. For the majority of patients, this late diagnosis will mean their cancer is inoperable and for them, this is a terminal diagnosis. For many patients this diagnosis and the prognosis can be truly shocking and they find it very difficult to assimilate the details. Patients struggle to accept that there really is so little treatment available to them, and that a diagnosis of inoperable CCA means their life will end soon – they have very little time left.

	Currently a resection is the only potentially curative treatment there is for CCA, so inoperable patients are left with very limited options. The standard first line treatment for those with inoperable CCA is the chemotherapy combination, Gemcitabine and Cisplatin – and this treatment has not been improved on for over a decade[1]. Undergoing this chemotherapy, which might or might not extend their life for a few months[2], is often at the expense of the quality of their life, and that of their families. For carers, understanding the diagnosis and its implications can be as difficult for them as for the patient. Many struggle to comprehend that there is no effective treatment for their loved one, and ask AMMF for advice on, 'treatments not available under the NHS'. Seeing loved ones enduring the side effects of chemotherapy, including repeated infections requiring hospitalisation which takes them away from their families when their life expectancy is so short, is very difficult. As is, of course, trying to come to terms to what is happening, not only to their loved one, but to their lives in general – especially as so many are in what should be the 'prime of their life'. Although CCA is considered a cancer affecting older people, at AMMF we hear from many in their 30s, 40s and up with this diagnosis. Information from the AMMF/PHE partnership for the project, "Incidence, mortality and survival for people diagnosed in England with cholangiocarcinoma between 2001-2017" shows that a third of patients are under 70 at diagnosis. (Data has been QA'd by PHE, and will be published later in 2020.):



When the survival rates are improving and more effective treatments are being discovered for many other cancers, a diagnosis of cholangiocarcinoma, and learning that there is so little in the treatment armoury, leaves people – patients and carers - feeling confused, isolated and helpless.

Many of the comments we receive at AMMF are, sadly, similar:

“After my diagnosis I felt so alone and afraid, I had no one to turn to for help.”

“I was shell shocked. I didn’t know who to turn to for help. I was alone.”

“I went through endless tests; the doctors didn’t know what was wrong with me. I lost valuable time.”

“They told me surgery was my only chance of survival, but it might already be too late.”

[1]*ABC-02 trial 2010: https://www.nejm.org/doi/full/10.1056/nejmoa0908721*

	[2]ABC-02 trial 2010: "The median survival in the cisplatin–gemcitabine group was 11.7 months (95% confidence interval [CI], 9.5 to 14.3), as compared with 8.1 months (95% CI, 7.1 to 8.7) for the gemcitabine-only group (P<0.001)."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	CCA patients and carers see that molecular profiling is now available in the USA, along with targeted and other therapies, eg, SIRT, in that and other countries. They find it very difficult to understand why there are no effective treatments available for cholangiocarcinoma patients within the NHS. Many will search for treatments available privately or internationally.
8. Is there an unmet need for patients with this condition?	There are a number of unmet needs for cholangiocarcinoma patients: <u>Effective treatments for CCA are desperately needed.</u> The incidence of this disease is increasing year on year, with mortality mirroring incidence[3], and many younger adults being diagnosed. Currently resection is the only potentially curative treatment, but few are eligible for this. Standard of care 1st line chemotherapy for inoperable CCA patients hasn't changed in years and offers modest, if any, benefit. New and more effective treatments for CCA are desperately needed. <u>Centres of Expertise for CCA patients are needed</u> There seems to be no set pathway/guidance for the care of cholangiocarcinoma patients, many are never seen by those with specialist knowledge, and many are not considered for surgery nor for clinical trials. AMMF strongly believes that all CCA patients should be seen in 'centres of expertise' for confirmation of their diagnosis (operable/inoperable), and where their treatment pathway should be endorsed by an HPB multidisciplinary team, experienced in the care of CCA patients. <u>Molecular profiling is needed for all CCA patients</u>

	Molecular profiling should be available for all those diagnosed with CCA – at diagnosis or during 1st line treatment. With the advent of targeted therapies, such as pemigatinib, this is essential so that all those eligible for such treatments can be considered in a timely manner. Currently molecular profiling is available to only very few in the UK, via clinical trials, or privately. [3]*Incidence and Mortality rates of cholangiocarcinoma in England* *https://www.annalsofoncology.org/article/S0923-7534(19)30962-7/fulltext*
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Patients, both inoperable and those with a recurrence after surgery, and their carers think that Pemigatinib offers a more personalised treatment for those with a certain 'molecular mutation', bringing with it the hope of extending survival over the more standard chemotherapies and/or best supportive care that might be offered. Plus, as an oral therapy, this has certain quality of life advantages over an intravenous therapy, including spending less time in hospital receiving treatment. Patients and carers also see that this therapy has been approved by the FDA and will be available to eligible patients in the USA.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	In the UK, currently Permigatinib is available to only a few through a randomised clinical trial, and the clinical trials are only available in certain centres.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those who have had first line chemotherapy and progressed, also those who have a recurrence of their CCA after surgery, who have been found to have the FGFR fusion could benefit from this targeted treatment. If a patient is found to have the FGFR2 rearrangement, Pemigatinib is a therapy which will specifically target that and so could have a positive impact on their cancer. Other, more general chemotherapies (Gemcitabine/Cisplatin, Capecitabine, etc) have been found to be effective for some with CCA, but not for all, and the effectiveness is not known until the patient has had several cycles of chemotherapy and may have endured a number of side effects and infections, only to find there has been no advantage for them in reducing or stabilising their cancer.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • Incidence of CCA in increasing, mortality mirrors incidence. • Currently there is very little effective treatment for CCA patients. • Many CCA patients are not considered for surgery nor for clinical trials – 'centres of expertise' are needed for confirmation of diagnosis and treatment pathway, and for molecular profiling. • All CCA patients should receive molecular profiling at diagnosis or during 1st line treatment • For those found to have an FGFR fusion, Pemigatinib offers a realistic treatment, extending survival with good quality of life.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Erasmus School of Health Policy & Management

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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None.

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
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.

Abbreviations

AACR	American Association for Cancer Research
AE	Adverse event
AiC	Academic in confidence
ALT	Alanine aminotransferase
ASC	Active symptom control
ASCO	American Society of Clinical Oncology
ASCO-GI	American Society of Clinical Oncology Gastrointestinal Cancers
AST	Aspartate transaminase
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian information criterion
BSC	Best supportive care
BSG	British Society of Gastroenterology
BTC	Biliary tract cancer
CADTH	Canadian Agency for Drugs and Technology in Health
CCA	Cholangiocarcinoma
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CHMP	Committee for Medical Products for Human Use
CI	Confidence interval
CiC	Commercial in confidence
CR	Complete response
CrCl	Creatinine clearance
CS	Company submission
CSR	Clinical study report
DCR	Disease control rate
DOR	Duration of response
DSU	Decision Support Unit
eCCA	Extrahepatic cholangiocarcinoma
ECOG	Eastern Cooperative Oncology Group
EGFR-TK	Epidermal Growth Factor Receptor – Tyrosine Kinase
EMA	European Medicines Agency
EORTC QLQ-BIL21	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (CCA and gallbladder cancer)
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D-3L	EuroQol five-dimension, three-level tool
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
ESMO-GI	European Society for Medical Oncology gastrointestinal Cancers
ESS	Effective sample size
EUR	Erasmus University Rotterdam
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FGFR2+	Fibroblast growth factor receptor 2-positive
FOLFIRI	5-fluorouracil+irinotecan + folic acid
FOLFOX	5-fluorouracil+oxaliplatin + folic acid
HAS	Haute Autorité de Santé
HCC	hepatocellular carcinoma
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment

iCCA	Intrahepatic cholangiocarcinoma
ICER	Incremental cost effectiveness ratio
ILCA	International Liver Cancer Association
IQWiG	German Institute for Quality and Efficiency in Healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IRC	Independent review committee
IRI	Irinotecan
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect comparison
KM	Kaplan–Meier
LY	Life year
LYG	Life year gained
MAA	Marketing authorisation application
MAIC	Matched-adjusted indirect comparison
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
NA	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not estimable
NGS	Next generation sequencing
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
NSCLC	Non-small-cell lung cancer
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Progressive disease
PFS	Progression-free survival
PLD	Patient-level data
PR	Partial response
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analyses
PSM	Parametric survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY(s)	Quality-adjusted life year(s)
QD	Once daily
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse events
SAS	Safety analysis set
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SOC	Standard of care
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event

TLV	Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket)
ToT	Time on treatment
TSD	Technical support document
ULN	Upper limit of normal
XELIRI	Capecitabine + irinotecan
XELOX	Oxaliplatin + capecitabine

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1. Evidence review group report executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 discusses the decision problem, section 1.3 describes issues related to the clinical effectiveness evidence, and section 1.4 describes issues related to the cost effectiveness evidence. Background information on the condition, technology and evidence and information on non-key issues are provided in the main ERG report, see sections 2 (background), 3 (decision problem), 4 (clinical effectiveness) and 5 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of the key issues

ID	Summary of issue	Report sections
1	There is a lack of direct evidence about the comparative efficacy and safety of pemigatinib vs standard of care (SOC), defined as systemic chemotherapy or BSC, in the specified population.	**Executive summary**: • Table 1.3 **Main report**: • Section 4.2 • Section 4.5
2	The evidence about the efficacy of pemigatinib is for a subset of the specified population.	**Executive summary**: • Table 1.2 **Main report**: • Section 3.1 • Section 4.2.3 • Section 4.5
3	There is a lack of any kind of evidence about the efficacy and safety of the comparator (systemic chemotherapy or BSC), in the specified population: a) The proportion of patients in, the main comparator study, with FGFR2 fusions/rearrangements was not reported, but estimated to be low. b) There were relatively few patients in the comparator studies who had intrahepatic cholangiocarcinoma (iCCA), compared to the pemigatinib study (FIGHT-202) where 98% of patients had iCCA.	**Executive summary:** • Table 1.4 **Main repor**t: • Section 2.2 • Section 2.3 • Section 4.1.2 • Section 4.5
4	The indirect evidence about the comparative efficacy of pemigatinib vs SOC is weak; the estimate of relative treatment effect in the model was based on an unanchored matched adjusted indirect comparison (MAIC) analysis between these two mismatched trials.	**Executive summary**: • Table 1.5 **Main report**: • Section 4.3 • Section 4.4 • Section 4.5

ID	Summary of issue	Report sections
5	There is a lack of evidence about the comparative safety of pemigatinib vs SOC.	**Executive summary**: • Table 1.6 **Main report**: • Section 4.2.8 • Section 4.5
6	It is not clear that pemigatinib meets the NICE end-of-life criteria.	**Executive summary**: • Table 1.12 **Main report**: • Section 8
7	It is not clear that all relevant comparators have been included in the cost effectiveness model.	**Executive summary**: • Table 1.7 **Main report**: • Section 5.2.4 • Section 7.4
8	The selection of the parametric curve for overall survival (OS) for pemigatinib.	**Executive summary**: • Table 1.8 **Main report**: • Section 5.2.6.1 • Section 7.4
9	The method used to extrapolate time on treatment (ToT).	**Executive summary**: • Table 1.9 **Main report**: • Section 5.2.6.4 • Section 7.4
10	There was no attempt by the company to conduct a MAIC analysis for adverse events (AEs). Therefore, the rates of AEs across the studies and their relevant populations remain unadjusted.	**Executive summary**: • Table 1.10 **Main report**: • Section 5.2.7 • Section 7.4
11	Health-related quality of life (HRQoL) was not measured using the EQ-5D in FIGHT-202 and had to be mapped from EORTC-QLQ-C30 data to EQ-5D-3L utilities using a published mapping algorithm.	**Executive summary**: • Table 1.11 **Main report**: • Section 5.2.8
12	The company base case model did not include wastage costs or the costs of genetic testing.	**Executive summary**: • Table 1.12 **Main report**: • Section 5.2.9

ID	Summary of issue	Report sections
		• Section 7.4

1.2 The decision problem: summary of the ERG's key issues

The evidence about the efficacy of pemigatinib is for a subset of the specified population only. Almost all of the participants in FIGHT-202 (98%) had iCCA and hence the ERG considers that this study is not fully representative of the population specified in the scope (CCA and FGFR2+). However, the ERG acknowledges that most patients with CCA, who have FGFR2 mutations, have intrahepatic disease.

Table 1.2: Key issue 2 – The evidence about the efficacy of pemigatinib is for a subset of the specified population.

Report section	Sections 3.1, 4.2.3 and 4.5
Description of issue and why the ERG has identified it as important	The population specified in decision problem in the NICE scope and the expected licensed indication is *'people with advanced cholangiocarcinoma (CCA) with FGFR2 fusion or rearrangement that is relapsed or refractory after at least one prior systemic therapy.'* Almost all of the participants in FIGHT-202 (98%) had iCCA and hence the ERG considers that this study is not fully representative of the population specified in the scope (CCA and FGFR2+). However, the ERG acknowledges that most patients with CCA, who have FGFR2 mutations, have intrahepatic disease.
What alternative approach has the ERG suggested?	If possible, future studies should include patients with extrahepatic CCA (eCCA) and FGFR2 fusion or rearrangement.
What is the expected effect on the cost effectiveness estimates?	The impact is unknown.
What additional evidence or analyses might help to resolve this key issue?	Robust evidence is needed for the whole population covered by the NICE scope and the expected licensed indication. Unresolvable uncertainty with the current evidence.

1.3 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG's major concern, which impacts all aspects of this submission, is the lack of evidence about the comparative efficacy and safety of pemigatinib vs standard of care (SOC), defined as systemic chemotherapy or BSC, in the specified population. There is no direct evidence about the comparative efficacy and safety of pemigatinib vs SOC (Table 1.3), there is a lack of any kind of evidence about the efficacy and safety of the comparator (systemic chemotherapy or BSC) in the specified population (Table 1.4) and consequently the indirect evidence about comparative efficacy and safety is weak (Table 1.5). There is a lack of evidence about the comparative safety of pemigatinib vs SOC (Table 1.6).

Table 1.3: Key issue 1 – Lack of direct evidence about the comparative efficacy and safety of pemigatinib vs SOC

Report section	Sections 4.2 and 4.5
Description of issue and why the ERG has identified it as important	There is a lack of direct evidence about the comparative efficacy and safety of pemigatinib vs SOC, defined as systemic chemotherapy or BSC, in the specified population. This means that there is no robust evidence about how the outcomes of

Report section	Sections 4.2 and 4.5
	patients treated with pemigatinib compare to those treated with SOC (systemic chemotherapy of BSC).
What alternative approach has the ERG suggested?	Without any evidence as to the effect on any bias in the treatment effect estimated without comparative evidence the ERG cannot think of a means of mitigating this issue.
What is the expected effect on the cost effectiveness estimates?	Lack of comparative data trial data to estimate the relative treatment effect in the model means that the estimate of the ICERs is highly uncertain and likely to be biased, with no knowledge of the direction of the potential bias.
What additional evidence or analyses might help to resolve this key issue?	Robust evidence about the comparative effectiveness of pemigatinib vs SOC, for the specified population, is needed. Unresolvable uncertainty with the current evidence.

Table 1.4: Key issue 3 – Lack of any kind of evidence about the efficacy and safety of the comparator (systemic chemotherapy or BSC), in the specified population

Report section	Sections 2.2, 2.3, 4.1.2 and 4.5
Description of issue and why the ERG has identified it as important	There is a lack of any kind of evidence about the efficacy and safety of the comparator (systemic chemotherapy or BSC), in the specified population: a) The proportion of patients in the main comparator study with FGFR2 fusions/rearrangements was not reported, but estimated to be low. b) There were relatively few patients in the comparator studies who had intrahepatic cholangiocarcinoma (iCCA), compared to the pemigatinib study (FIGHT-202) where 98% of patients had iCCA. The ERG considers that this is a major issue affecting the validity of any indirect comparison between pemigatinib and SOC in the specified population.
What alternative approach has the ERG suggested?	Without any evidence as to the effect of the discrepancy in population the ERG cannot think of a means of mitigating this issue.
What is the expected effect on the cost effectiveness estimates?	The impact is unknown.
What additional evidence or analyses might help to resolve this key issue?	Evidence is needed about the efficacy and safety of SOC (systemic chemotherapy regimens or BSC) in the specified population. Unresolvable uncertainty with the current evidence.

Table 1.5: Key issue 4 – The indirect evidence about the comparative efficacy of pemigatinib vs SOC is weak

Report section	Sections 4.3, 4.4 and 4.5
Description of issue and why the ERG has	The indirect evidence about the comparative efficacy and safety of pemigatinib vs SOC is weak. The company relied upon a matched-adjusted indirect comparison (MAIC) to provide estimates of comparative efficacy. The MAIC presented in the original submission utilised a single comparator study, ABC-06, a randomised phase 3, multicentre, open-label study of active symptom control (ASC) alone or

Report section	Sections 4.3, 4.4 and 4.5
identified it as important	5-fluorouracil + oxaliplatin + folic acid (mFOLFOX) + ASC for patients with locally advanced/metastatic biliary tract cancer (BTCs) previously treated with cisplatin/gemcitabine chemotherapy. This study investigated all BTCs and did not report FGFR2 mutation status, whereas FIGHT-202 investigated patients with advanced/metastatic or surgically unresectable CCA who had progressed on at least one line of prior systemic therapy and cohort A of FIGHT-202 (the source of data on the efficacy of pemigatinib) included only patients with FGFR2 fusions or rearrangements. The ERG considers that there is a high level of uncertainty about the results of the MAIC, as it was an unanchored comparison. The MAIC results are only applicable to the population in the comparator trial and the ABC-06 trial did not report any information about FGFR2 mutation status and included patients with all types of BTC, not just CCA as specified in the scope for this appraisal. This is a major limitation of the MAIC results. The ERG considers that, whilst the additional MAICs provided by the company in response to clarification questions do allow the inclusion of further comparators (different chemotherapy regimens) in the cost effectiveness analysis (CEA), they are subject to the same limitations as the original MAIC and hence do not increase certainty with respect to the comparative efficacy of pemigatinib.
What alternative approach has the ERG suggested?	The ERG requested additional MAICs to allow the inclusion of further comparators (different chemotherapy regimens) in the cost effectiveness analysis (CEA). However, the ERG wishes to emphasise that these analyses are subject to the same limitations as the original MAIC and hence do not increase certainty with respect to the comparative efficacy of pemigatinib.
What is the expected effect on the cost effectiveness estimates?	The estimate of relative treatment effect in the model was based on an unanchored MAIC analysis between two mismatched trials. The prognostic factors included in the MAIC were [redacted]. However, FGFR2+ status could not be included, and neither were type of BTC or site of tumour, both of which would have adjusted for important difference in patient population across the studies. Therefore, it is unclear if any difference in survival observed between the two studies can be attributed to the effect of the treatment with pemigatinib. Thus, the ERG would argue that the estimate of treatment effect in the model is highly uncertain and likely to be biased. As such, the estimate of the ICERS is also highly uncertain and likely to be biased, with no knowledge of the direction of the potential bias.
What additional evidence or analyses might help to resolve this key issue?	In order to provide meaningful indirect comparisons, evidence is needed about the efficacy and safety of SOC (systemic chemotherapy regimens or BSC) in the specified population. Unresolvable uncertainty with the current evidence.

Table 1.6: Key issue 5 – Lack of evidence about the comparative safety of pemigatinib vs SOC.

Report section	Sections 4.2.8 and 4.5
Description of issue and why the ERG has identified it as important	There is a lack of evidence about the comparative safety of pemigatinib vs SOC, in the specified population. Adverse events (AEs) data for comparator regimens mFOLFOX+ASC and ASC,

Report section	Sections 4.2.8 and 4.5
	from the ABC-06 trial, were included in the cost effectiveness section of the CS and in the company's base case. The MAICs did not include AEs
What alternative approach has the ERG suggested?	Future studies should consider AEs in people with advanced refractory CCA, who receive second line systemic chemotherapy regimens of BSC.
What is the expected effect on the cost effectiveness estimates?	There was no adjustment of the rates of AEs between the mismatched studies. The direction of impact on cost effectiveness is unknown, although AEs have limited impact on results.
What additional evidence or analyses might help to resolve this key issue?	Evidence is needed about the safety of SOC (second and further lines of systemic chemotherapy regimens or BSC) in the specified population. Unresolvable uncertainty with the current evidence.

1.4 The cost effectiveness evidence: summary of the ERG's key issues

The main issue in the cost effectiveness analysis is the uncertainties in the estimates of relative treatment effectiveness. These uncertainties stem from the mismatches in patient population and the weakness of MAIC analyses. The population in the ABC-06 study, from which comparator efficacy is estimated, does not match the scope population as this study was not restricted to patients with FGFR2 fusions or rearrangements nor to patients with iCCA. The proportion of patients in ABC-06 with FGFR2 fusions/rearrangements was not reported, but estimated to be low based on the FIGHT-202 study which identified 8.6% of UK patients to have FGFR2+ fusions/rearrangements at screening. Additionally, only 47% of patients in ABC-06 were iCCA, while the vast majority of patients with FGFR2 fusions/rearrangements are iCCA (98% in Cohort A of FIGHT-202).

As detailed in section 1.3, the estimate of relative treatment effect in the model was based on an unanchored MAIC analysis between these two mismatched trials. The prognostic factors included in the MAIC were [redacted]

However, FGFR2+ status could not be included, and neither were type of BTC or site of tumour, both of which would have adjusted for important difference in patient population across the studies. Therefore, it is unclear if any difference in survival observed between the two studies can be attributed to the effect of the treatment with pemigatinib. Thus, the ERG would argue that the estimate of treatment effect in the model is highly uncertain and likely to be biased.

Other issues were also identified within the cost effectiveness analyses which are still important to note, although secondary to the key issues of the extent to which the trial population represents the population in the scope and the extent to which the analyses conducted are able to reflect the relative efficacy in that population; these issues are summarised in Tables 7 to 12.

Table 1.7: Key issue 7 – It is not clear that all relevant comparators have been included in the cost effectiveness model.

Report section	Sections 5.2.4 and 7.4
Description of issue and why the ERG has identified it as important	Treatment with pemigatinib was compared to active symptom control and mFOLFOX+ASC. The ERG consider that it is likely that other treatments are also given in clinical practice, but given the uncertainty in the guidelines and in the absence of real world

Report section	Sections 5.2.4 and 7.4
	prescribing data in this population it is difficult for the ERG to ascertain whether the important comparators have been included or whether commonly prescribed comparators have been missed.
What alternative approach has the ERG suggested?	The ERG requested additional MAICs to allow the inclusion of further comparators (different chemotherapy regimens) in the cost effectiveness analysis (CEA). However, the ERG would like to emphasise that given the weaknesses in the estimates of relative treatment effectiveness which drive model results, the addition of more comparators (unless a key comparator has been missed) would not resolve the inherent uncertainties within the cost effectiveness analyses. Because of this, and the uncertainty about which treatments might be regarded as comparators, the alternative comparisons have not been presented in the ERG report.
What is the expected effect on the cost effectiveness estimates?	Could potentially have a substantial impact on the cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	Input from additional experts might provide more insight whether important comparators were missed. Unresolvable uncertainty with the current evidence.

Table 1.8: Key issue 8 – The selection of the parametric curve for overall survival (OS) for pemigatinib

Report section	Sections 5.2.6.1 and 7.4
Description of issue and why the ERG has identified it as important	In the selection of the parametric curve for OS for pemigatinib the company state that clinical validity was given priority in the selection given the immaturity of data. Two clinicians suggested that they may expect to observe 5% of patients alive at five years. The curve which provides the closest estimate is the generalised gamma, which estimates 3% survival at five years. However, this curve was not considered by the company, as it was not one of the three best performing curves in terms of statistical fit. The difference in fit between the log-logistic selected by the company and the generalised gamma was small.
What alternative approach has the ERG suggested?	The ERG agree that clinical plausibility should have priority and therefore the generalised gamma should be considered in the base-case for the extrapolation of OS for pemigatinib.
What is the expected effect on the cost effectiveness estimates?	The change from using log-logistic for modelling OS to Generalised Gamma had a substantial impact on the ICER, increasing it by approximately £26,000 as shown in Table 1.14.
What additional evidence or analyses might help to resolve this key issue?	With more mature survival data (ideally an additional 2 years) it may become easier to assess the appropriateness of the various parametric curves.

Table 1.9: Key issues 9 – The extrapolation of time on treatment (ToT)

Report section	Sections 5.2.6.4 and 7.4
Description of	In the extrapolation of time on treatment (ToT), clinical validation stated [redacted]

Report section	Sections 5.2.6.4 and 7.4
issue and why the ERG has identified it as important	[redacted]. In their base-case the company chose the exponential curve. However, the Weibull better aligned with the estimate of clinical validity, and the ERG would argue that this should be used in the base-case.
What alternative approach has the ERG suggested?	The ERG would argue that Weibull should be used in the base-case as it closer aligns to the estimate of clinical validity.
What is the expected effect on the cost effectiveness estimates?	Changing from exponential to Weibull decreased the ICER by approximately £1,500 as shown in Table 1.14.
What additional evidence or analyses might help to resolve this key issue?	This issue may be resolved with a longer follow-up for ToT.

Table 1.10: Key issue 10 – Lack of a MAIC analysis for adverse events

Report section	Sections 5.2.7 and 7.4
Description of issue and why the ERG has identified it as important	There was no attempt by the company to conduct a MAIC analysis for adverse events (AEs). Therefore, the rates of AEs across the studies and their relevant populations remain unadjusted.
What alternative approach has the ERG suggested?	Given the major issue of the MAIC evidence being of weak quality, there is little value in performing a MAIC on the AEs. Thus, direct comparative safety evidence is required in the scope population.

Report section	Sections 5.2.7 and 7.4
What is the expected effect on the cost effectiveness estimates?	The direction of impact is unknown but AEs have a limited impact on results in the current model.
What additional evidence or analyses might help to resolve this key issue?	Evidence is required directly comparing the safety of the intervention and comparators in the scope population.

Table 1.11: Key issue 11 – Health-related quality of life (HRQoL)

Report section	Sections 5.2.8 and 7.4
Description of issue and why the ERG has identified it as important	Health-related quality of life (HRQoL) was not measured using the EQ-5D in FIGHT-202 and had to be mapped from EORTC-QLQ-C30 data to EQ-5D-3L utilities using a published mapping algorithm. The company's preferred regression equation included coefficients for treatment status and progression as well as the interaction between treatment and progression status. This analysis resulted in an implausible value for the progression free off treatment state, which had a substantially lower utility than either of the progressed disease utility values. These strange results were likely due to the fact that certain states were left with very few observations for estimation.
What alternative approach has the ERG suggested?	The ERG prefers to use a utility value estimation model without treatment status in the base-case.
What is the expected effect on the cost effectiveness estimates?	Removing treatment status from the estimation of health state utilities decreased the ICER versus ASC by approximately £1,700 as shown in Table 1.14.
What additional evidence or analyses might help to resolve this key issue?	Measurement of HRQoL in a large sample of the scope population, both pre and post progression using the EQ-5D.

Table 1.12: Key issue 12 – Resource use and costs

Report section	Sections 5.2.9 and 7.4
Description of issue and why the ERG has identified it as important	The company base-case model did not include wastage costs for pemigatinib or the costs for genetic testing in the pemigatinib arm.
What alternative approach has the ERG suggested?	The ERG's preferred assumptions were to include wastage costs (included for completeness), and the costs of genetic testing (included to be in line with the decision problem as formulated in the final scope by NICE).
What is the expected effect on the cost effectiveness estimates?	The inclusion of wastage costs and genetic testing increased the ICER by approximately £4,000 and £5,000, respectively.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence or analyses will resolve this issue, as it is a matter of judgement for the committee and experts.

1.5 Other key issues: summary of the ERG's view

It is not clear that pemigatinib meets the NICE end-of-life criteria.

Table 1.13: Key issue 6 – End-of-life criteria

Report section	Section 8
Description of issue and why the ERG has identified it as important	The model results suggest that pemigatinib meets the end of life criteria as mean survival in the ERG base-case (life expectancy) is approximately 6.1 months for patients receiving ASC and approximately 7.2 months for those receiving mFOLFOX+ASC and the incremental life years are approximately 1.2 and 1.1 for these comparators respectively versus pemigatinib in the company base-case. However the ERG considers that, given the high level of uncertainty about the results of the MAIC and the uncertainty about the outcomes of people with advanced CCA with FGFR2 fusion or rearrangement treated with second-line systemic chemotherapy (none of the comparator studies used in the MAICs provided data specific to this population), it is not clear that pemigatinib meets the NICE end-of-life criteria. The ERG notes that OS data were not mature at the 22 March 2019 cut-off.
What alternative approach has the ERG suggested?	Given the current evidence, the ERG cannot suggest any alternative approach.
What is the expected effect on the cost effectiveness estimates?	The judgement of whether or not pemigatinib meetings the end-of-life criteria determines the relevant QALY weighting and resulting threshold.
What additional evidence or analyses might help to resolve this key issue?	Unresolvable uncertainty with the current evidence.

1.6 Summary of the ERG's preferred assumptions and resulting ICER

The ERG preferred assumptions are described in detail in section 7.1.2 of this report and summarised in Table 1.14, with the impact on results of each assumption applied in isolation also shown. The assumption change which had the largest impact on results was using the Generalised Gamma to extrapolate OS instead of the log-logistic.

The full deterministic cost effectiveness results of the ERG preferred base-case are presented in Table 1.15. When pemigatinib is considered in a fully incremental analysis mFOLFOX+ASC is extendedly dominated as the incremental cost effectiveness ratio (ICER) for pemigatinib versus ASC is slightly lower at £91,883 than the ICER comparing mFOLFOX+ASC to ASC (£97,523), thus rendering the comparison of pemigatinib to mFOLFOX+ASC irrelevant. However, for the sake of completeness, the ICER of pemigatinib versus mFOLFOX+ASC can be estimated to be £91,508.

The probabilistic sensitivity analysis (PSA) results, shown in Table 1.16, were similar to the deterministic results, with the exception of the total quality-adjusted life years (QALYs) gained on pemigatinib treatment, which are slightly higher in the probabilistic analysis, resulting in lower ICERs across all analyses. However, mFOLFOX+ASC is still extendedly dominated. This higher number of QALYs for pemigatinib is a result of the skewed uncertainty around the generalised gamma distribution for OS, leading to some PSA iterations where the OS curve has a heavy tail. In both comparisons, all simulations fall in the north-east quadrant, with the majority falling above the £50,000 per QALY

gained threshold line. At a threshold of £50,000 pemigatinib, ASC and mFOLFOX+ASC have approximately a [redacted], [redacted] and [redacted] chance of being considered cost effective respectively.

The scenarios conducted by the ERG are displayed in section 7.2.2.2. Of note is the scenario which includes an adjustment for FGFR2 status in the MAIC analysis, which increased the ICER by approximately £15,000 compared to mFOLFOX+ASC and approximately £11,500 compared to ASC.

Table 1.14: Summary of ERG's preferred assumptions and ICER

	Pemigatinib vs. mFOLFOX+ASC			Pemigatinib vs. ASC		
	Incr. Costs (£)	Incr. QALYs	ICER (£)	Incr. Costs (£)	Incr. QALYs	ICER (£)
Company base case at submission	[redacted]	[redacted]	57,315	[redacted]	[redacted]	61,084
Company base post-clarification corrections	[redacted]	[redacted]	57,467	[redacted]	[redacted]	60,806
Extrapolation of OS using generalised gamma	[redacted]	[redacted]	83,073	[redacted]	[redacted]	87,417
Extrapolation of time on treatment using Weibull	[redacted]	[redacted]	55,814	[redacted]	[redacted]	59,208
Utility values from Model 3 (health state utility values independent of treatment status)	[redacted]	[redacted]	57,685	[redacted]	[redacted]	59,340
Application of pemigatinib drug costs per 3-week prescription	[redacted]	[redacted]	60,153	[redacted]	[redacted]	63,450
Application of the relative dose intensity for pemigatinib in drug wastage calculation	[redacted]	[redacted]	58,748	[redacted]	[redacted]	62,067
Inclusion of costs of genetic testing for pemigatinib	[redacted]	[redacted]	62,970	[redacted]	[redacted]	66,222
ERG preferred base case	[redacted]	[redacted]	91,508	[redacted]	[redacted]	91,883

Based on the model provided with the clarification response.[1]
ASC = active symptom control; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYGs = life years gained; mFOLFOX = oxaliplatin; L-folinic acid and fluorouracil; OS = overall survival; QALYs = quality-adjusted life years.

Table 1.15: ERG base-case deterministic results (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus ASC (£/QALY)	ICER incr. (£/QALY)	ICER versus mFOLFOX + ASC (£/QALY)
ASC	[redacted]	0.51	[redacted]						
mFOLFOX + ASC	[redacted]	0.60	[redacted]	[redacted]	0.09	[redacted]	£97,523	Extendedly dominated	
Pemigatinib	[redacted]	1.73	[redacted]	[redacted]	1.22	[redacted]	£91,883	£91,883	£91,508

Based on the model provided with the clarification response.[1]
ASC = active symptom control; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYGs = life years gained; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; QALYs = quality-adjusted life years.

Table 1.16: ERG base-case probabilistic results (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£) versus ASC	Incr. LYGs versus ASC	Incr. QALYs versus ASC	ICER versus ASC (£/ QALY)	Full incr. ICER (£/ QALY)	ICER versus mFOLFOX +ASC (£/QALY)
ASC	[redacted]	0.51	[redacted]						
mFOLFOX + ASC	[redacted]	0.61	[redacted]	[redacted]	0.09	[redacted]	£89,282	Extendedly dominated	
Pemigatinib	[redacted]	2.04	[redacted]	[redacted]	1.53	[redacted]	£73,976	£73,976	£73,096

Based on the model provided with the clarification response.[1]
ASC = active symptom control; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYGs = life years gained; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; QALYs = quality-adjusted life years.

1.7 Conclusions

The ERG considers that the lack of evidence about the comparative efficacy and safety of pemigatinib is a major limitation of this submission.

As is stated in TSD 18, "An unanchored MAIC…effectively assumes that absolute outcomes can be predicted from the covariates; that is, it assumes that all effect modifiers and prognostic factors are accounted for. This assumption is very strong, and largely considered impossible to meet. Failure of this assumption leads to an unknown amount of bias in the unanchored estimate." (p. 5) The company have failed to demonstrate that this assumption has been met in any of the MAICs, which casts serious doubt on the effectiveness and therefore the cost effectiveness of pemigatinib versus any comparator.

Given the problems with the estimation of the effect of treatment with pemigatinib based on only a single-arm study, all ICERs mentioned are potentially biased, reflecting a level of uncertainty much larger than that indicated by all sensitivity and scenario analyses. Unfortunately, given the data available, these uncertainties cannot be resolved.

2. Background

2.1 Introduction

In this report, the Evidence Review Group (ERG) provides a review of the evidence submitted by Incyte Biosciences UK in support of pemigatinib, trade name Pemazyre®, for the treatment of relapsed or refractory advanced cholangiocarcinoma with fibroblast growth factor receptor 2 *(*FGFR2) alterations.

2.2 Critique of company's description of underlying health problem

Cholangiocarcinoma (CCA), also known as bile duct cancer, is a rare cancer that develops from the epithelial lining of the gallbladder and bile ducts.[2, 3] CCA is classified as either intrahepatic (iCCA) or extrahepatic (eCCA), based on the location of the primary tumour.[2, 3] Data from the Advanced Biliary Tract Cancer (ABC) trials, conducted in the UK, suggest that iCCAs account for approximately 34% of all CCA cases.[2, 4]

Worldwide, CCA is the second most common primary liver tumour, after hepatocellular carcinoma (HCC).[2] The company submission (CS) (pg15) reports data indicating increasing age-standardised incidence and mortality rates for CCA, in England, over the period from 2001 to 2017.[2, 5] Between 2001 and 2017, there were 35,585 CCAs diagnosed in England, of which 26,307 (78%) were iCCAs and 7,278 (22%) were eCCAs.[5] The CS (pg15) further states that: '*There are a lack of data in England and Wales regarding incidence and prevalence for the population of interest in this submission—previously treated, unresectable, locally advanced, or metastatic CCA with fibroblast growth factor receptor 2 (FGFR2) fusions/rearrangements.* '[2] A review article[6] is cited, which reported that mutations involving FGFR2 activation account for nearly 20% of all iCCA cases. The CS (pg15-17) also summarises a number of review articles[6-12] and pre-clinical studies[13-18] concerning the potential tumourigenic role of FGFR mutations in CCA.[2]

A number of studies have reported that FGFR/FGFR2 mutations are associated with increased overall survival (OS).[18-21] FGFR/FGRFR2 mutations were also associated with younger age at onset, female gender and presentation at an earlier stage.[18, 21] The CS[2] reports results from one study, Jain *et al* (2018),[21] which found that CCA patients with FGFR mutations had longer OS times compared to patients without FGFR mutations (median OS, from date of initial CCA diagnosis until death, 37 vs 20 months) and that this difference remained after excluding 36 patients treated with FGFR inhibitors (median OS, 30 vs 20 months). The CS notes that: *'The limitations of this analysis to fully characterise the prognostic role of FGFR alterations are worth highlighting - one being the cohort analyses included patients with early-stage disease who were likely to receive curative treatment options like surgery and/or radiation.'*[2]

ERG comment: Due to the apparent increased OS in patients with FGFR mutations, irrespective of targeted treatment with FGFR inhibitors, the company were asked: *'Given that the comparator study used in the matched-adjusted indirect comparison (MAIC) does not report the FGFR mutation status of participants, please provide evidence to demonstrate that the efficacy of second line systemic chemotherapy does not vary with FGFR mutation status.'*[1]

The company responded: *'There are no published, prospective data to date that have assessed the efficacy of chemotherapy in FGFR-altered CCA, either in 1L or ≥2L settings. Published data are limited to retrospective literature reviews and analyses.*

In the ≥ 2L setting, a retrospective study of 37 patients with FGFR2 fusions treated with another FGFR inhibitor (NCT02150967), showed that outcomes from ≥2L chemotherapy in patients with CCA and

FGFR2 fusions before entering the trial were similar to those reported in the literature for all patients with CCA regardless of genomic status and remain dismal. Median progression-free survival (PFS) with standard 2L chemotherapy was 4.6 (95% CI 2.7-7.2) months and the objective response rate was 5.4% (95% CI 0.7-18.2%).[22] These data align with the results reported in the ABC-06 study where median PFS was 4.0 months (95% CI 3.2-5.0) and the best response (complete response and partial response) rate was 5%.[23]'

ERG comment: The ERG agrees that the estimates quoted, for median PFS and response rate in patients with CCA and FGFR2 fusions who were treated with *'standard second line chemotherapy'* are similar to the median PFS and response rates reported for participants in the ABC-06 study. However, unlike the study by Jain *et al*[21] no within study comparison of outcomes, between participants with and without FGFR mutations, is provided.

The company also stated: *'Jain et al (2018)[21] conducted a retrospective analysis of 377 patients with CCA, including 95 patients with FGFR molecular alterations (63 of whom had FGFR2 fusions), and showed that patients with FGFR molecular alterations not treated with an FGFR inhibitor had a longer median OS from the time of initial diagnosis than patients without FGFR molecular alterations (30 versus 20 months, respectively; p<0.003). Median PFS for the subset of patients who received 1L chemotherapy for disease (31 patients with FGFR molecular alterations and 146 patients without FGFR molecular alterations) showed a non-significant result of 7.8 and 5.8 months, respectively (p=0.074). Furthermore, in a related updated analysis, differences between PFS in patients with tumours harbouring FGFR2 fusions and those without FGFR2 fusions were not statistically significant (6.0 vs 6.0 months, hazard ratio [HR] 1.19, p=0.36).[24] Although cross-trial comparisons are not recommended, compared to historical data in the 1L setting, it seems that CCA patients with FGFR2 fusions may respond similarly to chemotherapy or even worse than unselected biliary tract cancer (BTC) population, supporting the notion that these patients may benefit from a targeted treatment, based on the data from FIGHT-202.[25]'*

ERG comment: The ERG notes that Jain *et al* (2018)[21] does not report any data on PFS. The updated analysis cited[24] found no significant differences in PFS between iCCA patients with FGFR2 fusions and those without FGFR2 mutations, when treated with gemcitabine-platinum based chemotherapy (0.5 v 0.5 yrs., HR 1.19, P=0.36). However, this publication[24] also confirmed the previously reported difference in median OS between patients whose tumours exhibited FGFR2 fusions compared to those that were wild type for FGFR2 fusions (2.7 vs 1.3 yrs., HR 0.44, p=0.002).

'The hypothesis that FGFR2-rearranged CCA may benefit similarly or less from chemotherapy compared to non-FGFR2 rearranged CCA was replicated in another retrospective study conducted by Boileve et al (2019).[26] They showed a median PFS duration of 4.7 months (95% CI: 2.1, 6.0) for 30 patients with FGFR2 fusions on 1L gemcitabine and platinum therapy. These results were updated recently at American Society of Clinical Oncology (ASCO) 2020 and confirmed the previous mPFS result of 4.7 months.[26] In a related retrospective analysis that included 135 patients, Goyal et al (2020)[27] showed that for the 55 patients with FGFR2 fusions who received gemcitabine/cisplatin as 1L palliative systemic therapy, the median time on treatment (ToT) was 6.2 months and the median OS from time of initial diagnosis was 36.1 months.[27]'

ERG comment: The ERG notes that neither of the two studies cited, Boileve *et al* (2019)[26] and Goyal (2020),[27] provide within study comparative survival data for patients with FGFR2 mutations vs those without, when treated with systemic chemotherapy.

ERG comment: In summary, the ERG considers that the extent to which the efficacy of second-line systemic chemotherapy, in people with advanced CCA, may vary with FGFR mutation status remains uncertain. This uncertainty casts doubts on the relevance of the company's MAICs, which are discussed further in sections 4.3 and 4.4.

2.3 Critique of company's description of current service provision.

The CS (Section B.1.3.2) states that CCA has a poor prognosis but notes that UK survival data, from large scale, retrospective, database analyses are lacking.[2] Approximately 70% of patients are diagnosed late with unresectable, locally advanced, or metastatic disease and these patients have an estimated five-year survival rate of ≤10%.[7, 28, 29] Of the 30% of patients initially classified as having resectable disease, 10-45% are determined to be unresectable during explorative laparotomy.[3] For patients with biliary tract cancer (BTC) who have progressed on first-line treatment, the reported median OS was 6.2 months when treated with systemic chemotherapy (mFOLFOX plus active symptom care [ASC]).[23]

Treatment for unresectable, locally advanced, or metastatic patients is limited to chemotherapy for patients with Eastern Cooperative Oncology Group (ECOG) performance status 0–1.[2] Current standard of care (SOC) for these patients, in the UK, is combination treatment with cisplatin-gemcitabine, as established by the 2009/2010 ABC-02 trial[30] and supported by the 2012 British Society of Gastroenterology (BSG) guidelines[31] and the European Society for Medical Oncology (ESMO) 2016 practice guidelines.[32] The CS notes that there are no UK approved targeted therapeutic options for patients with CCA with *FGFR2* fusions/rearrangements.[2]

The CS (pg20) states that: *'There are no data on the efficacy of second-line (2L) systemic chemotherapy in previously treated, unresectable, locally advanced, or metastatic CCA with FGFR2 fusions/rearrangements—the target population of this submission.* '[2] A systematic review of second-line chemotherapy in advanced biliary cancer evaluated 14 phase 2 clinical trials,[33] and concluded that there was insufficient evidence to establish a SOC due to the small patient cohorts, variation in chemotherapy regimens, lack of consensus on primary endpoint, heterogeneity of patients, and poor outcomes.

ERG comment: The company were asked: *'Please provide evidence to show that there are no studies which provide efficacy data second-line (2L) systemic chemotherapy in previously treated, unresectable, locally advanced, or metastatic CCA with FGFR2 fusions/rearrangements, i.e. that there are no studies which can provide comparator data for a population comparable to that of the FIGHT-202 study (the target population of this submission).* '[1]

The company responded: *'This statement was meant to reflect that there are no prospective studies on the effect of second-line or above (≥2L) systemic chemotherapy specifically in patients with previous treated, unresectable, locally advanced or metastatic CCA with FGFR2+ fusions/rearrangements. We suggest amending this statement to specify the term 'prospective', as two recent published abstracts describe retrospective analyses in patients with previously treated advanced/metastatic CCA with FGFR2 fusions/rearrangements from clinical trials.[22, 34] The relevance of these publications is limited as they were post-hoc, retrospective, analyses of patients within a clinical trial setting. All other published data were limited to retrospective literature reviews and analyses in the first-line (1L) setting with no published data on PFS or OS in CCA patients with FGFR2 fusions/rearrangements in the ≥2L setting.*

Overall, limitations of these retrospective studies relate to differing definitions of survival time, enrolment of patients outside CCA or, more specifically, intrahepatic CCA, and recruitment of patients

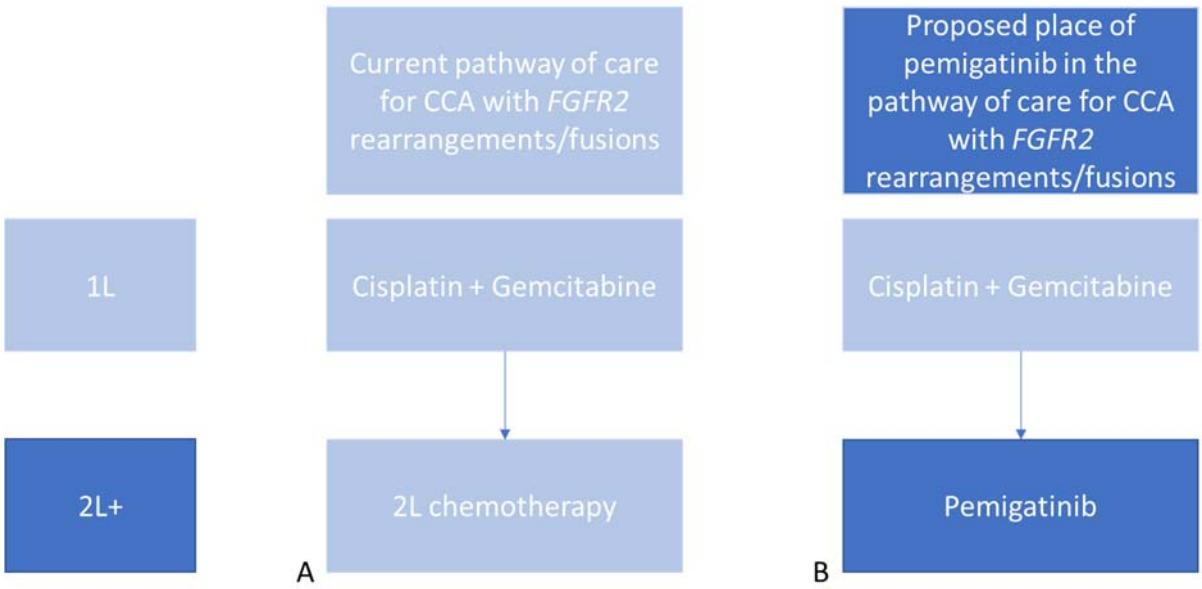
in different stages of their disease journey, as well as data limited to reference centres that can have inherent selection bias.'

ERG comment: The ERG notes that the first reference cited[34] reports a post-hoc analysis of participants in the FIGHT-202 study, where the stated objective was: *'to evaluate PFS on standard systemic therapy received prior to study enrolment among pts with CCA harbouring FGFR2 fusions or rearrangements (FGFR2+).'* Whilst acknowledging that the participants in this study would have been at a more advanced stage of disease as they commenced treatment with pemigatinib, the ERG considers that the potential for a within-patient comparison of PFS on ≥2L chemotherapy versus pemigatinib, in the specified population, remains worthy of consideration. The second retrospective study,[22] provides a similar analysis in relation to a trial of infigratinib, an oral FGFR1–3-selective TKI, as a third- or later-line treatment for patients with advanced or metastatic CCA and FGFR2 fusions; the ERG considers that this study is also a potentially relevant source of comparator data.

The CS (pg22) further states that: *'There are no studies evaluating real-world treatment patterns specifically in patients with previously treated, unresectable, locally advanced, or metastatic CCA with FGFR2 fusions/rearrangements.'*[2] A retrospective multicentre study, conducted in Italy between 2004 and 2103 to explore second-line treatment outcomes for patients with advanced BTC, was described.[2, 35] This study reported the use of a variety of regimens (monotherapy with 5-fluorouracil or capecitabine, gemcitabine plus 5-fluorouracil or capecitabine, capecitabine plus mitomycin-C, 5-fluorouracil+irinotecan + folic acid (FOLFIRI) or capecitabine + irinotecan (XELIRI), retreatment with gemcitabine plus cisplatin or oxaliplatin, FOLFOX or oxaliplatin + capecitabine (XELOX), epirubicin plus cisplatin plus 5-flurouracil, gemcitabine plus irinotecan, monotherapy with gemcitabine, and 'other regimens'), across ten Italian institutions, indicating the absence of a SOC.[2, 35] The median PFS with second-line treatment regimens, in 174 patients, was 3.0 months (95% CI: 2.7 to 3.4 months) and the median OS was 6.6 months (95% CI: 5.7 to 8.1 months).[35]

Figure 2.1 shows the current care pathway (A) and the care pathway proposed by the company (B) for patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements in England and Wales.

Figure 2.1: Proposed place of pemigatinib in the care pathway for previously treated, unresectable, locally advanced, or metastatic CCA patients with FGFR2 fusions/rearrangements in England and Wales



1L = first line; 2L = second line
Source: CS, figure 5, pg. 25[2]

The CS (pg26)[2] notes that the national Health Service (NHS) Long Term Plan[36] (beginning 2020/2021) aims to extend the use of genomic testing so it will be routinely available to all cancer patients. The initial goal is that by 2023 over 100,000 patients will have received a genomic test for their cancer.[36] The company asserts that: *'as a result of conversations with providers based at some of the hubs, it is our understanding that a wider range of FGFR tests will be added imminently including FGFR2 fusions/arrangements for CCA. Considering this, it is worth noting that pemigatinib is not the sole FGFR inhibitor in development for the treatment of CCA. It is likely other such molecules will soon be introduced to the UK thus the availability of genetic testing for this indication will not solely support pemigatinib.'*[2]

ERG comment: The ERG notes that, with respect to genomic testing, different methods of testing FGFR mutation status may differ both in terms of the mutations targeted and limit of detection (the lowest proportion of tumour cells with a mutation that can be detected). The exact definition of FGFR mutation positive is therefore likely to vary according to which test is used. All testing methods are essentially reference standard methods for classifying mutation status, as defined by the specific test characteristics. If any benefits observed in research settings are to translate to benefits in real world clinical practice, it is important that the characteristics of the test used in clinical practice match those of the test used in the research studies (i.e. the tests used will select similar populations for treatment). The company was asked: *'Please provide details of the method used to determine FGF/FGFR mutation status in the FIGHT-202 study: e.g. specify which mutations were included in each cohort; what was the limit of detection (i.e. the minimum percentage of mutation in tumour cells required to produce a positive result). Please also provide an indication of whether or not the test used in FIGHT-202 is currently available/used in the UK NHS, and whether any alternative tests used in the UK NHS share the same operating characteristics.'*[1]

The company responded: *'Archival, formalin-fixed, paraffin-embedded tumour samples from all pre-screened or enrolled patients in FIGHT-202 were analysed for genomic alterations using the FoundationOne® targeted next-generation DNA sequencing assay (Foundation Medicine Inc.), which uses hybrid capture–based DNA target enrichment to identify somatic genomic alterations in the coding regions of 315 cancer-related genes and introns from 28 genes often rearranged in cancer. The sensitivity of this assay for the detection on gene rearrangements was >90% for samples with ≥20% tumour content.'*[1]

And: *'Whilst the FoundationOne® assay itself is not available/used in the UK NHS, genomic testing with next-generation sequencing (using similar assays) is commonplace and used extensively throughout the NHS as a diagnostic tool in cancer. Testing for genetic alterations such as EGFR, ALK, BRAF, RET and ROS1 and others is commonplace in diseases such as non-small cell lung cancer and melanoma. In addition to the FoundationOne® assay, there are a variety of commercially available assays that can detect FGFR2 fusions (e.g. Illumina TSO500, ArcherDX FusionPlex, and other locally developed tests), thus the detection of FGFR2 fusions for CCA may use the same technology as is current standard of care for these cancers.'*[1]

ERG comment: The ERG does not consider that this response adequately addresses the question of the availability of appropriate FGFR mutation testing methods (comparable to those used in the FIGHT-202 study) in the UK NHS. As highlighted by NICE Diagnostic guidance DG9 (EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer),[37] it is important to establish a link between each test that is to be used to select patients for treatment and patient outcomes. This point is supported by the following research recommendation, included in DG9: *'NICE recommends that studies directly comparing different epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation test methods are performed. These studies should include the re-testing of stored non-small-cell lung cancer (NSCLC) tumour samples using different EGFR-TK mutation test methods and should link to patient outcomes.'*[37]

3. Critique of company's definition of decision problem

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with advanced cholangiocarcinoma (CCA) with FGFR2 fusion or rearrangement that is relapsed or refractory after at least one prior systemic therapy.	As final scope	NA	The ERG has some concern that the population included in FIGHT-202, which is 98% intrahepatic cholangiocarcinoma (iCCA), might not be fully representative of the population in the decision problem, which is CCA regardless of whether intrahepatic or not. However, the ERG acknowledges that most (approximately 95%)[21] patients with CCA, who have FGFR2 mutations, have intrahepatic disease.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Intervention	Pemigatinib	As final scope	NA	The ERG has concerns about the method(s) that will be used, in UK clinical practice, to determine FGFR mutation status and hence to select patients for treatment with pemigatinib. It is unclear whether the method(s) used in clinical practice will be consistent with that used in the FIGHT-202 study.
Comparator(s)	• Chemotherapy • Best supportive care (including stent insertion)	As final scope	NA	The ERG is concerned that the submission only considered one possible chemotherapy regimen.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates	As final scope	NA	None

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	• adverse effects of treatment • health-related quality of life			
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The use of pemigatinib is conditional on the presence of *FGF/FGFR* gene alteration. The economic modelling should include the costs associated with diagnostic testing for the *FGF/FGFR* gene alteration in people with relapsed or refractory advanced CCA who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.	Cost effectiveness of the treatments specified are expressed in terms of incremental cost per quality adjusted life year. The time horizon for estimating clinical and cost effectiveness in the cohort simulation model is lifetime Costs are included from an NHS and Personal Social perspective Testing costs are not included in the base case analysis as patients will be tested routinely according to NHS plans	A sensitivity analysis is provided with an estimated cost of the genetic test. Incyte understands from clinician and NHS service provider input that genetic testing for CCA (including *FGFR2* gene alterations) will become part of routine practice due to availability of new treatment options for this particular patient population and the current intent of the NHS Long Term Plan for the service to offer whole genome sequencing as part of routine care. Genetic testing by next generation sequencing (NGS) uses sequencing panels to detect alterations across a wide range of genes including FGFR.	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Subgroups to be considered	None	As final scope	NA	None
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	As final scope	NA	None

Based on Table 1 of the CS[2]
CCA = cholangiocarcinoma; CS = company submission; FGFR = fibroblast growth factor receptor; HRQoL = health-related quality of life; NA = not applicable; NGS = next generation sequencing; NHS = national health service

3.1 Population

The population in the submission is a subset of that defined in the scope and the expected licenced indication for pemigatinib, as described in the summary product characteristics (SmPC).[38]

The submission relies, primarily, on one open-label, single arm, phase 2 study (FIGHT-202).[25] This study included 146 patients with histologically or cytologically confirmed CCA who had failed at least one prior treatment.[2, 25] Patients were grouped into three cohorts: cohort A, those with *FGFR2* fusions/rearrangements (n=107); cohort B, those with other FGF/FGFR fusions/rearrangements (n=20); cohort C, those with FGF/FGFR fusions/rearrangements (n=18).[2, 25]

ERG comment: With respect to the FIGHT-202 study, only those patients in cohort A are relevant to the scope of this submission. Data from cohort A are summarised in the clinical effectiveness sections of this report. The ERG has some concern that the population included in FIGHT-202, which is 98% intrahepatic cholangiocarcinoma (iCCA), might not be fully representative of the population in the decision problem, which is CCA regardless of whether intrahepatic or not. However, the ERG acknowledges that most (approximately 95%)[21] patients with CCA, who have FGFR2 mutations, have intrahepatic disease.

3.2 Intervention

The key product characteristics are summarised in Table 3.2.

Table 3.2: Pemigatinib product characteristics

UK approved name and brand name	**Pemigatinib (Brand name Pemazyre®)**
Mechanism of action	Pemigatinib is a potent and selective FGFR1, 2, and 3 inhibitors. Pemigatinib blocks autophosphorylation and activation of major FGF/FGFR signalling pathways, inhibiting the growth of cells with *FGFR2* fusions/rearrangements.
Marketing authorisation/CE mark status	MAA submitted to EMA: November 2019 CHMP opinion anticipated: December 2020 Full MAA anticipated: January 2021
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Pemigatinib monotherapy is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (*FGFR2*) fusion or rearrangement that is relapsed or refractory after at least one line of systemic therapy.
Method of administration and dosage	Pemigatinib is administered 13.5 mg QD on a 14 day on, seven day off schedule. Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity.
Additional tests or investigations	Incyte understands from clinician and NHS service provider input that genomic testing for CCA patients is likely to become part of routine practice due to availability of new treatment options for this particular patient population and the current intent of the NHS Long Term Plan for the service to offer whole genome sequencing as part of routine care. As testing represents broader assessment of different oncogenic alterations the cost of the FGFR2

UK approved name and brand name	Pemigatinib (Brand name Pemazyre®)
	genetic test which represents just one target has therefore been included as scenario analysis.
List price and average cost of a course of treatment	The drug acquisition cost of pemigatinib is £37.88 per mg (£511.36 per 13.5mg tablet). Under the administration schedule of 14 days on, seven days off, the weekly total drug cost is [redacted] and £7,159 per treatment cycle (21 days).
Patient access scheme (if applicable)	A submission has been made to NHS England regarding a patient access scheme (PAS) which includes a simple discount arrangement.
Based on Table 2 of the CS.[2] CCA = cholangiocarcinoma; CE = Conformité Européenne (Eng. European conformity); CHMP = Committee for Medicinal Products for Human Use; CS = company submission; EMA = European Medicines Agency; FGF = fibroblast growth factor; FGFR = fibroblast growth factor receptor; MMA = marketing authorisation application; NHS = National Health Service; PAS = patient access scheme; QD = once daily; SmPC = Summary of product characteristics; UK = United Kingdom	

ERG comment: The dosing schedule used in the included study (FIGHT-202)[25] is consistent with the expected recommended dosing schedule, as described in Table 3.2.

3.3 Comparators

The NICE scope[39] lists the comparators as:

- Chemotherapy
- Best supportive care (including stent insertion)

but does not define specific chemotherapy regimens of interest.

ERG comment: The ERG agrees with the company assertion, in section B.1.3.3 of the submission, that there is currently no standard of care (SOC) for second-line chemotherapy for patients with advanced CCA. In light of this, the ERG considers that the inclusion of only one chemotherapy regimen (mFOLFOX + ASC), in the MAIC used to estimate the comparative effectiveness of pemigatinib in the original submission, was inadequate.

3.4 Outcomes

The NICE scope[39] lists the following outcome measures:

- overall survival
- progression-free survival
- response rates
- adverse effects of treatment
- health-related quality of life

ERG comment: The CS[2] included an additional relevant outcome from the FIGHT-202 study,[25] duration of response (DOR), defined as the time from the date of complete response (CR) or partial response (PR) until progressive disease (PD). The ERG notes that the FIGHT-202 study[25] assessed health-related quality of life using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the EORTC QLQ-BIL21 (CCA and

gall bladder cancer). Results for this outcome were not included in the summary of the FIGHT-202 study provided in the clinical effectiveness section of the CS,[2] but were reported in full in the CSR. [25]

3.5 Other relevant factors

The CS (Section B.1.4) states*: 'There are no known equality issues relating to the use of pemigatinib in patients with previously treated, unresectable, locally advanced, or metastatic CCA with FGFR2 fusions/rearrangements.'*[2]

ERG comment: The ERG has no further comments on other factors.

4. Clinical effectiveness

4.1 Critique of the methods of review(s)

The company conducted a systematic review *'to identify the available clinical evidence for efficacy, safety, and tolerability of existing and upcoming treatments for patients with advanced/metastatic or surgically unresectable CCA for whom at least one treatment has failed, irrespective of any translocations.'*[40] This section of the ERG report describes and critiques the methods of the review including searching, inclusion criteria, data extraction, quality assessment and evidence synthesis.

The systematic review was described, in detail, in Appendix D of the CS.[40]

4.1.1 Searches

Section B.2.1 and Appendix D of the CS detail a systematic literature review (SLR) conducted to identify relevant clinical evidence in previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements. Searches were conducted in November 2018, with a subsequent update in April 2020. No language or publication date limits were reported. Databases were searched from date of inception. The searches were broad and so the same strategies were used in the update even though the inclusion criteria were revised. A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

	Resource	Host/source	Date ranges	Dates searched
Electronic databases	MEDLINE, Embase	EMBASsE.com	(i)not provided (ii)1.10.18-21.4.20	(i)9.11.18 (ii)21.4.20
	MEDLINE in-Process	PubMed.com	(i)not provided (ii)1.10.18-21.4.20	(i)9.11.18 (ii)21.4.20
	Cochrane CDSR	Wiley.com	(i)not provided (ii)not provided	(i)9.11.18 (ii)21.4.20
	Cochrane CENTRAL	Wiley.com	(i)not provided (ii)not provided	(i)9.11.18 (ii)21.4.20
	Cochrane Protocols, Clinical Answers, Editorials and Special Collections			
Conference proceedings	European Society for Medical Oncology (ESMO)	No information	2016-2020	(i)9.11.18 (ii)21.4.20
	American Society of Clinical Oncology (ASCO)			
	International Liver Cancer Association (ILCA)			
	American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI)			
	European Society for Medical Oncology			

	Resource	Host/source	Date ranges	Dates searched
	Gastrointestinal Cancers (ESMO-GI)			
	American Association for Cancer Research (AACR)			
Additional resources	National Institute for Health and Care Excellence (NICE) guidance	No information	No restriction	(i)9.11.18 (ii)21.4.20
	Scottish Medicines Consortium (SMC)			
	All Wales Medicines Strategy Group (AWMSG)			
	Canadian Agency for Drugs and Technology in Health (CADTH)			
	German Institute for Quality and Efficiency in Healthcare			
	Pharmaceutical Benefits Advisory Committee (PBAC)			
	Haute Autorité de Santé (HAS)*			
	Haute Autorité de Santé (HAS)*			
(i) - original search; (ii) - update search *English publications only				

ERG comment:

- Searches was undertaken to identify clinical effectiveness data. The CS provided sufficient details for the ERG to appraise the literature searches. A good range of database and conference proceedings were searched, as well as health technology assessment (HTA) agencies and reference checking. Both the original and the update searches were overall well conducted and documented, making them transparent and reproducible. The date segments were not reported for the MEDLINE, EMBASE or Cochrane library databases so it is unclear if they were searched from inception.
- No date or language limits were unnecessarily applied to the database searches.
- Study design filters were appropriately used; however, these were not referenced. A facet to restrict the results to advanced disease was also employed and this used a range of appropriate terms.

4.1.2 Inclusion criteria

The inclusion/exclusion criteria for the clinical efficacy and safety component of this systematic review are reproduced in Table 4.2. The target population of the original SLR (November 2018) was adults (≥ 18 years) with advanced/metastatic or surgically unresectable CCA for whom at least one treatment has failed, with *FGFR2* rearrangements/fusions.[40] The inclusion criteria were revised, when update searches were conducted (April 2020), to also include adults (≥ 18 years) with advanced/metastatic or surgically unresectable CCA for whom at least one treatment has failed, irrespective of *FGFR2* mutation status.[40] As part of the update SLR, 581 articles flagged as reporting data for BTC at primary screening, 79 articles flagged for non-availability of FGFR2+ CCA at secondary screening and 32 articles flagged for reporting data for the BTC population at secondary screening, in the original SLR, were also screened to ensure consistency across the search period. [40]

Appendix D of the CS listed citations for 209 publications, relating to 108 studies that met the inclusion criteria for the update SLR.[40]

ERG comment: The company's estimates of the comparative effectiveness of pemigatinib vs. chemotherapy initially relied upon a MAIC (section B.2.9 of the CS),[2] which utilised data from a single RCT of mFOLFOX + ASC vs. ASC alone.[23] However, this trial was conducted in a population which does not match the scope for this assessment; patients with locally advanced or metastatic BTC (only 60/117 [51.3%] of patients had CCA) who were previously treated with cisplatin-gemcitabine chemotherapy and whose *FGFR2* mutation status was not reported.[2, 23]

The company was asked: *'Please provide evidence to show that there are no studies which provide efficacy data second-line (2L) systemic chemotherapy in previously treated, unresectable, locally advanced, or metastatic CCA with FGFR2 fusions/rearrangements, i.e. that there are no studies which can provide comparator data for a population comparable to that of the FIGHT-202 study (the target population of this submission).'*[1]

The company responded: *'This statement was meant to reflect that there are no prospective studies on the effect of second-line or above (≥2L) systemic chemotherapy specifically in patients with previous treated, unresectable, locally advanced or metastatic CCA with FGFR2+ fusions/rearrangements. We suggest amending this statement to specify the term 'prospective', as two recent published abstracts describe retrospective analyses in patients with previously treated advanced/metastatic CCA with FGFR2+ fusions/rearrangements from clinical trials.[22, 34] The relevance of these publications are limited as they were post-hoc, retrospective, analyses of patients within a clinical trial setting. All other published data were limited to retrospective literature reviews and analyses in the first-line (1L) setting with no published data on PFS or OS in CCA patients with FGFR2+ fusions/rearrangements in the ≥2L setting.*

Overall, limitations of these retrospective studies relate to differing definitions of survival time, enrolment of patients outside CCA or, more specifically, intrahepatic CCA, and recruitment of patients in different stages of their disease journey, as well as data limited to reference centres that can have inherent selection bias.'

ERG comment: The ERG notes that the first reference cited[34] reports a *post-hoc* analysis of participants in the FIGHT-202 study, where the stated objective was: *'to evaluate progression free survival (PFS) on standard systemic therapy received prior to study enrolment among pts with CCA harbouring FGFR2 fusions or rearrangements (FGFR2+).'* Whilst acknowledging that the participants in this study

would have been at a more advanced stage of disease as they commenced treatment with pemigatinib, the ERG considers that the potential for a within-patient comparison of PFS on ≥2L chemotherapy versus pemigatinib, in the specified population, remains worthy of consideration. The second retrospective study,[22] provides a similar analysis in relation to a trial of infigratinib, an oral FGFR1–3-selective TKI, as a third- or later-line treatment for patients with advanced or metastatic CCA and FGFR2 fusions; the ERG considers that this study is also a potentially relevant source of comparator data.

The company were also asked[1] to explain why studies, cited in the report SLR in appendix C of the CS[40] but not included in the submission, which appeared to concern the efficacy of second-line (2L) systemic chemotherapy in previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2+* fusions/rearrangements, were not used to provide comparator data for the submission.

The company stated that the two studies discussed above were *'retrospective analyses of single-arm studies and therefore, lack the robustness of a randomised controlled trial (RCT) such as ABC-06. Inadequate data were reported from these abstracts, and they represent a limited risk as they are broadly in line with ABC-06.'*

The ERG does not agree with the use of study design (RCT) to select studies for inclusion in the MAIC. All studies were treated as single arm studies in the MAIC, so single arm intervention and observational studies would be eligible and there was no need to specify that data came from a comparative trial. The extent to which the populations of the selected studies match that specified in the scope for this appraisal is of greater importance than study design. The ERG also notes that the justification for exclusion that '*inadequate data were reported from these abstracts'* cannot reasonably be applied to Bibeau 2020,[34] since this abstract reports a *post-hoc* analysis of data from the FIGHT-202 study. The company also stated that: *'The relevant extracted data from these studies in the 2L+ treatment of FGFR2+ CCA can be found in Tables 15 (Response rate of non-randomised controlled trials [RCT] and observational studies) and 16 (Survival outcomes of non-RCT and observational studies) of the SLR.'* However, these tables were not included in the submission: *'Data from these studies were not included in the NICE appendices, which only included studies relevant from a MAIC perspective.'*

Further inclusion criteria were subsequently applied,[40] in order to select studies for the MAIC:

- Availability of Kaplan–Meier plots for OS and PFS (must have both as they are needed to derive the patient-level data (PLD) needed for MAICs)
- Minimum sample size (n ≥ 20)
- The treatment used is representative of SOC (chemotherapy or pemigatinib)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 close to 100% – this is due to the high percentage in FIGHT-202 and matching being difficult on this variable (must be 80% ECOG 0–1)
- iCCA percentage as high as possible – as above, FIGHT-202 is 98% for this variable and thus will be difficult (impossible) to match on

Eight studies met the inclusion criteria for the update SLR and the additional inclusion criteria for the MAIC.[40] None of these studies reported the proportion of patients with FGFR2+, however, it was not clear whether any of the studies that met the inclusion criteria for the update SLR, but failed one or

more of the additional MAIC inclusion criteria, reported the proportion of patients with FGFR2+. Of the eight remaining studies the company selected only one (ABC-06)[23] for inclusion in the MAIC, stating that selection was based on larger sample size, recency of publication and inclusion of a UK population.[40]

ERG comment: The ERG is concerned that the application of both the listed inclusion criteria for the MAIC and the *post-hoc* process used to finally select a single study may have resulted in the exclusion of relevant comparators from the MAIC and/or the exclusion of studies which may have provided comparator data for a population closer to that specified for this submission.

Given that FIGHT-202 was a multinational study, whereas ABC-06 was based in the UK, the company were asked: *'Please provide a justification for the selection of the ABC-06 study for use in MAIC based on its inclusion of only UK patients.'*[1]

The company responded: *'Acknowledging that there is no comparator study identified in the SLR that perfectly matches the pemigatinib target population, ABC-06 was deemed by clinicians as the most appropriate study for reflecting standard of care for these patients in England and for MAICs.[41] Since the treatment and patient population in ABC-06 is most likely to match the standard of care and patient profile in the UK compared to the other six originally identified studies (Table 14, Appendix D in CS), this was deemed the most suitable comparator study for this decision problem.'*[1]

ERG comment: The ERG does not consider that this response provides sufficient justification for the exclusion of studies not conducted in the UK, particularly given that cohort A of the FIGHT-202 study[25] only included six UK patients.

The company was also asked:

'Were any studies excluded because they only provided Kaplan–Meier plots for either OS or PFS or only reported response rates? If yes, please provide a revised MAIC, using separate data sources for PFS and OS, so that data from all relevant studies are utilised.'[1]

The company responded*: 'From the SLR, there were eight studies that reported an OS curve only and four studies reported a PFS curve only. These were previously excluded from consideration of the MAIC since a HR for both OS and PFS is required in the model, and it was considered appropriate to use the same data source to inform both model inputs.'*

The company have provided additional MAICs utilising data from two of these studies,[42, 43] both of which provided OS data only. The following reasons were given for exclusion of the remaining 10 studies:

'Of the 12 studies only reporting a Kaplan-Meier (KM) curve for one of either OS or PFS:

- *4/12 of these studies did not have a sample size >20 and were excluded as they did not meet the original criteria, leaving eight studies for consideration*
- *4/8 of these studies did not include a standard of care treatment, leaving four studies for consideration*
- *1 study[44] had a very low number of patients with intrahepatic CCA (34%), whereas FIGHT-202 has 98%, so this study was not considered sufficiently comparable to FIGHT-202*

- *1 study[45] had a very low number of patients with ECOG 0–1 performance status (66%), whereas FIGHT-202 had 95%, so this study was not considered comparable to FIGHT-202'*[1]

ERG comment: The ERG agrees with the reasons provided for exclusion in the first two bullet points. However, given that all of the identified studies have limitations with respect to matching to the FIGHT-202 population, the ERG questions the validity of excluding Moik 2019[44] and Kang 2014;[45] with respect to the reason given for the exclusion of Moik 2019, it should be noted that only 44% of participants in the ABC-06 trial[23] had iCCA (cf. 34% in Moik 2019 and 98% in FIGHT-202).

The ERG also asked:

'Appendix D of the submission (Table 14) lists seven studies which met the inclusion criteria specified for the MAIC (D.1.6.1). Each of these studies evaluated a different chemotherapy regimen. Given that section B.1.3.3 of the submission argues (with supporting evidence) that there is currently no SOC for second line chemotherapy for patients with advanced CCA, please provide a revised MAIC, including all studies which met the inclusion criteria specified for the MAIC (D.1.6.1). With reference to question A18, such studies might not have been conducted solely in the UK.'[1]

The company have provided additional MAICs utilising data from a further two[46, 47] of the seven studies, in addition to ABC-06.[23] The following reasons were given for exclusion of the remaining four studies:

'Upon further investigation of the publications, the following studies were not considered appropriate for the MAIC:

- *The retrospective study by Croitoru et al 2012 focused on first-line patents and reported baseline characteristics at first line, rather than second line (but reported KMs for second line OS and PFS).[48] As KMs were reported for second line OS and PFS, it would not be possible to match to the previously-treated population*

- *The Rogers et al. 2014 study was made up of four arms, each of which had low patient numbers (11, 16, 21, and 8).[49] As such, criteria for sample size, one of the initial MAIC inclusion criteria, were not met. Additionally, the baseline characteristics were only reported for the overall population and not per arm*

- *The Belkouz et al. 2020 study had a very low number of patients with intrahepatic CCA (16.7%),[50] whereas FIGHT-202 had 98%.[25] This study was not considered sufficiently comparable to FIGHT-202*

- *The Westin et al. 2017 study had a very low number of patients with ECOG 0–1 performance status (64%),[51] whereas FIGHT-202 had 95%.[25] This study was also considered not sufficiently comparable to FIGHT-202'*[45]

ERG comment: The ERG agrees with the reasons provided for exclusion of Croitoru 2012[48] and Rogers 2014.[52] However, given that all of the identified studies have limitations with respect to matching to the FIGHT-202 population, the ERG questions the validity of excluding Belkouz 2020[50] and Westlin 2017,[51] studies which could have provided comparator data for further systemic chemotherapy options.

ERG comment: Overall, the ERG agrees that all identified studies, which could provide comparator data for this submission, have limitations. However, the ERG does not consider that all of the potentially informative options for provision of comparator data have been adequately explored.

Table 4.2: Eligibility criteria for the updated (April 2020) systematic review of clinical effectiveness

Domain	Inclusion criteria	Exclusion criteria
Patient population	• Adults (≥ 18 years) with advanced/metastatic or surgically unresectable *FGFR2*+ CCA for whom at least one treatment has failed • Adults (≥ 18 years) with advanced/metastatic or surgically unresectable CCA for whom at least one treatment has failed	• Publications reporting on patient populations in the following categories: • Children • Patients without metastatic/advanced stage • Treatment-naïve patients • Resectable CCA
Line of therapy	Second- or later-lines of therapy*	First-line therapy
Intervention	All pharmacological interventions	• Non-pharmacological interventions • Surgical procedures • Adjuvant/neoadjuvant treatment • Stents • Chemoradiotherapy/ radiotherapy • Photodynamic therapy (except Photofrin®)
Comparators	• Placebo • Best supportive care (author defined) • Any other pharmacological intervention • No comparator limit for single-arm trials	None
Outcomes (not exhaustive)	• Response rate • Overall survival • Progression-free survival • Time to treatment discontinuation • Duration of response • Mortality • HRQoL	None

Domain	Inclusion criteria	Exclusion criteria
	• Incidence of adverse events • Study/treatment discontinuation • Relationship between intermediate outcomes (progression-free survival, response rate) and overall survival • Disease control rate • Stable disease • Time on treatment • Time to response • ORR • QoL/PRO	
Study design	• RCTs • Non-RCTs including single-arm and observational studies e.g. retrospective studies • Systematic reviews**	• Preclinical studies • Case reports, case series • Pharmacokinetic and economic studies
Date	• Original SLR: Data inception to 9 November 2018 • Update SLR: 1 October 2018 to 21 April 2020	None
Language	English	Any other language
Publication type	Journal articles and conference abstracts	• Editorials • Commentaries • Letters

Based on Table 11 of Appendix D of the CS[40]

* Citations assessing patients receiving multiple lines of therapy were included at primary screening

** Systematic reviews of RCTs, non-RCTs, single-arm and observational studies were utilised only for bibliography searches.

CCA = cholangiocarcinoma; FGFR2+ = fibroblast growth factor receptor-2; HRQL = health-related quality of life; ORR = overall response rate; PRO = patient-reported outcome; QoL = quality of life; RCT = randomised controlled trial

ERG comment: Appropriate measures to reduce the potential for error and bias in the study selection process were reported in Appendix D of the CS: *'Primary (Level 1) screening was performed by two independent reviewers who reviewed each reference (title and abstract) identified by the literature search, applied basic study selection criteria (population, intervention, and study design) and decided whether to include or exclude the reference at that stage. Any uncertainty regarding the inclusion of studies was checked by a senior reviewer independently of the initial reviewers. For secondary (Level 2) screening of potentially relevant articles, the full articles were obtained. These were independently reviewed by two independent reviewers against each eligibility criterion; any uncertainty regarding the inclusion of a study was checked by a senior reviewer independently of the initial reviewers.'*[40]

4.1.3 Critique of data extraction

The CS did not include any information on measures to reduce the potential for error and bias in the data extraction process.

ERG comment: The ERG is unable to assess the potential for error and bias in the data extraction process.

4.1.4 Quality assessment

The company assessed the methodological quality of the FIGHT-202 study,[25] based on one publication,[53] using 27 criteria adapted from the Downs and Black checklist[54] Appendix D of the CS[40] included methodological quality assessments, based on the Downs and Black checklist, for all 103 non-RCTs which net the inclusion criteria for the updated SLR (including FIGHT-202). No specific tool was cited for the risk of bias assessment reported for ABC-06[23] in Appendix D of the CS,[40] however, this assessment appears to have been based on the Cochrane risk of bias tool. No risk of bias assessments were reported for the remaining four studies (RCTs) which met the inclusion criteria for the updated SLR.

No information was provided on the number of reviewers who assessed the quality of included studies.

ERG comment: The ERG considers that appropriate criteria were used to assess the methodological quality of included studies. However, it was not possible to assess the potential for error and bias in the quality assessment process, and no risk of bias assessments were reported for four RCTs which met the inclusion criteria for the updated SLR.

4.1.5 Evidence synthesis

There was only one relevant study (FIGHT-202)[25] for the population specified in the scope for this submission, therefore a meta-analysis was not performed.

In the absence of randomised controlled trials comparing the efficacy of pemigatinib directly to that of SoC, an indirect treatment comparison (ITC) was warranted to provide relative treatment effect evidence. The CS states that, because FIGHT-202 was a single arm study, a MAIC was conducted in line with NICE Decision Support Unit (DSU) technical support document (TSD 18), as this enables the calculation of adjusted relative treatment effect estimates (e.g., HRs) in one direct step and allows a set of weights to be derived; the same set of weights can be used for all relevant outcome models (e.g., OS and PFS).[2, 55]

The MAIC is described and critiqued in sections 4.3 and 4.4 of this report.

4.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

Section B.2.2 of the CS[2] identified one ongoing, single arm, phase 2 study (FIGHT-202), (NCT02924376; INCB 54828-202), which is the sole source of data on the clinical effectiveness of pemigatinib in adults with advanced/metastatic or surgically unresectable FGFR2+ CCA for whom at least one treatment has failed.[25, 53] The CS also cites Incyte 'data on file' in relation to the FIGHT-202 study,[56, 57] but these data sources were not supplied in the original submission.

ERG comment: The company were asked to provide copies of all information sources cited in the submission and copies all relevant data sources were subsequently supplied.

The CS (section B.2.2) states that all sources reported the data for the FIGHT-202 study as of the 22 March 2019 cut-off date.

ERG comment: The company were asked to provide all results for the most recent data cut and, at the time of submission of this report, discussions about data provision were ongoing with NICE.

The FIGHT-202 study is summarised in sections 4.2.1 and 4.2.8 of this report.

4.2.1 Details of the included pemigatinib study

The FIGHT-202 study[25, 53] assessed the efficacy and safety of pemigatinib for the treatment of adults with advanced/metastatic or surgically unresectable FGFR2+ CCA for whom at least one treatment had failed. Patients were grouped into three cohorts: cohort A, those with *FGFR2* fusions/rearrangements (n=107); cohort B, those with other FGF/FGFR fusions/rearrangements (n=20); cohort C, those with FGF/FGFR fusions/rearrangements (n=18). Only those patients in cohort A are relevant to the scope of this submission and only data from cohort A are summarised in this report. The intervention was pemigatinib 13.5 mg QD on a 14 day on, seven day off schedule.[25]A summary of study methodology for the FIGHT-202 study is provided in Table 4.3.

ERG comment: The ERG notes that the evidence for the efficacy and safety of pemigatinib, in the population specified for this submission, is limited to one single arm study. No studies comparing pemigatinib to chemotherapy or best supportive care and no studies assessing the efficacy of second-line systemic chemotherapy in previously treated, unresectable, locally advanced, or metastatic CCA with FGFR2 fusions/rearrangements were identified for inclusion in the CS.[2]

Representativeness of UK population

FIGHT-202 is a multi-centre study (67 study sites), conducted across 12 countries.

The company were asked to confirm the number of participants in the FIGHT-202 study who were from the UK.[1] The company stated that: *'A total of six patients (n=6/145; 4.1%) in FIGHT-202 were from the UK. All six patients were in Cohort A (n=6/107; 5.6%).'*

British Society for Gastroenterology treatment guidelines for CCA[2, 58] recommend cisplatin-gemcitabine combination chemotherapy for locally advanced or metastatic unresectable CCA (Grade A). Details of the prior chemotherapy regimens received by patients in cohort A of the FIGHT-202 study are provided in the CSR[25]; 91/107 (85%) had previously received gemcitabine and 81/107 (75.7%) had previously received cisplatin.

ERG comment: The ERG considers that systemic chemotherapy received by patients prior to entry into the FIGHT-202 study is likely to be broadly representative of current UK practice. The extent to which the FIGHT-202 study population is representative of UK patients, with respect to demographic and disease characteristics, may warrant discussion by the appraisal committee.

Table 4.3: Summary of study methodology for the included pemigatinib study

	FIGHT-202
Location	FIGHT-202 enrolled participants at 67 study sites in the United Kingdom, United States, South Korea, France, Italy, Thailand, Germany, Belgium, Israel, Spain, Japan, and Taiwan.
Trial design	A phase 2, open-label, single-arm, multicentre study to evaluate the efficacy and safety of pemigatinib in patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements.
Inclusion criteria	• Adult (≥18 years) patients with histologically or cytologically confirmed CCA who failed one prior treatment • Documentation of *FGF/FGFR* gene alteration status • Radiographically measurable disease per RECIST v1.1 • ECOG PS ≤2 and a life expectancy of at least 12 weeks at the time of screening • Adequate hepatic function (total bilirubin <1.5 x ULN; <2.5 X ULN for patients with Gilbert syndrome or metastatic disease involving liver; aminotransferases ≤2.5 x ULN; ≤5 x ULN for patients with liver metastases) • Adequate renal function (CrCl >30 mL/min) • Serum phosphate ≤ institutional ULN • Serum calcium within institutional normal range
Exclusion criteria	• Prior treatment with select FGFR inhibitors • History of calcium phosphate homeostasis or ectopic mineralisation/calcification • Current evidence of clinically significant corneal or retinal disorder confirmed by ophthalmologic examination • Treatment with other investigational study drug for any indication for any reason, or receipt of anticancer medications within 28 days before first dose of study drug • Untreated brain or central nervous system (CNS) metastases or brain/CNS metastases that have progressed (e.g., evidence of new or enlarging brain metastasis or new neurological symptoms attributable to brain/CNS metastases) • Known additional malignancy that is progressing or requires active treatment • Total bilirubin ≥ 1.5 × ULN; ≥2.5 × ULN if Gilbert syndrome or disease involving liver • AST and ALT > 2.5 × ULN (AST and ALT >5 × ULN in the presence of liver metastases)

	FIGHT-202
	• Potassium levels below institutional lower limit of normal • History of human immunodeficiency virus, or evidence of active hepatitis B or C virus infection • History of clinically significant or uncontrolled heart disease • Concurrent anticancer therapy (e.g., chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, investigational therapy, or tumour embolization) • Received prior radiation therapy administered within 4 weeks of first dose of study drug • History and/or current evidence of ectopic mineralization/calcification
Intervention(s)	Pemigatinib 13.5 mg QD on a 14 day on, seven day off schedule
Comparator(s)	NA
Permitted and disallowed concomitant medication	Concomitant medications were permitted to treat comorbidities or AEs during the study, except: • Potent cytochrome P450 3A4 inhibitors and inducers (note: there were no restrictions on topical ketoconazole) • Another selective FGFR inhibitor • Investigational study drug for any indication • Any anticancer medications other than the study drug
Primary outcomes	ORR in participants with *FGFR2* fusions/rearrangements based on the central genomics laboratory results (Cohort A) Objective response rate was defined as the proportion of participants who achieved a complete response (disappearance of all target lesions) or a partial response (≥ 30% decrease in the sum of the longest diameters of target lesions) based on RECIST v1.1. Clinical response is determined by an independent review committee (IRC).
Secondary outcomes	• DOR: time from the date of CR or PR until PD (all cohorts). • PFS: first dose to progressive disease or death (all cohorts). • ORR in participants with other *FGF/FGFR* alterations (Cohort B). • ORR in all participants with *FGF/FGFR* alterations (Cohorts A and B). • DCR: CR + PR + stable disease (all cohorts). • OS: first dose to death due to any cause (all cohorts)
Patient-reported outcomes	HRQoL evaluation (EORTC QLQ-C30 and EORTC QLQ-BIL21)

	FIGHT-202
Safety outcomes	Safety and tolerability assessed by evaluating the frequency, duration, and severity of AEs
Pre-planned subgroups	NA

Based on Tables 9 in the CS[2] and information from the CSR[25] and study protocol[59]
AEs = adverse events; ALT = alanine aminotransferase; AST = aspartate transaminase; CCA = cholangiocarcinoma; CR = complete response; CrCl = creatinine clearance; CS = company submission; CSR = clinical study report; DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FGF = fibroblast growth factor; FGFR = fibroblast growth factor receptor; HRQoL = health-related quality of life; IRC = independent review committee; NA = not applicable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; ULN = upper limits of normal

4.2.2 Statistical analysis of the included pemigatinib study

Analysis populations in FIGHT-202 included the:

- Efficacy evaluable population: all patients who received at least one dose of pemigatinib and had a known FGF/FGFR alteration. All efficacy analyses were conducted using the efficacy evaluable population.
- Per protocol population: participants in the efficacy evaluable population who were considered to be sufficiently compliant with the study protocol. The clinical team identified the participants for exclusion from the per protocol population and documented the rationales for exclusion before database lock based on the procedures described in the FIGHT-202 Statistical Analysis Plan. The per protocol population was used for sensitivity analyses of ORR.
- Safety population: enrolled participants who received at least one dose of pemigatinib. All safety analyses were conducted using the safety population.

A total of 146 participants were enrolled in the study, received at least one dose of pemigatinib, and were included in the safety population. The efficacy evaluable population included 145 participants of which 107 had FGFR2 rearrangements or fusions (Cohort A). [redacted]

Safety analyses of a pooled safety population from participants in FIGHT 101, -102, -201, -202, and -203 who received pemigatinib as monotherapy were also presented in this submission.

The primary endpoint of the study was ORR in participants with tumours with FGFR2 fusions or rearrangements (Cohort A) based on the central genomics laboratory results. The primary endpoint – ORR was defined as the proportion of participants who achieved a complete response (CR) or a partial response (PR) based on RECIST v1.1. The primary analysis of ORR was based on IRC-assessed confirmed tumour responses. It was predetermined that the study outcome would be considered positive if the lower limit of the 95% CI for ORR exceeded 15%. Details of definitions of secondary outcomes are given in Section 4.2.5.

ERG comment: Statistical analysis appeared to be conducted appropriately.

4.2.3 Participant characteristics for the included pemigatinib study

Table 4.4 shows the baseline characteristics of the Cohort A participants in FIGHT-202. This trial cohort included a total of 107 participants. The majority of participants, 64/107 (60%), were from North America. [60 60 59 59 59]

Most study participants, 82/107 (77%), were 65 years of age or younger. The median age of the cohort was 56 years (range 26 to 77 years). Although both female and male participants were represented in the trial, more participants (60%) were female. Most participants had an Eastern Cooperative Oncology Group performance score (ECOG PS) of 0 or 1 with just five (5%) patients having an ECOG PS of 2. The majority of participants, 60/107 (61%) had received one prior treatment, 29/107 (27%) had received two prior treatments and just 13/107 (12%) had received between three and five therapies. Approximately one third of study participants, 38/107 (36%) had previously had cancer surgery and 28/107 (26%) had received radiation therapy. All but two of the study participants had iCCA.[2, 25]

Table 4.4: Baseline characteristics of participants in FIGHT-202

Baseline characteristics	Cohort A FGFR2 fusions/rearrangements
Patients analysed	**107**
Age	
Median (range), years	56 (26 – 77)
<65 years, n (%)	82 (77)
65 - 75 years, n (%)	20 (19)
≥75 years, n (%)	5 (5)
Sex	
Male, n (%)	42 (39)
Female, n (%)	65 (60)
Region, n (%)	
North America	64 (60)
Western Europe	32 (30)
Rest of the world[+]	11 (10)
ECOG PS, n (%)	
0	45 (42)
1	57 (53)
2	5 (5)
Number of prior regimens,[‡] n (%)	
1	65 (61)
2	29 (27)
≥3	13 (12)
Prior cancer surgery, n (%)	38 (36)
Prior radiation, n (%)	28 (26)
CCA location, n (%)	
Intrahepatic	105 (98)
Extrahepatic	1 (1)
Other/missing	1 (1)

Source: Table 11 of the CS[2]
†Includes Israel, South Korea, Taiwan, Thailand, and Japan.
‡Maximum number of five therapies in cohort A.
CCA = cholangiocarcinoma; ECOG PS = Eastern Cooperative Oncology Group performance status; FGF/FGFR = fibroblast growth factor/FGF receptors.

ERG comment: The ERG has some concern that the population included in FIGHT-202, which is 98% intrahepatic cholangiocarcinoma (iCCA), might not be fully representative of the population specified in the scope,[39] which is CCA regardless of whether intrahepatic or not. However, the ERG acknowledges that most (approximately 95%)[21] patients with CCA, who have FGFR2 mutations, have intrahepatic disease.

4.2.4 Risk of bias assessment for the included pemigatinib study

As reported in Section 4.1.4, the company assessed the methodological quality of the FIGHT-202 study,[25] based on one publication,[53] using 27 criteria adapted from the Downs and Black checklist[54]. No information was provided on the number of reviewers who assessed the quality of included studies. No statements were provided to support the judgements made by the company. The ERG re-assessed the study using the same quality criteria and results are shown in Table 4.5.

Table 4.5: Quality assessment for FIGHT-202 (Abou-Alfa et al. 2020)[53]

Question	Response	
	CS	ERG
Reporting		
1. Is the hypothesis/aim/objective of the study clearly described?	Y	Y
2. Are the main outcomes to be measured clearly described in the introduction or methods section?	Y	Y
3. Are the characteristics of the patients included in the study clearly described?	Y	Y
4. Are the interventions of interest clearly described?	Y	Y
5. Are the distributions of principal confounders in each group of patients to be compared clearly described?	Y	NA
6. Are the main findings of the study clearly described?	Y	Y
7. Does the study provide estimates of the random variability in the data for the main outcomes?	Y	Y
8. Have all important adverse events that may be a consequence of the intervention been reported?	Y	Y
9. Have the characteristics of patients lost to follow-up been described?	Y	Y
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Y	NA
External validity		
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Y	Y
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Y	Y
13. Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	N	N
Internal validity		
14. Was an attempt made to blind study subjects to the intervention they have received?	NA	NA
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	N	N
16. If any of the results of the study were based on 'data dredging', was this made clear?	Y	Y
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Y	Y
18. Were the statistical tests used to assess the main outcomes appropriate?	Y	Y

Question	Response	
	CS	ERG
19. Was compliance with the intervention(s) reliable?	Y	Y
20. Were the main outcome measures used accurate (valid and reliable)?	Y	Y
Internal validity – confounding		
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Y	NA
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Y	NA
23. Were study subjects randomized to intervention groups?	NA	NA
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	NA	NA
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Y	NA
26. Were losses of patients to follow-up considered?	Y	Y
Power		
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Y	NA
Source: Table 10 of the CS[2]		

ERG comment: The ERG considers that appropriate criteria were used to assess the methodological quality of the included study of pemigatinib. The ERG considers that FIGHT-202 was a generally well conducted, non-comparative, observational study. Where the ERG's assessment (Table 4.6) differed from that provided in the CS,[2] this was because the ERG considered that the item was not applicable (NA) to non-comparative studies.

4.2.5 Clinical effectiveness results for the included pemigatinib study

The results for Cohort A of the FIGHT-202 trial only (participants with FGFR2 fusions/rearrangements) are presented here as this is the relevant population for this appraisal. The median duration of treatment with pemigatinib was 219 days (range seven to 730 days) at the 22 March 2019 data cut-off. At the time of this cut-off, 76 patients (71.0%) had discontinued treatment. The median duration of follow-up was 15.44 months (range, 7.0 to 24.7 months).[2, 25] The efficacy results for Cohort A of the FIGHT-202 trial are summarised in Table 4.6.

The primary endpoint of FIGHT-202 was ORR defined as the proportion of patients who achieved a confirmed CR or a confirmed PR based on RECIST v1.1 criteria. In the trial patients in Cohort A had an ORR of 35.5% (95% CI: 26.5% to 45.4%) according to independent review. The majority of responses were either partial or stable disease (79%).[2, 25]

The key secondary endpoint was DOR, defined as the time from the date of CR or PR until PD. Median DOR among responders was 7.5 months (95% CI: 5.7 months to 14.5 months). The median time to first response was 2.7 months (interquartile range: 1.4, 3.9). The company reported other secondary endpoints of the trial. Median PFS was 6.9 months (95% CI: 6.2 months to 9.6 months). OS data were not mature at the time of data cut-off: 67 of 107 patients (63%) were alive and censored for OS at the

last date known alive with a median follow-up of 15.44 months. The median OS was 21.1 months (95% CI: 14.8 to not estimable).[2, 25]

The median time to response, in the 38 participants with confirmed tumour response, was 2.7 months (range 0.7 to 6.9 months); three participants had target lesions that did not meet the criteria for confirmed PR until after six months of pemigatinib treatment.[25] The majority of participants, 65/107 (61%) had a duration of pemigatinib treatment >6 months.[25]

Table 4.6: Efficacy results of FIGHT-202, 22 March 2019 cut-off

Outcome	**Cohort A FGFR2 fusions/rearrangements**
Median duration of treatment (range) days	219 (7 to 730)
Median follow-up (range) months	15.44 (7.0 to 24.7).
ORR (95% CI), %	35.5 (26.5 to 45.4)
Best OR,* n (%)	
CR	3 (2.8)
PR	35 (32.7)
Stable disease	50 (46.7)
PD	16 (14.9)
Not evaluable†	3 (2.8)
DCR** (95% CI), %	82 (74 to 89)
DOR	
Median DOR (95% CI), months	7.5 (5.7 to 14.5)
Patients with events, n (%)	21/38 (55)
Patients censored, n (%)	17/38 (45)
KM estimated probability of retaining a response at 6 months, % (range)	68 (49 to 82)
KM estimated probability of retaining a response at 12 months, % (range)	37 (19 to 56)
PFS	
Median PFS (95% CI), months	6.9 (6.2 to 9.6)
Patients with events, n (%)	71 (66)
Patients censored, n (%)	36 (34)
KM estimated probability of retaining a response at 6 months, % (range)	62 (52 to 70)
KM estimated probability of retaining a response at 12 months, % (range)	29 (19 to 40)
OS	
Median OS (95% CI), months	21.1 (14.8 to NE)
Patients with events, n (%)	40 (37)
Patients censored, n (%)	67 (63)

Outcome	Cohort A FGFR2 fusions/rearrangements
KM estimated probability of retaining a response at 6 months, % (range)	89 (81 to 93)
KM estimated probability of retaining a response at 12 months, % (range)	68 (56 to 76)
Discontinuations	
Total	76
Adverse event	4
Progressive disease	57
Death	1
Physician decision	4
Withdrawal by patient	5
Other	5

Source: Table 12 and Figure 8 of the CS[2] and CSR[25]
*Assessed and confirmed by independent central review.
**sum of CR, PR and stable disease indicating the percentage of patients who were able to achieve at minimum disease stabilisation
†Postbaseline tumour assessment was not performed owing to study discontinuation (2 participants) or was performed prior to the minimum interval of 39 days for an assessment of stable disease (1 participant).
CI = confidence interval; CR = complete response; FGF/FGFR = fibroblast growth factor/FGF receptors; FGFR2 = fibroblast growth factor receptors 2; KM = Kaplan-Meier; NE = not estimable; OR = overall response; ORR = overall response rate; PD = progressive disease; PR = partial response.

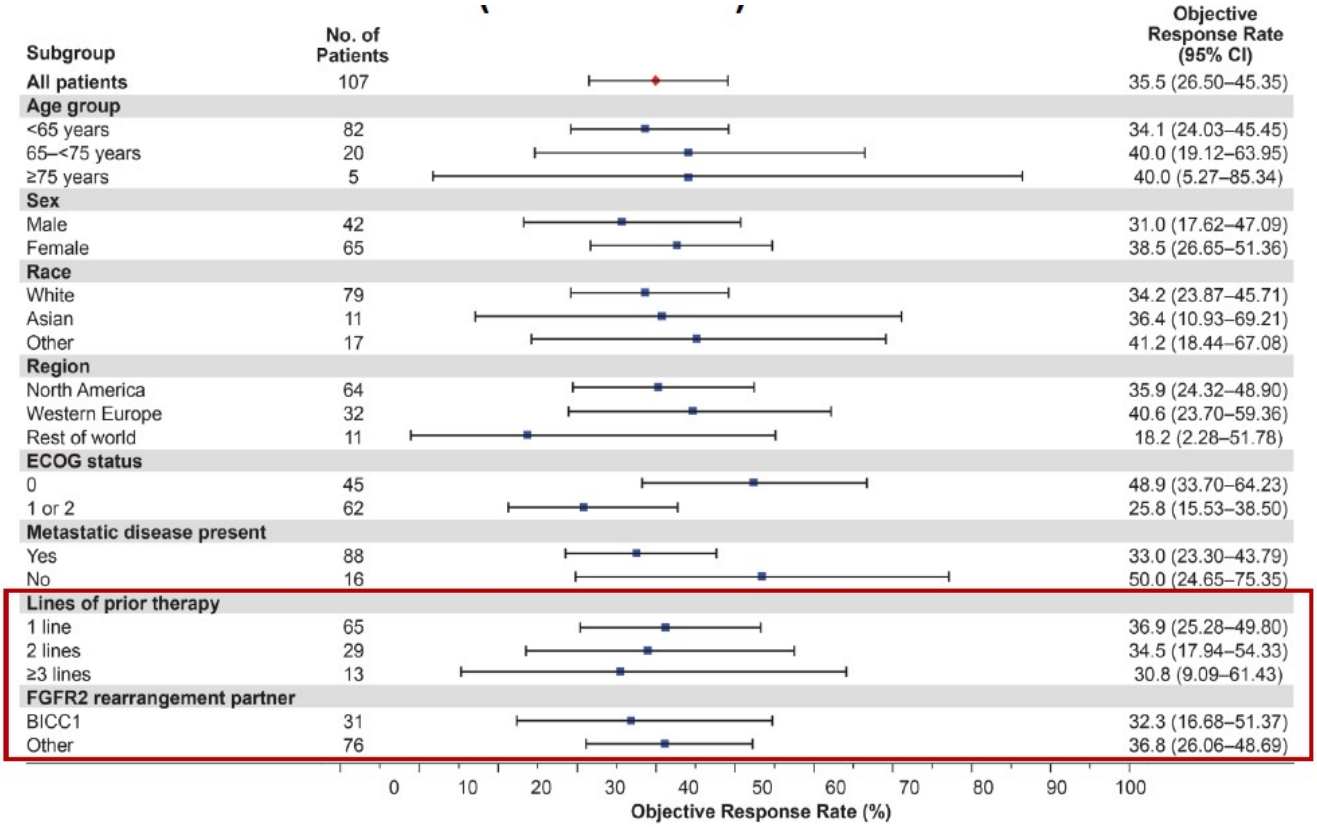
ERG comment: The ERG notes that OS data were not mature at the 22 March 2019 cut-off.

4.2.6 Subgroup analyses for the included pemigatinib study

Although the company stated that there were no pre-specified subgroup analyses based on baseline demographics and characteristics, they provided results of a subgroup analysis for the primary outcome ORR. The figure provided is shown below (Figure 4.1). The company specifically stated that ORR was similar in patients who had received 1, 2, or ≥3 lines of prior therapy and in patients with FGFR2-BCC1 vs any other FGFR2 fusions or rearrangements.

Figure 4.1: ORR by subgroup (cohort A)

Source: Figure 10, CS[2]



ERG comment: The company were asked to clarify whether any further subgroup analyses were undertaken (secondary outcomes) and provide results for all such analyses.[1] The company's response provided the results of further sub-group analyses, specified as exploratory, which were conducted to assess the consistency of pemigatinib treatment effect. The results of these analyses are reproduced below (Figure 4.2, and Tables 4.7 and 4.8).

Figure 4.2: PFS by subgroup (cohort A)

Source: Figure 2, response to clarification[1]

4.7: Summary of DOR by baseline renal impairment grade based on IRC assessment according to RECIST v1.1 (Cohort A, efficacy evaluable population)

Variable	Pemigatinib 13.5 mg once daily (QD) on a 14 days-on/7 days-off schedule		
	Renal Impairment Grade		
	[redacted]	[redacted]	[redacted]
Number (%) of participants with confirmed objective responses	[redacted]	[redacted]	[redacted]
Number (%) of participants with events	[redacted]	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Number (%) of participants censored	[redacted]	[redacted]	[redacted]
Median duration of response (months) (95% CI)[a]	[redacted]	[redacted]	[redacted]
Kaplan-Meier estimates of duration of response (95% CI)			
3 months	[redacted]	[redacted]	[redacted]

Variable	Pemigatinib 13.5 mg once daily (QD) on a 14 days-on/7 days-off schedule		
	Renal Impairment Grade		
	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
Source: CSR[25] and response to clarification[1] CI, confidence interval; NE = not estimable			

4.8: Summary of DOR by baseline hepatic impairment grade based on IRC assessment according to RECIST v1.1 (Cohort A, efficacy evaluable population)

Variable	Pemigatinib 13.5 mg once daily (QD) on a 14 days-on/7 days-off schedule		
	Hepatic Impairment Grade		
	[redacted]	[redacted]	[redacted]
Number (%) of participants with confirmed objective responses	[redacted]	[redacted]	[redacted]
Number (%) of participants with events	[redacted]	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Number (%) of participants censored	[redacted]	[redacted]	[redacted]
Median duration of response (months) (95% CI)[a]	[redacted]	[redacted]	[redacted]
Kaplan-Meier estimates of duration of response (95% CI)			
3 months	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]
9 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
Source: CSR[25] and response to clarification[1] CI = confidence interval; NE, not estimable			

ERG comment: The ERG notes that all subgroup analyses were exploratory in nature and were likely to have been underpowered.

4.2.7 Health-related quality of life results for the included pemigatinib study

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EORTC QLQ-BIL21 were administered every three cycles starting with Cycle 3. The QLQ-BIL21 was given to participants in the United States, United Kingdom, Italy, Germany and South Korea only.

The company stated that mean and median changes from baseline in EORTC QLQ-C30 and EORTC QLQ-BIL21 scores were variable, and no consistent trends were observed.

ERG comment: The CSR includes full results, for the evaluable population, at baseline and on day one of each treatment cycle, for both EORTC QLQ-C30 and EORTC QLQ-BIL21.[25] The ERG agrees with the company's observation that no consistent trends were apparent from these data.

4.2.8 Safety results for the included pemigatinib study

This section considers the information about adverse events (AEs) provided in the CS. All adverse events data were derived from a pooled data set of FIGHT -101, -102, -201, and -202 trials.[2] The safety analysis set (SAS) included all randomised patients who were treated at least once with trial medication as monotherapy.[2] Table 4.9 provides an overall summary of adverse events (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.02. If the toxicity was not included in CTCAE v4.03, it was rated on a scale of 1 to 4 as follows: 1=mild, 2=moderate, 3=severe, and 4=life-threatening) in three populations.[25] These were- the 'All Cancer' population (N=466), 'CCA' population (N=161), and the 'FIGHT-202' (N=146) population.[2]

The overall frequency of treatment-emergent adverse effects (TEAEs) is similar across the three populations.

4.9: Summary of adverse events SAS

Category, n (%)	FIGHT-202 (N=146)	CCA Population (N=161)	All Cancer Population (N=466)
Any TEAE	146 (100.0)	161 (100.0)	465 (99.8)
Any ≥grade 3 TEAE	93 (63.7)	100 (62.1)	284 (60.9)
Any fatal TEAE	6 (4.1)	7 (4.3)	36 (7.7)
Treatment-related TEAE‡, n (%)			
Any treatment-related TEAEs	134 (91.8)	152 (94.4)	441 (94.6)
Hyperphosphataemia	78 (53.4)	92 (57.1)	245 (52.6)
Alopecia	67 (45.9)	76 (47.2)	186 (39.9)
Dysgeusia	55 (37.7)	62 (38.5)	140 (30.0)
Diarrhoea	53 (36.3)	55 (34.2)	148 (31.8)
Fatigue	47 (32.2)	51 (31.7)	129 (27.7)
Stomatitis	47 (32.2)	52 (32.3)	148 (31.8)
Serious TEAE‡, n (%)			
Any serious TEAE	65 (44.5)	67 (41.6)	194 (41.6)
Gastrointestinal disorders	23 (15.8)	23 (14.3)	51 (10.9)

Category, n (%)	FIGHT-202 (N=146)	CCA Population (N=161)	All Cancer Population (N=466)
General disorders and administration site conditions	8 (5.5)	9 (5.6)	42 (9.0)
Hepatobiliary disorders	8 (5.5)	8 (5.0)	12 (2.6)
Infections and infestations	18 (12.3)	18 (11.2)	49 (10.5)
Metabolism and nutrition disorders	13 (8.9)	14 (8.7)	29 (6.2)
Renal and urinary disorders	3 (2.1)	2 (1.2)	26 (5.6)
Respiratory, thoracic, and mediastinal disorders	8 (5.5)	8 (5.0)	22 (4.7)
TEAEs leading to drug discontinuation†, n (%)			
Any TEAE leading to discontinuation	13 (8.9)	13 (8.1)	45 (9.7)
Gastrointestinal disorders	3 (2.1)	3 (1.9)	9 (1.9)
General disorders and administration site conditions	1 (0.7)	1 (0.6)	6 (1.3)
Infections and infestations	0	0	2 (0.4)
Metabolism and nutrition disorders	0	1 (0.6)	4 (0.9)
Renal and urinary disorders	2 (1.4)	2 (1.2)	4 (0.9)
TEAEs leading to dose interruption, n(%)			
Any TEAE leading to dose interruption	62 (42.5)	68 (42.2)	202 (43.3)
Any TEAE leading dose reduction	20 (13.7)	NR	NR

Based on Tables 24, 26, 27, and 28 of the CS[2]
AEs according to MedDRA System Organ Class preferred term or MedDRA preferred term
ǂ- Across populations
‡- in ≥2% of participants in FIGHT-202, the Cholangiocarcinoma Population, or the All Cancer Population
†- in ≥2 participants in FIGHT-202, the Cholangiocarcinoma Population, or the All Cancer Population
AE = adverse event; CCA = Cholangiocarcinoma; CS = company submission; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; n = number of patients in category; NR = not reported; SAE = Serious adverse event; SAS = safety analysis set; TEAE = Treatment-emergent adverse event

In Table 4.9 several Medical Dictionary for Regulatory Activities (MedDRA) System Order Classes that led to pemigatinib discontinuation are listed, and consistent in frequency across the three populations. In the FIGHT-202 trial, thirteen patients permanently discontinued pemigatinib usage mostly due to gastrointestinal disorders like intestinal obstruction and small intestine obstruction.[2] Gastrointestinal disorders such as stomatitis (11 (7.5%)) remained the most common event leading to dose modification in FIGHT-202.[2]

Table 4.10 provides a more detailed breakdown of TEAEs in the FIGHT-202 trial population, summarising the frequency of AEs of MedDRA System Order Classes preferred term occurring in ≥10% of patients in different treatment cohorts. Consistent with pemigatinib usage across the three populations, according to the MedDRA System Order Classes, gastrointestinal disorders were the most serious TEAEs experienced by patients in the FIGHT-202 trial, with the 'metabolism and nutrition disorder', hyperphosphatemia (58.2%) being the most frequently occurring TEAE.[2]

The most common clinically notable AEs associated with pemigatinib use such as hyperphosphataemia, were those associated with a "class effect" common to all FGFR inhibitors.[2] Other associated adverse events such as alopecia, diarrhoea, fatigue, dysgeusia, nausea, constipation, stomatitis, dry mouth, and decreased appetite occurred in ≥30% of participants in FIGHT-202.[2] As can be seen from the ≥ Grade 3 column, most of these events were grade 1 or 2 in severity.[2]

4.10: Summary of TEAEs Occurring in ≥10% of patients in FIGHT-202

MedDRA Preferred Term, n (%)	Pemigatinib 13.5 mg intermittent dose*			
	Cohort A (N=107)	Cohort B (N=20)	Cohort C (N=18)	≥ Grade 3
Hyperphosphataemia	59 (55.1)	13 (65.0)	12 (66.7)	0
Alopecia	63 (58.9)	4 (20.0)	4 (22.2)	0
Diarrhoea	56 (52.3)	5 (25.0)	6 (33.3)	4 (2.7)
Fatigue	48 (44.9)	5 (25.0)	9 (50.0)	7 (4.8)
Dysgeusia	51 (47.7)	3 (15.0)	4 (22.2)	0
Nausea	43 (40.2)	7 (35.0)	8 (44.4)	3 (2.1)
Constipation	43 (40.2)	5 (25.0)	3 (16.7)	1 (0.7)
Stomatitis	41 (38.3)	6 (30.0)	3 (16.7)	8 (5.5)
Dry mouth	41 (38.3)	5 (25.0)	2 (11.1)	0
Decreased appetite	32 (29.9)	8 (40.0)	7 (38.9)	2 (1.4)
Vomiting	33 (30.8)	3 (15.0)	4 (22.2)	2 (1.4)
Dry eye	34 (31.8)	1 (5.0)	1 (5.6)	1 (0.7)
Arthralgia	31 (29.0)	4 (20.0)	1 (5.6)	9 (6.2)
Abdominal pain	24 (22.4)	4 (20.0)	4 (22.2)	7 (4.8)
Hypophosphataemia	26 (24.3)	4 (20.0)	2 (11.1)	18 (12.3)

Based on Table 25 of the CS[2]
*Pemigatinib was administered QD on a 14 days on, 7 days off schedule.
Notes: Cohort determination is based on tumour FGF/FGFR status from central genomics laboratory. Cohort A: FGFR2 fusions or rearrangements; Cohort B: other FGF/FGFR alterations; Cohort C: negative for FGF/FGFR alterations.
CS = company submission; FGF/FGFR = fibroblast growth factor/fibroblast growth factor receptor; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants; QD = once daily

In the FIGHT-202 trial, treatment-related serious AEs like anaemia, acute kidney injury, hyponatraemia, abdominal pain, dysphagia, decreased appetite, and thrombosis, occurred in six unique participants.[2] Six patients with TEAEs also had a fatal outcome that was reported to be unrelated to the treatment.[2]

ERG comment: Overall, the ERG agrees with the company's conclusions that the pooled safety data from FIGHT -101, -102, -201, and -202 trials indicate that adverse event rates, treatment-related adverse events, and treatment-related adverse events that lead to drug discontinuation or dose interruptions were similar across the FIGHT-202, CCA, and All Cancer populations. The ERG notes that the incidence of ≥grade 3 treatment-related adverse events associated with pemigatinib use is quite high across all three populations (>60%). The ERG also notes that there are no comparative safety data for pemigatinib vs.

drugs currently being used as second-line chemotherapy for previously treated, unresectable, locally advanced, or metastatic CCA patients, due to the available evidence being a single arm study.

ERG comment: Adverse events (AEs) data for comparator regimens mFOLFOX+ASC and ASC, from the ABC-06 trial, were included in the cost effectiveness section of the CS, but no safety data were provided for any other comparators. The company were asked to provide information about the adverse event rates associated with the comparator(s) considered in the MAICs.[1] The company responded: *'MAICs for adverse events (AEs) were not conducted. Instead, the MAICs focussed on the clinical outcomes of OS and PFS."*[53]

The ERG notes that this omission means that no conclusions can be drawn about the safety profile of pemigatinib, relative to second-line systemic chemotherapy regimens, in the specified population.

4.2.9 Supporting evidence from additional/ongoing studies

The CS did not include any supporting evidence from additional/ongoing studies.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

In the absence of randomised controlled trials comparing pemigatinib directly to SOC, and because FIGHT-202 is a single-arm study, a MAIC was conducted, details of which were reported in Appendix D.

The company stated that the source of evidence to inform the effectiveness of current SOC was identified through the SLR, which is referred to in Section 4.1 above. The company concluded that there was one appropriate trial for the MAIC analyses, i.e. ABC-06, which was based on its inclusion of only UK patients (as indicated in appendix D of the submission, page 54). This was a randomised phase 3, multicentre, open-label study of mFOLFOX + ASC vs. ASC alone in patients with locally advanced/metastatic BTCs previously treated with cisplatin/gemcitabine chemotherapy. The company stated that both arms could be considered current SOC. The reasons given was that, although the ABC-06 trial showed that mFOLFOX + ASC significantly improves OS versus ASC alone *", it is unclear whether this has resulted in a universal change in the SOC for this patient population."*, even though clinical experts reported that mFOLFOX is likely to be used in a second-line setting.[41]

The company provided a summary of differences between FIGHT-202 AND ABC-06, which included:

- FIGHT-202 was a multinational study, whereas ABC-06 was based in the UK
- ABC-06 investigated all BTC, whereas the population of FIGHT-202 investigated patients with advanced/metastatic or surgically unresectable CCA who had progressed on at least one line of prior systemic therapy and included a majority of patients with iCCA
- Cohort A of FIGHT-202 included only patients with *FGFR2* fusions or rearrangements; the proportion of patients with these mutations was not reported in ABC-06

Table 16 in the CS also reported differences in patient characteristics between Cohort A of FIGHT-202 and ABC-06, which showed that patients in FIGHT-202 were younger (median age: 56 vs. 65). It also showed that fewer were men (39% vs. 46%/53% in ASC/mFOLFOX + ASC arm), far more had intrahepatic CCA (98% vs. 47%/42% in ASC/mFOLFOX + ASC arm, slightly fewer had an ECOG PS

of 0-1 (95% vs. 100%) and fewer had an albumin <35 g/L (20% vs. 26%/23% in ASC/mFOLFOX + ASC arm).

ERG comment: In the clarification letter, the ERG requested a justification for the selection of the ABC-06 study for use in MAIC based on its inclusion of only UK patients. In response, the company stated that it was, compared to the other six originally identified studies (Table 14, Appendix D in CS)[40]: *'…deemed by clinicians as the most appropriate study for reflecting standard of care for these patients in England and for MAICs.'*[1] A further reason cited was that ABC-06 was an RCT, whereas four of the remaining six studies were retrospective studies. However, in their response to the clarification letter the company performed four additional MAICs using other studies, each with two treatment arms:

- Kim 2017, which was retrospective and included only Korean patients and compared fluoro mono to fluoro+platinum.[46]
- Zheng 2018, which included only Chinese patients and compared irinotecan (IRI) to XELIRI.[47]

Two further MAICs were performed in response to clarification question A18, which requested the company to consider studies where only either OS or PFS data and not both were available. These were where only OS data were available and they used two retrospective single arm studies, both of which examined chemotherapy:

- Lowery 2019[42]
- Schweitzer 2019[43]

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The MAIC was unanchored (based on single arms only as there were no common comparators) and OS and PFS were the only outcomes analysed. The MAIC was performed as follows:

- Pseudo IPD were generated from KM curves of OS and PFS for the comparator treatments.
- Weights were derived using a propensity score logistic regression model which modelled the odds of being in the pemigatinib trial or the comparator trial. This used IPD for the pemigatinib trial and published aggregate data from the comparator trial and estimates were obtained using the method of moments.
- OS and PFS were compared between treatment groups using a weighted Cox proportional hazards model incorporating the weights from the propensity score model. Bootstrapping was used to estimate the 95% CI for the HR estimates.

Results were presented for OS and PFS as KM plots, median survival estimates and HRs between pemigatinib and the comparator. No other efficacy outcomes were analysed, and AE were not analysed.

4.4.1 MAIC vs. mFOLFOX + ASC or ASC only

The KM plot of PFS was not available for ASC in ABC-06, so this comparison was not possible. On the basis of the differences observed between FIGHT-202 and ABC-06, the MAIC adjusted for:

[redacted]The company reported that it was not possible to match on FGFR2 status or subtype of BTC, as Cohort A in FIGHT-202 included only CCA patients with *FGFR2* fusions or rearrangements.

The effect of the adjustment was to match the summary statistics of those four baseline characteristics of cohort A of FIGHT-202 to those of either those of the mFOLFOX + ASC or the ASC only arm, as shown in Table 4.11.

4.11: Effect of MAIC adjustment using ABC-06

Treatment (study)	N/ESS	Mean age (years)	Male %	ECOG PS 0–1 %	Albumin ≥35 g/L %
Pemigatinib unadjusted (FIGHT-202, cohort A)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemigatinib weighted to mFOLFOX + ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemigatinib weighted to ASC only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 17, CS[2]
ASC = active symptom control; ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size.
Sources: Abou-Alfa et al, 2020;[53] Lamarca et al., 2019.[23]

Results for OS are presented in Table 4.12 and results for PFS are presented in Table 4.13.

4.12: MAIC results for OS

Treatment (study)	N/ESS	Events	Median (95% CI) months
OS			
Pemigatinib unadjusted (FIGHT-202)	[redacted]	[redacted]	[redacted]
Pemigatinib weighted (FIGHT-202)	[redacted]	[redacted]	[redacted]
mFOLFOX + ASC (ABC-06)	[redacted]	[redacted]	[redacted]
ASC (ABC-06)	[redacted]	[redacted]	[redacted]
Pemigatinib vs. mFOLFOX + ACS	[redacted]		[redacted]
Pemigatinib vs. ACS			[redacted]

Source: Tables 18, 19, 22, 23 CS[2]
ASC; active symptom control; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; NE, not estimable.
Sources: Abou-Alfa et al, 2020;[53] Lamarca et al., 2019.[23]

4.13: MAIC results for PFS

Treatment (study)	N/ESS	Events	Median (95% CI) months
PFS			
Pemigatinib unadjusted (FIGHT-202)	[redacted]	[redacted]	[redacted]
Pemigatinib weighted (FIGHT-202)	[redacted]	[redacted]	[redacted]
mFOLFOX + ASC (ABC-06)	[redacted]	[redacted]	[redacted]
Pemigatinib vs. mFOLFOX + ACS	[redacted]		[redacted]

Source: Tables 20, 21 CS[2]
ASC; active symptom control; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; NE, not estimable.
Sources: Abou-Alfa et al, 2020;[53] Lamarca et al., 2019.[23]

For pemigatinib vs. mFOLFOX + ASC, the MAIC results favoured pemigatinib for both OS and PFS:

- OS HR: [redacted]) compared with [redacted] from an unadjusted comparison
- PFS HR: [redacted] compared with [redacted] from an unadjusted comparison

For pemigatinib vs. ASC only, the MAIC results also favour pemigatinib for OS, no analysis was possible for PFS:

- OS: HR: [redacted] compared with [redacted] from an unadjusted comparison.

4.4.2 MAIC vs. fluoro mono, fluoro + platinum, IRI or XELIRI

In response to clarification, the company stated that the same matching covariates as those used with ABC-06 were used to ensure consistency between this analysis and the analyses presented in the CS, [redacted]. They were described in response to Question A19, which explicitly requested that other studies from the SLR be considered. The effect of the adjustment on those covariates is shown in Table 4.14.

4.14: Effect of MAIC adjustment using either of the arms of either Kim 2017 or Zheng 2018

Treatment (study)	N/ESS	Mean age (years)	Male %	ECOG PS 0–1 %
Pemigatinib unadjusted (FIGHT-202, cohort A)[53]	107.0	55.3	39.3	95.3
Pemigatinib weighted to SoC (fluoro mono, Kim 2017)[46]	82.8	60.0	57.3	91.3

Treatment (study)	N/ESS	Mean age (years)	Male %	ECOG PS 0–1 %
Pemigatinib weighted to SoC (fluoro + platinum, Kim 2017)[46]	82.8	60.0	57.3	91.3
Pemigatinib weighted to SoC (IRI, Zheng 2018)[47]	81.2	55.0	63.3	100.0
Pemigatinib weighted to SoC (XELIRI, Zheng 2018)[47]	92.4	54.0	53.0	100.0

The effect of the adjustment on OS is shown in Table 4.15.

4.15: HRs using either arm of ABC-06, Kim 2017 or Zheng 2018

Comparison	Study	Endpoint	Unadjusted hazard ratio (95% CI)	Weighted hazard ratio (95% CI)
Pemigatinib vs mFOLFOX + ASC	ABC-06[23] (n=81)	[redacted]	[redacted]	[redacted]
Pemigatinib vs ASC	ABC-06[23] (n=81)	[redacted]	[redacted]	[redacted]
Pemigatinib vs SoC (fluoro mono)	Kim 2017[46] (n=255)	[redacted]	[redacted]	[redacted]
Pemigatinib vs SoC (fluoro + platinum)	Kim 2017[46] (n=66)	[redacted]	[redacted]	[redacted]
Pemigatinib vs SoC (IRI)	Zheng 2018[47] (n=30)	[redacted]	[redacted]	[redacted]
Pemigatinib vs SoC (XELIRI)	Zheng 2018[47] (n=30)	[redacted]	[redacted]	[redacted]
Pemigatinib vs mFOLFOX + ASC	ABC-06[23] (n=81)	[redacted]	[redacted]	[redacted]
Pemigatinib vs ASC	ABC-06[23] (n=81)	[redacted]	[redacted]	[redacted]
Pemigatinib vs SoC (fluoro mono)	Kim 2017[46] (n=255)	[redacted]	[redacted]	[redacted]
SoC (fluoro + platinum)	Kim 2017[46] (n=66)	[redacted]	[redacted]	[redacted]

Comparison	Study	Endpoint	Unadjusted hazard ratio (95% CI)	Weighted hazard ratio (95% CI)
SoC (IRI)	Zheng 2018[47] (n=30)	[redacted]	[redacted]	[redacted]
SoC (XELIRI)	Zheng 2018[47] (n=30)	[redacted]	[redacted]	[redacted]

4.4.3 MAIC vs. chemotherapy

Again, an attempt was made to use the same matching covariates, [redacted] and Lowery 2019[42] [redacted] (Schweitzer 2019[43] only). The effect of the adjustment on those covariates is shown in Table 4.16.

4.16: Effect of MAIC adjustment using either Lowery 2019[42] or Schweizer 2019[43]

Treatment (study)	N/ESS	Mean age (years)	Male %	ECOG PS 0–1 %
Pemigatinib unadjusted (FIGHT-202, cohort A)[53]	107.0	55.3	39.3	95.3
Pemigatinib weighted to SoC (chemotherapy, Lowery 2019)[42]	79.0	62.0	43.4	NR
Pemigatinib weighted to SoC (chemotherapy, Schweitzer 2019)[43]	68.0	59.6	56.9	83.6

The effect of the adjustment on OS is shown in Table 4.17.

4.17: HRs using either of the arms of ABC-06, Lowery 2019[42] or Schweizer 2019[43]

Comparison	Study	Endpoint	Unadjusted hazard ratio (95% CI)	Weighted hazard ratio (95% CI)
Pemigatinib vs mFOLFOX + ASC	ABC-06[23]	[redacted]	[redacted]	[redacted]
Pemigatinib vs ASC	ABC-06[23]	[redacted]	[redacted]	[redacted]
SoC (chemotherapy)	Lowery 2019[42]	[redacted]	[redacted]	[redacted]
SoC (chemotherapy)	Schweitzer 2019[43]	[redacted]	[redacted]	[redacted]

ERG comment: In response to the clarification question A16 to provide evidence of the AEs for the comparators in the MAIC, the company stated: " *MAICs for adverse events (AEs) were not conducted. Instead, the MAICs focussed on the clinical outcomes of OS and PFS*."[1]

In general, there is a high level of uncertainty about the results of the MAIC as it was an unanchored comparison due to the fact that the only study evaluating pemigatinib in the specified population was a single-arm phase II trial. Unanchored MAICs should adjust for all effect modifiers and prognostic variables but the primary MAIC only adjusted for four variables and no justification was provided for their choice or whether they were considered to be effect modifiers.[55] The MAIC results are only applicable to the population in the comparator trial, which in the original analysis was the ABC-06 trial. However, no details were reported in the ABC-06 trial for the numbers of patients with FGFR2 fusions or rearrangements, whereas FIGHT-202 only included CCA patients with FGFR2 fusions or rearrangements. In addition, almost all of the participants (98%) in cohort A of FIGHT-202 had iCCA, whereas ABC-06 included participants with any type of BTC, 44% of whom had iCCA. This is a major limitation of the MAIC results, as even though they showed favourable OS with pemigatinib compared to mFOLFOX + ASC and ASC alone, and favourable PFS compared to mFOLFOX + ASC we do not know whether these results are applicable to the population with FGFR2 fusions or rearrangements. A comparator trial containing a population with a high percentage with FGFR2 fusions or rearrangements would be required to answer this question.

The company provided six additional MAICs, in response to clarification questions.[1] However, these analyses included five additional comparators, and none provided data for a population which matched FIGHT-202, in particular with respect to the presence of FGFR2 fusions or rearrangements. The ERG considers that, whilst these additional MAICs do allow the inclusion of further comparators (different chemotherapy regimens) in the cost effectiveness analysis (CEA), they do not increase certainty with respect to the comparative efficacy of pemigatinib.

4.5 Conclusions of the clinical effectiveness section

The CS included a systematic review *'to identify the available clinical evidence for efficacy, safety, and tolerability of existing and upcoming treatments for patients with advanced/metastatic or surgically unresectable CCA for whom at least one treatment has failed, irrespective of any translocations.'*[40] The ERG has no substantive concerns regarding the search strategies used to identify potentially relevant studies.

From the systematic review, the company identified and presented evidence from one ongoing, single arm, phase 2 study (FIGHT-202), (NCT02924376; INCB 54828-202), which was the sole source of data on the clinical effectiveness of pemigatinib in adults with advanced/metastatic or surgically unresectable FGFR2+ CCA for whom at least one treatment has failed.[25, 53] Almost all of the participants in FIGHT-202 (98%) had iCCA and hence the ERG considers that this study is not representative of the full population specified in the scope. Data from the Advanced Biliary Tract Cancer (ABC) trials, conducted in the UK, suggest that iCCAs account for only around 34% of CCA cases.[2, 4] However, the ERG acknowledges that most patients with CCA, who have FGFR2 mutations, have intrahepatic disease.

The company acknowledged the lack of direct evidence about the comparative efficacy and safety of pemigatinib vs SOC (systemic chemotherapy or best supportive care [BSC]), in the specified population.[2] The ERG considers that this is a major limitation of the submission.

In the absence of randomised controlled trials comparing the efficacy of pemigatinib directly to that of SOC the company relied upon a MAIC to provide estimates comparative efficacy. The systematic review, described above, was used to identify suitable studies to provide comparator data for the MAIC. However, the ERG considers that the criteria used to select studies for the MAIC were somewhat arbitrary and were not adequately justified; the original submission[2] selected a single study, ABC-06,[23] a randomised phase 3, multicentre, open-label study of ASC alone or mFOLFOX + ASC for patients with locally advanced/metastatic BTCs previously treated with cisplatin/gemcitabine chemotherapy. As noted in the CS,[2] ABC-06[23] investigated all BTCs, whereas the population of FIGHT-202[25] investigated patients with advanced/metastatic or surgically unresectable CCA who had progressed on at least one line of prior systemic therapy and included a majority of patients with iCCA. In addition, Cohort A of FIGHT-202 (the source of data on the efficacy of pemigatinib) included only patients with FGFR2 fusions or rearrangements, whereas the proportion of patients with these mutations was not reported in ABC-06. The ERG considers that there is a high level of uncertainty about the results of the MAIC, as it was an unanchored comparison. The MAIC results are only applicable to the population in the comparator trial and the ABC-06 trial did not report any information about FGFR2 mutation status and included patients with all types of BTC, not just CCA as specified in the scope for this appraisal. This is a major limitation of the MAIC results.

The company provided four additional MAICs, in response to clarification questions.[1] However, none of these analyses provided data for a population that matched that of FIGHT-202, in particular with respect to the presence of FGFR2 fusions or rearrangements. The ERG considers that, whilst these additional MAICs do allow the inclusion of further comparators (different chemotherapy regimens) in the CEA, they do not increase certainty with respect to the comparative efficacy of pemigatinib. The MAICs also did not include AEs and the CS only included information about comparator regimens mFOLFOX+ASC and ASC; no AE data were reported for any other comparator.

The ERG considers that the lack of evidence about the comparative efficacy and safety of pemigatinib is a major limitation of this submission. Indeed, as is stated in TSD 18, *"An unanchored MAIC…effectively assumes that absolute outcomes can be predicted from the covariates; that is, it assumes that all effect modifiers and prognostic factors are accounted for. This assumption is very strong, and largely considered impossible to meet. Failure of this assumption leads to an unknown amount of bias in the unanchored estimate."* (pg5)[55] The company have failed to demonstrate that this assumption has been met in any of the MAICs, which casts serious doubt on the effectiveness and therefore the cost effectiveness of pemigatinib versus any comparator.

5. Cost effectiveness

5.1 ERG comment on company's review of cost effectiveness evidence

5.1.1 Searches performed for cost effectiveness section

Appendices G, H and I of the CS detail SLRs conducted to identify all cost effectiveness, health related quality of life (HRQoL) and cost and resource use literature published in patients with advanced cholangiocarcinoma. Searches were conducted in June 2018, with a subsequent update in April 2020. No language or publication date limits were reported. No details were given for the date span of each databases searched so it is unclear if they were searched from inception. A summary of the sources searched is provided in Table 5.1.

Table 5.1: Data sources for the cost effectiveness systematic review (as reported in CS)

	Resource	Host/source	Date range	Date searched
Electronic databases	MEDLINE, Embase	Embase.com	(i)not provided (ii)2018-2020	(i)20.6.18 (ii)22.4.20
	MEDLINE In-Process	PubMed.com	(i)not provided (ii)2018-2020	(i)20.6.18 (ii)22.4.20
	EconLit	EBSCO.com	(i)not provided (ii)2018-2020	(i)20.6.18 (ii)22.4.20
	HTAD	Wiley.com	(i)not provided (ii)not provided	(i)20.6.18 (ii)22.4.20
	NHS EED			
Conference proceedings	American Society of Clinical Oncology Gastrointestinal Cancers (ASCO-GI)	No information	2016-2020	(i)20.6.18 (ii)22.4.20
	European Society for Medical Oncology Gastrointestinal Cancers (ESMO-GI)			
	American Association for Cancer Research (AACR)			
	International Society for Pharmacoeconomics and Outcomes Research (ISPOR)			
Additional resources	NICE		No restriction	(i)20.6.18 (ii)22.4.20
	Scottish Medicines Consortium (SMC)			
	All Wales Medicines Strategy Group (AWMSG)			

	Resource	Host/source	Date range	Date searched
	Canadian Agency for Drugs and Technologies in Health (CADTH)			
	Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket; TLV)			
	German Institute for Quality and Efficiency in Healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; IQWiG)			
(i) - original search; (ii) - update search				

ERG comment:

- Individual searches were undertaken for SLRs conducted to identify all cost effectiveness, HRQoL and cost and resource use studies. The CS provided sufficient details for the ERG to appraise the literature searches. A good range of database and conference proceedings were searched, including additional grey literature resources and reference checking. The original and the update searches were overall well conducted with some minor errors in documentation, however they were on the whole transparent and reproducible; more details on databases date segments could have been provided.
- No date or language limits were unnecessarily applied to the database searches.
- Study design filters were appropriately used but were not referenced.
- The NHS EED and HTA databases searched for the update report the host as Wiley.com, however these resources are not available on this platform and it appears that these resources were perhaps searched using the CRD website instead.

5.1.2 Inclusion/exclusion criteria

Across all three SLRs, titles and abstracts were screened by a single BresMed reviewer using the basic study selection criteria.[40] Studies which passed the first stage of screening were obtained at full text and assessed for eligibility by a single reviewer using the full eligibility criteria. At both stages a random 20% of studies were checked by a second independent reviewer.

The eligibility criteria for the original economic evaluation, HRQoL and cost and resource use SLRs are shown in Tables 5.2, 5.3 and 5.4 respectively. In the updated SLRs, studies were screened according to the same criteria, with searches run from 1 January 2018.

Table 5.2: Eligibility criteria for economic evaluation review (original SLR)

Criteria	Description
Study population	• Adult (age ≥ 18 years) patients with advanced/metastatic or surgically unresectable CCA with FGFR2 translocations, for whom ≥ 1 previous treatment has failed • Adult (age ≥ 18 years) patients with advanced/metastatic or surgically unresectable CCA irrespective of prior treatment

Criteria	Description
Study designs	Full economic evaluations: • Cost consequence • Cost effectiveness • Cost utility • Cost benefit
Interventions/ comparators	No limits
Outcomes	All economic modelling related outcomes such as model structure, health states, ICER, incremental QALYs/LYs, etc.
Language	English language only
Time limit	No limit
Country	No limit
Source: Table 29 Appendix G of the CS.[40] CCA = cholangiocarcinoma; FGFR2+ = fibroblast growth factor receptor 2 positive status; ICER = cost effectiveness acceptability curve; LY = life year; QALY = quality adjusted life year; SLR = systematic literature review.	

Table 5.3: Eligibility criteria for HRQoL studies (original SLR)

Criteria	Description
Study population	• Adult (age ≥ 18 years) patients with advanced/metastatic or surgically unresectable CCA with FGFR2 translocations, for whom ≥ 1 previous treatment has failed • Adult (age ≥ 18 years) patients with advanced/metastatic or surgically unresectable CCA irrespective of prior treatment
Study designs	Studies reporting utility/disutility data
Interventions/ comparators	No limits
Outcomes	Utility and disutility data
Language	English language only
Time limit	No limit
Country	No limit
Source: Table 43 Appendix H of the CS.[40] CCA = cholangiocarcinoma; FGFR2+ = fibroblast growth factor receptor 2 positive status; SLR = systematic literature review.	

Table 5.4: Eligibility criteria for cost and resource use review (original SLR)

Criteria	Description
Study population	• Adult (age ≥ 18 years) patients with advanced/metastatic or surgically unresectable CCA with FGFR2 translocations, for whom ≥ 1 previous treatment has failed • Adult (age ≥ 18 years) patients with advanced/metastatic or surgically unresectable CCA irrespective of prior treatment
Study designs	• Cost studies • Resource use studies • Economic evaluations reporting costs or resource use
Interventions/ comparators	No limits
Outcomes	• Resource use data • Cost of management of treatment related adverse events • Direct and indirect cost
Language	English language only
Time limit	No limit
Country	No limit
Source: Table 56 Appendix I of the CS.[40] CCA = cholangiocarcinoma; FGFR2+ = fibroblast growth factor receptor 2 positive status; SLR = systematic literature review.	

ERG comment: Criteria appear reasonable with the note that the English language restriction could have led to relevant studies being missed.

5.1.3 Identified studies

Economic evaluations

A total of 1,750 unique publications were identified for review and screened at title and abstract level, of which 1,692 were excluded, as displayed in Figure 4 of Appendix G of the CS.[40] A total of 58 publications were assessed at full text. Of these, 51 were excluded for the following reasons: reviews/editorial (n=15), disease (n=15), disease stage (n=8), study design (n=6), not retrieved (n=6), language (n=1). No publications were included from bibliographic/conference/HTA searches and a total of seven publications were included in this review. As some studies were associated with multiple publications, secondary publications were combined; this resulted in inclusion of six studies identified from seven publications.

In the updated economic evaluation SLR, 769 unique publications were screened at title and abstract level, of which 763 were excluded. Six publications were assessed at full text. Of these, five were excluded based on the following reasons: reviews/editorial (n=2), disease (n=1), disease stage (n=1), duplicate (n=1). No publications were included from bibliographic/conference/HTA searches and only one publication was included in this review. This publication was linked to a study identified in the original SLR and the results of this study were updated in the original SLR.

Five of the six studies evaluated the cost effectiveness of stent placement compared with palliative care or any other conventional treatment and one compared hepatic resection followed by adjuvant systemic

chemotherapy to systemic chemotherapy. Further details can be found in section G1.4.2 of the CS Appendices.[40]

Health-related quality of life

In the original HRQoL SLR, A total of 1,119 unique publications were identified for review and screened at title and abstract level, as shown in the PRISMA diagram in Figure 6 of Appendix H of the CS.[40] Of these, 1,064 were excluded. A total of 55 publications were assessed at full text. Of these, 50 were excluded for the following reasons: disease (n=20), reviews/editorial (n=10), study design (n= 8), not retrieved (n=6), no outcome (n=3), disease stage (n=2), language (n=1). No publications were included from bibliographic/conference/HTA searches and a total of five publications were included in this review. As some studies were associated with multiple publications, secondary publications were combined; this resulted in the inclusion of three studies identified from five publications.

The updated HRQoL SLR identified 559 unique records for screening, of which 554 were excluded at title and abstract stage. Four of the remaining five records were excluded at full text. Two publications were included from bibliographic/conference/HTA searches and a total of three publications were included in this review. As some studies were associated with multiple publications, secondary publications were combined; this resulted in the inclusion of two studies identified from three publications. Five studies from eight publications were therefore included in total.

Three of the included studies were economic evaluation studies[61-63] and one each was a prospective observational study[64] and a cross-sectional survey[65].

Four of the five included studies assessed utilities using the EQ-5D visual analogue scale (VAS)[64, 65], EQ-5D-3L[61] and EQ-5D[63]. In the remaining study, the method of elicitation was not reported.[62] It was reported that CCA patients who underwent liver transplantation had significantly better quality of life than patients without CCA.[65] In another study, a significant improvement in EQ-5D score was noted in patients with iCCA who received ERCP and metallic stent placement with adequate drainage.[64] Additionally, in one study, the quality of life for curative hepatic resection was 0.9. In contrast, the quality of life after systemic chemotherapy in non-responders was estimated to be the same as the value for incurable metastatic colorectal cancer of 0.4.[62]

Cost and resource use

The original cost and resource use SLR identified 1,864 unique publications for screening at title and abstract level, of which 1,488 were excluded. Of the 376 assessed at full text, 364 were excluded for the following reasons: disease (n = 201), disease stage (n = 118), study design (n = 18), reviews/editorial (n = 15), language (n = 6), not retrieved (n = 5), children (n = 1). One publication was included from bibliographic/conference/HTA searches. As some studies were associated with multiple publications, secondary publications were combined; this resulted in inclusion of eight studies identified from 13 publications.

The updated SLR identified 827 unique publications, of which 799 were excluded at title/abstract level. Twenty-seven of the 28 publications assessed at full text were excluded for the following reasons: disease stage (n = 11), study design (n = 11), disease (n = 3), reviews/editorial (n = 1), animal/in vitro (n = 1). Three publications were included from bibliographic/conference/HTA searches. As some studies were associated with multiple publications, secondary publications were combined; this resulted in the inclusion of three studies identified from four publications.

In total, 11 studies from 17 publications were included in the cost and resource use review. Of these, one was a prospective observational study and six were retrospective data analyses, which did not appear in the main CS. Four were economic evaluations which were used in the main CS.[62, 66-68]

5.1.4 Interpretation of the review

No issues were identified for the economic evaluation, HRQoL and cost and resource use SLRs.

Since the economic evaluation studies identified in the SLR addressed very different types of interventions (mostly invasive) than the one assessed in the current study, none of the included studies were considered relevant for evaluating pemigatinib for the treatment of patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2* fusions/rearrangements.

The HRQoL studies identified in the SLR concern studies in patients treated with earlier stages of disease, prior to the use of systemic therapies. Of the included utility estimates, the majority were from studies in patients from Thailand, using the country's corresponding EQ-5D value set.[40] Thus, these studies are not considered relevant for the current study.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.5: Summary of the company submission economic evaluation

	Approach	Source/Justification	Signpost (location in ERG report)
Model	The company developed a de-novo partitioned survival model in Excel.	None of the studies identified in the SLR were considered relevant for evaluating pemigatinib for the treatment of patients with previously treated, unresectable, locally advanced, or metastatic CCA with *FGFR2*+ fusions/rearrangements.[2]	Section 5.2.2
States and events	The company included the following five states: PFS on treatment, PFS off treatment, progressed disease on treatment, progression disease off treatment and death. Patients enter the model in the progression-free health state, despite having already received at least one line of prior therapy. Patients in each treatment arm start in the on-treatment state, where they can either: remain; discontinue treatment and transition to the PFS- off treatment state; progress or die. Given treatment rules and expert opinion, the progressed disease on treatment state was not used.	The chosen model structure provides a framework that suitably captures the experience of patients with CCA, both in terms of the current treatment pathway as well as disease progression.[2] As patients receiving treatment for CCA can discontinue therapy while remaining progression-free, ToT was also included and as a result the chosen model structure includes five health states, with patients in both the PFS and post-progression survival health states either being on or off treatment.	Section 5.2.2
Comparators	The included comparators were ASC and mFOLFOX + ASC	There are no approved targeted therapies for patients with advanced or metastatic CCA who have progressed on at least one line of prior therapy in the UK.[25, 32] Clinical expert opinion suggests that oxaliplatin, mFOLFOX+ASC are now considered SOC therapy for previously treated CCA patients.[41]	Section 5.2.4

	Approach	Source/Justification	Signpost (location in ERG report)
Natural history	In this study, rather than first modelling the natural history and then applying the treatment effectiveness the treatment arm (pemigatinib) is first estimated, and then the treatment effectiveness is used to estimate the comparator arm (i.e. ASC and mFOLFOX+ASC)	The clinical data on pemigatinib is based on a single arm phase 2 study.	Section 2.1
Treatment effectiveness	The effectiveness of pemigatinib was estimated from Cohort A of the FIGHT-202 trial, while the effectiveness of the comparators was estimated from the ABC-06 trial. Relative treatment effectiveness in terms of OS and PFS was estimated using unanchored MAIC analyses.	Unanchored MAIC analyses were required as no trial was identified which compared pemigatinib either directly to either comparator or via common comparators.[2] Therefore an unanchored MAIC was conducted to generate outcomes data adjusted for prognostic variables observed for both pemigatinib and the relevant comparators.	Section 5.2.6
Adverse events	Treatment related grade ≥3 or higher AEs which impacted at least 5% of patients in the FIGHT-202 or either arm of the ABC-06 trial were included in the model as well as any others considered important by clinicians. For ASC and mFOLFOX+ASC, where AE incidence data were not publicly available, AE incidence was assumed to be zero as a conservative assumption. No adjustments or MAIC analyses were conducted.	Grade ≥3 AE are expected to have the greatest impact on patients	Section 5.2.7
Health-related QoL	HRQoL data was collected from patients in Cohort A of the FIGHT 202 study using the EORTC-QLQ-C30. This data was mapped to the EQ-5D-3L and UK specific utility values were produced using the mapping algorithm by Longworth et al. 2014.[69]	EQ-5D data was not collected in the trial. Therefore, the EORTC-QLQ-C30 trial data was mapped to produce EQ-5D-3L utility values based on the UK value set.	Section 5.2.8

	Approach	Source/Justification	Signpost (location in ERG report)
Resource utilisation and costs	Costs were included from an NHS and PSS perspective, and pertain to drug acquisition costs, drug administration costs, other health care resource use costs related to monitoring and pain management, costs associated with AEs, and end-of-life costs. The company did not include the cost of genetic testing in the base case economic analysis, providing justification suggesting that patients will be tested routinely according to NHS plans. The impact of genetic testing costs for pemigatinib were explored in scenario analyses.	According to NICE reference case.	Section 5.2.9
Discount rates	A 3.5% discount rate was used for both costs and effects.	According to NICE reference case.	Section 5.2.5
Sensitivity analysis	Probabilistic and one-way sensitivity analysis.	According to NICE reference case.	Section 6.2

AE = adverse event; ASC = active symptom control; CCA = Cholangiocarcinoma; FGFR2+ = Fibroblast growth factor receptor 2-positive; HRQoL = health related quality of life; MAIC = matching-adjusted indirect comparisons; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression free survival; PSS = personal social services; QoL = quality of life; SLR = systematic literature review; ToT = time on treatment.

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.6: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	According to NICE reference case
Perspective on costs	NHS and PSS	According to NICE reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	According to NICE reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The choice of the time horizon (40 years) appears to be appropriate in this population given the baseline age of 55.3 years and that all patients in the simulation die before reaching the time horizon.
Synthesis of evidence on health effects	Based on systematic review	Systematic literature reviews were conducted for relevant cost effectiveness studies, and studies on HRQoL, cost and resource utilisation for the target population.
Measuring and valuing health effects	Health effects should be expressed in quality adjusted life years (QALYs). The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects are expressed in QALYs. Health state utility values (HSUVs) are measured using the EORTC-QLC-C30 and mapped to EQ-5D utilities.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	HRQoL measured in patients
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	EORTC-QLC-C30 data mapped to EQ-5D UK utility values, which were valued in a representative sample of the UK population.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	According to NICE reference case

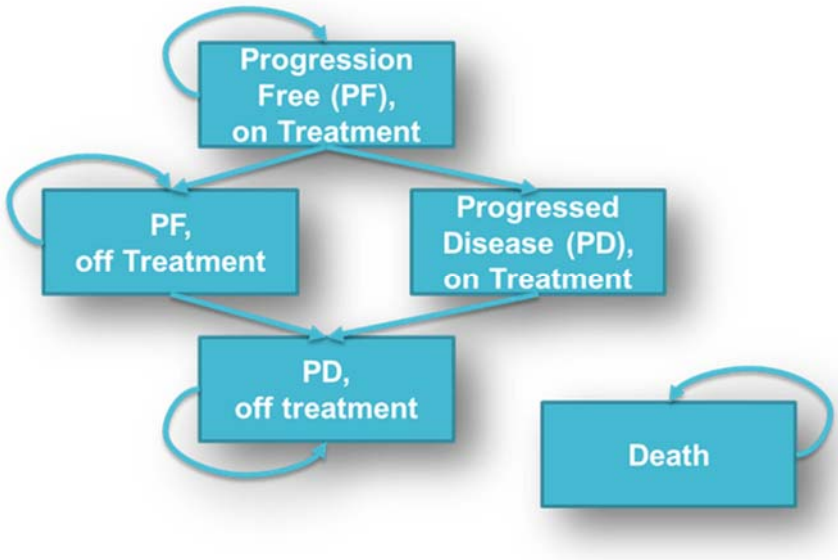
Element of health technology assessment	Reference case	ERG comment on company submission
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	According to NICE reference case
Discounting	The same annual rate for both costs and health effects (3.5%)	According to NICE reference case

EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; HSUVs = health state utility values; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = personal social services; QALY = quality-adjusted life year; UK = United Kingdom.

5.2.2 Model structure

The model applies a partitioned survival approach, using parametric survival models to predict outcomes including time-on-treatment (ToT), PFS and OS. As patients receiving treatment for CCA can discontinue therapy while remaining progression-free, ToT was also included and as a result the chosen model structure includes five health states, with patients in both the PFS and post-progression survival health states either being on or off treatment, as shown in Figure 5.1.

Figure 5.1: Markov model health states



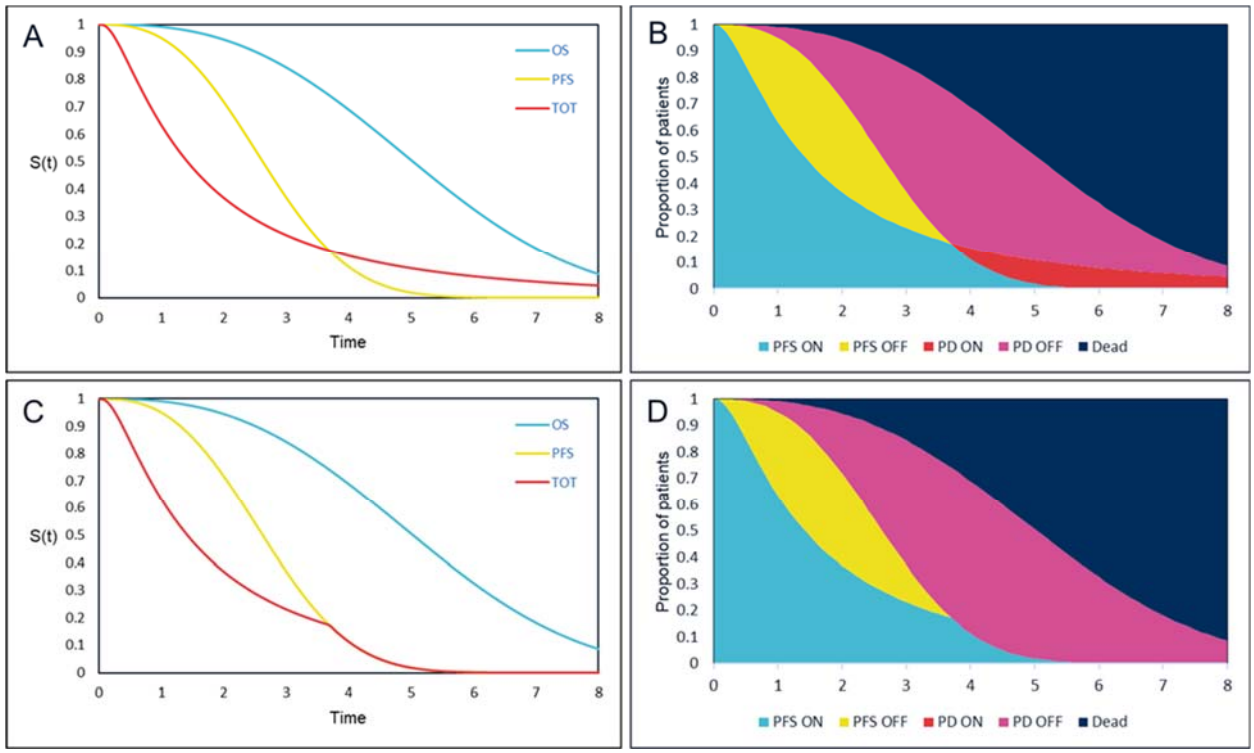
Source: Figure 18 from the CS.[2]

Note: The progressed disease on treatment state was not included in the base case analysis due to treatment scheduling rules and clinical expert opinion stating that treatment would cease upon progression for both the intervention and comparators.

The health states descriptions reflect that patients enter the model in the progression-free health state, despite having already received at least one line of prior therapy. Therefore, progression refers to disease progression during or after receiving pemigatinib or a comparator. Figure 5.2 shows how the ToT, PFS

and OS curves translate into Markov traces. As in clinical practice treatment will stop upon progression, once the ToT and PFS curves cross, the ToT is set to PFS, implying that patients stop treatment (compare A and C below).

Figure 5.2: Example parametric survival models and Markov trace to demonstrate partitioned survival analysis approach and ToT assumptions



Source: Figure 19 of the CS.[2]

(A) Example parametric survival distributions fitted to OS, PFS and ToT, where ToT is permitted to exceed PFS. (B) Corresponding Markov trace for A with patients permitted to enter the 'PD ON' health state. (C) Duplicate parametric survival distributions, while applying the assumption that all patients must discontinue treatment upon disease progression. (D) Corresponding Markov trace for C with no patients entering the "PD ON" health state.

PFS, progression-free survival; OFF, off-treatment; ON, on treatment; OS, overall survival; PD, progressive disease; St, survival function; ToT, time-on-treatment.

The model has a cycle length of one week to ensure short-term changes in disease progression are accurately captured. This relatively short cycle length is considered appropriate due to the poor prognosis of patients with advanced/metastatic CCA, frequently resulting in rapid disease progression. Due to the short cycle length, half-cycle correction is not required.[70]

The model's base case captures a lifetime time horizon, in line with the NICE reference case. This is estimated to be 40 years, at which point more than 99% of patients have died, whether receiving pemigatinib or a relevant comparator. A discount rate of 3.5% per annum is also applied to costs and effects, in line with the NICE reference case.[71]

ERG comment: The model presented by the company is fit for purpose.

5.2.3 Population

The population considered in the cost effectiveness analysis is adult patients with previously treated, unresectable, locally advanced, or metastatic CCA with FGFR2 fusions/rearrangements.[2] This population is consistent with patients included in Cohort A of the prospective, open-label FIGHT-202 phase 2 study and is also in line with the expected licensed indication of pemigatinib.

Baseline patient characteristics were informed by the planned subgroup Cohort A of the FIGHT-202 study.[25] The mean age and gender distribution were used to adjust general population mortality data sourced from the Office for National Statistics (ONS) to match the demographics of Cohort A.[72] Mean body surface area was calculated using height and weight data for patients in Cohort A, using the Mostellar formula.[73] Body surface area was used to calculate accurate weight-based dosing for relevant comparator treatments.

Cohort A of the FIGHT-202 study consists of a molecularly selected population with 100% of patients having FGFR2 fusions or rearrangements confirmed by genetic testing. As the prevalence of FGFR2 fusions/rearrangements in the ABC-06 study is unknown, the company considered the prevalence observed during screening of the FIGHT-202 study to be the most suitable alternative proxy. Data from patients enrolled from the UK are used for the prevalence estimate in the base-case (8.6%).[74] However, FGFR2 fusion/rearrangement prevalence was shown to vary considerably by country of origin in the FIGHT-202 study and alternative literature sources provide an even wider range of plausible estimates. Therefore, alternative estimates using all European patients from FIGHT-202 and data from Jain et al. (2018) are tested in scenario analyses, as shown in Table 5.7 below.[21, 74] This FGFR2 fusion/rearrangement prevalence only informs genetic testing costs or efficacy adjustments in the cost effectiveness model, neither of which were included in the company's base-case.

Table 5.7: Summary of population inputs

Model	Value (SD)	Source
Mean age	55.3 (12.02)	Cohort A, FIGHT-202 Study.[53]
Percentage male (%)	39.3	Cohort A, FIGHT-202 Study.[53]
Body surface area (m2)	1.88 (0.30)	Cohort A, FIGHT-202 Study.[53] Calculated using Mostellar equation.[73]
FGFR2+ prevalence* (%)	8.6% (base-case)	Hollebecque et al. 2019[74]
	19.6%	Jain et al. 2018 Table A1 frequency of FGFR2 genetic aberrations as a proportion of total study patient number (74/377). [21]
	7.4%	Hollebecque et al. 2019[74]

*FGFR2+ prevalence only informs genetic testing costs or efficacy adjustment scenarios in the cost-effectiveness model, neither of which were included in the company's base-case
Source: Table 33 from the CS.[2]
FGFR2+ = fibroblast growth factor receptor 2-positive; SD = standard deviation.

ERG comment: The ABC-06 comparator study does not reflect the population in the scope, as it is not restricted to patients with FGFR2 fusions or rearrangements nor patients with iCCA. The prevalence of FGFR2 fusions/rearrangements in the ABC-06 study is unknown, but given that the prevalence of FGFR2 mutations observed during screening of the FIGHT-202 study in the UK was 8.6%, the prevalence of FGFR2 fusions/rearrangements in the ABC-06 study is likely to be low. Other estimates of the prevalence of FGFR2+ provided in Table 5.7 also support the likelihood that patients with FGFR2 fusions/rearrangements make up a small part to the ABC-06 sample. Additionally, the ABC-06 study

included patients with all types of BTC, not just iCCA. Therefore, the results of the ABC-06 study are also likely to be unrepresentative of the population identified in the scope.

5.2.4 Interventions and comparators

Pemigatinib, the intervention under consideration, is self-administered orally as a 13.5 mg tablet once daily dose on a 14 days-on seven days-off treatment schedule.[25] Treatment with pemigatinib may continue until documented disease progression or unacceptable toxicity related to pemigatinib. Dose interruptions and reductions, to either 9 or 4.5 mg daily, are permitted to manage any treatment related toxicity not thought to warrant permanent treatment discontinuation.[25] In cohort A of the FIGHT-202 study, [redacted] of the FGFR2+ patients treated with pemigatinib had one or more dose reductions, and [redacted] had one or more dose interruptions.[25]

Although there are currently no approved targeted therapies for patients with advanced or metastatic CCA who have progressed on at least one line of prior therapy,[25, 32] clinical expert opinion consulted by the company indicated that mFOLFOX + ASC is considered to be the current SOC therapy for these patients in the UK. However, one clinician did indicate that as these patients have been previously treated, they may be unsuitable for a chemotherapy port – in which case oxaliplatin (administered intravenously, in combination with oral capecitabine; together referred to as CAPOX) is preferred, despite this regimen being more toxic than mFOLFOX.[41] This was stated to have followed from the results of the phase 3 ABC-06 study, in which mFOLFOX+ASC demonstrated a significant improvement in OS in comparison to ASC alone.[23]

ABC-06 was a randomised phase 3, multicentre, open-label study of active symptom control (ASC) alone or mFOLFOX+ASC for patients from the UK with locally advanced/metastatic BTCs that were previously treated with cisplatin/gemcitabine chemotherapy. Importantly, this does not match the patient population of interest for the cost-effectiveness model (ABC-06 investigates all BTCs, whereas Cohort A of FIGHT-202 only included those who have FGFR2 fusions/rearrangements and mainly consisted of iCCA patients). According to the company, the ABC-06 study provided the strongest and most relevant data that is available for use as a comparison to pemigatinib in the economic model. See Section 4.3 for the justification by the company for this ABC-06 trial.

Patients receiving mFOLFOX+ASC received a chemotherapy administration of oxaliplatin (85 mg/m2), L-folinic acid (175 mg) and 5 fluorouracil (FU; 400 mg/m2 bolus) in addition to a 46-hour continuous infusion of 5 FU (2,400 mg/m2) once every 14 days.

Patients receiving ASC alone may have received biliary drainage, antibiotics, analgesia, steroids and anti-emetics as well as palliative radiotherapy and blood transfusions. The costs for these drugs and procedures are not explicitly included in the model, because the company expects these to apply to both arms equally. Radiotherapy is not included in the model, despite the company noting that it may be used in clinical trials. The company states that clinical interviews indicated that radiotherapy is not routinely commissioned by the NHS.[41] Biliary stents are also not included in the model, despite these being included in the final scope for this appraisal. The company notes that biliary stents are mostly used for patients presenting with hilar or extrahepatic CCAs,[32] primarily as a treatment option in the earlier stages of the disease. Maintenance or replacement of stents may be required, but insertion of a new stent is unlikely to be considered after failure of previous lines of chemotherapy.[58] The economic SLR identified various studies evaluating the use of stenting in early stages of disease progression, which the company notes is a confirmation of it being unlikely that biliary stents are considered after failure of previous lines of chemotherapy. Also, in FIGHT-202 no patients in Cohort A received a bile duct

stent during the trial, which, according to the company, suggests that stents would not be used in standard clinical practice for this indication.[25]

ERG comment: The ERG agrees that ASC alone and mFOLFOX+ASC can be considered as relevant comparators for pemigatinib in the indicated population. However, the document that is provided as validation notes that some clinicians may prefer CAPOX over mFOLFOX because chemotherapy ports are often not suitable for previously treated patients.[41] Yet, it was also noted that use of CAPOX is more toxic due to the dosing, and different liver and renal function constraints may impose additional restrictions to its use.[41] As such, it is uncertain whether the use of CAPOX instead of mFOLFOX would lead to a similar clinical effectiveness. According to clinical opinion provided in the validation document, mFOLFOX would certainly be looked at as the current standard of care in the UK based on the ABC-06 publication.[41] As reported in Section 4.3, the process of selection of the ABC-06 trial was questionable and in their response to clarification the company provided evidence for five other comparators in four other trials.[1] It is unclear how commonly used these alternative comparators are compared to mFOLFOX or ASC alone. Regarding radiotherapy, clinicians confirmed in the validation document that it is not used as part of UK current standard of care for previously treated cholangiocarcinoma patients since there is no evidence that it is better than chemotherapy, and it is not routinely funded by the NHS.[41]

5.2.5 Perspective, time horizon and discounting

The analysis is performed from an NHS and PSS perspective, in line with the NICE reference case. A time horizon of 40 years is used in the model, at which point all patients in the model have died regardless of which extrapolation is used. As such, this represents a lifetime time horizon as per the NICE reference case. All costs and benefits (i.e. life years and QALYs gained) are discounted at 3.5% per annum, which is in line with the NICE reference case.

5.2.6 Treatment effectiveness and extrapolation

In the absence of a direct treatment comparison or a common comparator, an unanchored MAIC was conducted to estimate outcomes data adjusted for prognostic variables observed for both pemigatinib and the relevant comparators.[2] The MAIC-adjusted relative treatment effect accounted for the prognostic factors [redacted] The evidence for the comparators was only available in molecularly unselected patients with CCA, rather than for patients with FGFR2 fusions and studies reporting outcomes data for relevant comparators did not report data on the proportion of patients with FGFR2 fusions/rearrangements. In the absence of any robust data to the contrary, the company assumed that patients with and without FGFR2 fusions or rearrangements have the same prognosis.

In their base-case, the company fitted standard parametric survival functions recommended by NICE DSU TSD 14 to survival outcomes observed in Cohort A of the FIGHT-202 study (with Cohort A consisting of 100% of patients having FGFR2 fusions or rearrangements confirmed by genetic testing).[75] The most appropriate curve was selected based on visual and statistical fit within the trial period and the clinical plausibility of the extrapolated curves beyond the trial period. Statistical fit was assessed using the Akaike information criterion (AIC) and Bayesian information criterion (BIC) measures. Relative treatment effect was estimated by applying HRs estimated in the MAIC analysis for each of the relevant comparators to the pemigatinib outcome data. To address the considerable structural uncertainty of modelled survival outcomes, additional functionality of the model used estimates of relative treatment effect estimated by naïve comparisons (Cox proportional hazards models) as well as independently fitted PSMs to observed unadjusted survival data.[2]

ERG comment: The lack of evidence for a direct comparison and reliance on MAIC analyses introduces substantial uncertainty into the estimates of treatment effectiveness in the model described throughout this section. The MAIC analysis has been critiqued in more detail in Section 4.4 of this report.

This uncertainty is compounded by the fact that the comparator study used in the MAIC is not reflective of the population in the scope (patients with CCA and FGFR2 fusions or rearrangements). It is unclear whether the assumption that patients with and without FGFR2 fusions or rearrangements have the same prognosis is appropriate, as differences between these groups have been observed in the literature in terms of OS.[21] These issues call into question how reflective the estimates of treatment effectiveness produced by the MAIC are of the patient population in the scope, particularly as we have no data on the effectiveness of either comparator in the actual scope population. The company estimates from the FIGHT-202 study that only 8.6% of CCA patients in the UK present with FGFR2 fusions or rearrangements and therefore results of the ABC-06 study will likely be driven by the prognosis of the vast majority of patients outside of the scope population. This issue is compounded by the fact that the MAIC results apply to the population in the comparator trial, rather than the pemigatinib trial as the MAIC is conducted by matching the FIGHT-202 data to the ABC-06 study.

Additionally, it is unclear to what extent the matching variables included in the MAIC reflect those which are prognostically important in clinical practice. Or, in other words, it is not clear to what extent they represent all confounding variables. As already discussed, presence of FGFR2 fusions or rearrangements is not included, which has been seen to impact overall survival in the literature.[21] Another potentially important factor is tumour site, as this has been shown to vary between FIGHT-202 and ABC-06.

The alternative naïve comparisons and individually fitted parametric survival models (PSMs) do not make any attempt to control for even observed differences between the studies, increasing uncertainties and potential bias even further. Therefore, given the data available, uncertainties regarding the treatment effect cannot be resolved.

The hazard ratios (HRs) estimated from the MAIC analysis of the KM data from FIGHT-202 and ABC-06 were applied over the entire extrapolation to estimate relative treatment efficacy. This implies lifetime relative efficacy for pemigatinib without any waning. There is no evidence available for the efficacy of pemigatinib beyond approximately 20 months.

5.2.6.1 Overall survival

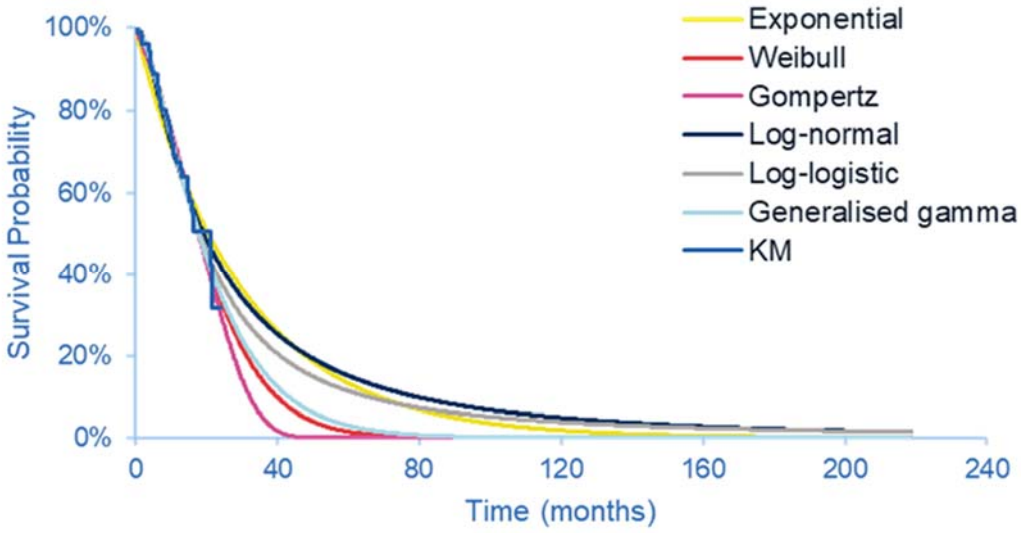
In the base-case for pemigatinib, PSMs were fitted to unadjusted OS observed from Cohort A of the FIGHT-202 study.[2] Comparator survival was informed by relative treatment effects estimated from the MAIC analysis.

Pemigatinib

For pemigatinib, all models showed acceptable visual (Figure 5.3) and statistical fit (Table 5.8) to the observed KM data from Cohort A of the FIGHT-202 study (participants with FGFR2+ fusions/rearrangements), although the Weibull, Gompertz and log-logistic curves had marginally better statistical fit. Given the immaturity of the observed data the company claimed to place greater weight on the clinical plausibility of extrapolations, to determine which curve should be used for the base-case. When validating the extrapolations of pemigatinib OS, both interviewed clinicians struggled to choose the most feasible curve, but suggested that they may expect to observe 5% of patients alive at five years.[41] Literature sources also report that approximately 70% of patients are diagnosed late with

unresectable, locally advanced, or metastatic disease and that these patients have an estimated five-year survival rate of ≤ 10%.[7, 28, 29, 76, 77]

Figure 5.3: Pemigatinib OS KM data and fitted PSM models



Source: Figure 20 from the CS.[2]
KM = Kaplan–Meier; OS = overall survival; PSM = parametric survival model.

Table 5.8: Pemigatinib OS – AIC, BIC and five-year survival estimates

Model	AIC	AIC Rank	BIC	BIC Rank	5-year survival estimate	Survival Rank
Exponential	353.28	6	355.95	6	13%	5
Generalised gamma	349.91	3	357.93	5	3%	1
Gompertz	349.92	4	355.27	3	0%	3
Log-logistic	348.17	2	353.51	2	11%	4
Log-normal	349.99	5	355.33	4	15%	6
Weibull	347.98	1	353.32	1	1%	2

Based on Table 35 of the CS.[2]
AIC = Akaike information criterion; BIC = Bayesian information criterion; OS = overall survival.

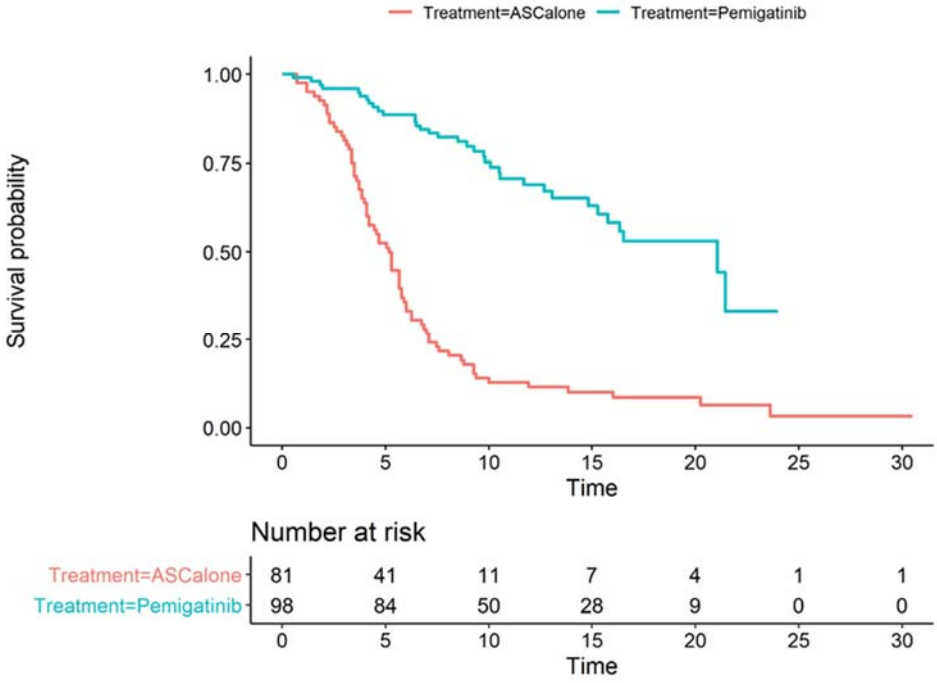
The company reported that neither the log-logistic (11%), the Weibull (1%) or the Gompertz (0%) curves had five-year survival estimates close enough to the clinicians' estimates to be considered better than the other. The log-logistic curve was selected for the base-case, due to the selection of Weibull causing crossing of OS and PFS extrapolations when selecting best fitting PFS curves. The use of a Weibull model was explored in scenario analyses.

Active symptom control

Overall survival for patients treated with ASC was informed by the relative treatment effect derived from the MAIC analysis using digitised pseudo-patient level data from the ABC-06 study.[23] The MAIC-adjusted relative treatment effect accounted for the prognostic factors [redacted] (Figure 5.4). The HR derived from the MAIC, of [redacted] was applied to the base-case PSM fitted for pemigatinib. The company reported that the assessment of the log-cumulative hazards plot showed that the hazards remained parallel for most of the follow-up period, despite

crossing initially (Appendix L, Figure 11). Therefore, the company considered that the proportional hazards assumption holds for OS when comparing pemigatinib versus ASC.

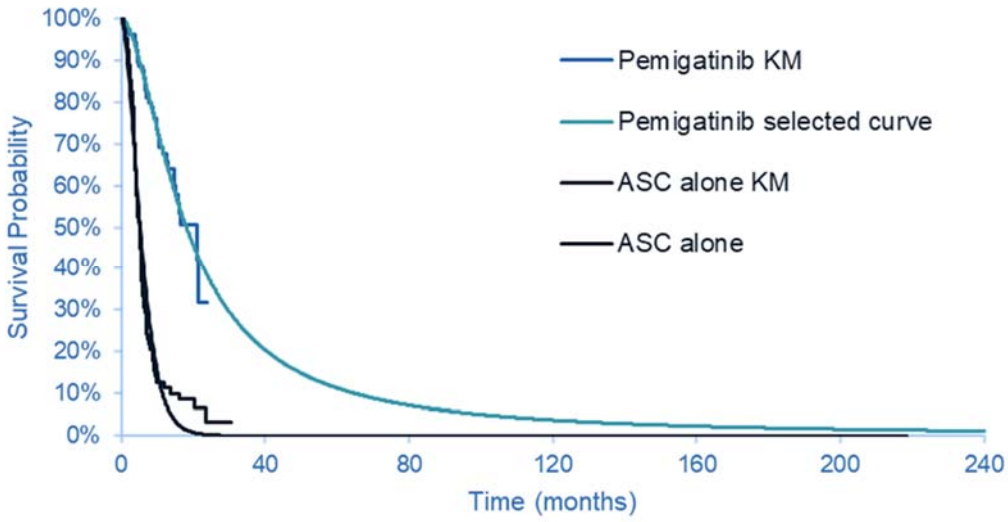
Figure 5.4: Unadjusted OS KM – Pemigatinib versus ASC (ABC-06)



Source: Figure 21 from the CS.[2]
ASC = active symptom control; KM = Kaplan-Meier; OS = overall survival.

The resulting base-case comparator OS curve is shown in Figure 5.5. Alternative options for modelling comparator OS including using relative treatment effects derived from a naïve comparison using a Cox proportional hazards model, as well as extrapolating using independently fitted PSMs to observed KM data were tested in scenario analyses. OS including an adjustment for FGFR2 status, as described in Section 5.2.6.5 of this report, was also tested in scenario analyses.

Figure 5.5: ASC alone OS informed by MAIC HR, compared with pemigatinib OS

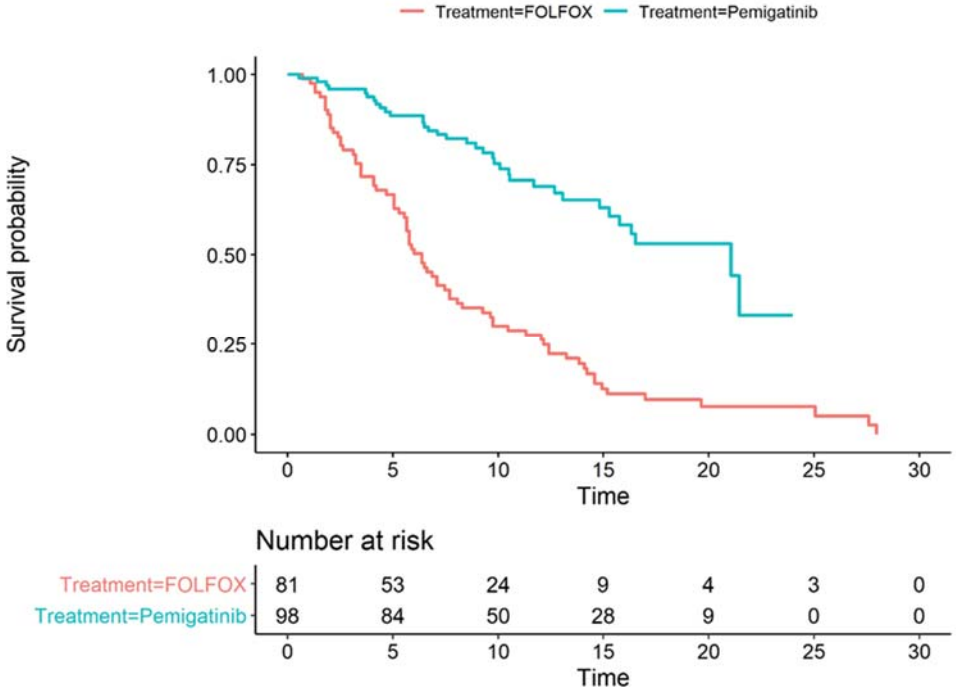


Source: Figure 22 from the CS.[2]
ASC = active symptom control; HR = hazard ratio; KM = Kaplan–Meier; OS = overall survival.

mFOLFOX+ASC

Overall survival for patients treated with mFOLFOX+ASC was also informed by a relative treatment effect derived from the MAIC analysis using digitised pseudo-patient level data from the ABC-06 study, with the MAIC-adjusted relative treatment effect considering the same prognostic factors as for ASC alone (Figure 5.6).[23] The HR derived from the MAIC of [redacted]) was applied to the base case PSM fitted for pemigatinib. The company reported that the log-cumulative hazards plot for pemigatinib versus mFOLFOX+ASC was consistent with ASC alone and that the proportional hazards assumption was considered to hold.

Figure 5.6: Unadjusted OS KM – Pemigatinib versus mFOLFOX+ASC (ABC 06)



Source: Figure 23 of the CS.[2]
ASC = active symptom control; KM = Kaplan-Meier; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; OS = overall survival.

As with ASC alone, the results reported in Table 37 of the CS show the mFOLFOX+ASC OS modelled using the MAIC HR without an adjustment for FGFR2 status (Figure 22 of the CS).[2] Notwithstanding the differences in population between FIGHT-202 and ABC-06, OS data for both ASC alone and mFOLFOX+ASC were mature with survival less than 3% in both arms at the maximum follow-up of 30 months.

ERG comment: In the selection of the extrapolation curve for pemigatinib the company state that clinical validity was given priority in the selection given the immaturity of data.[2] The CS also states that both interviewed clinicians suggested that they may expect to observe 5% of patients alive at five years.[41] The curve which provides the closest estimate to 5% survival at five years is the generalised gamma, which estimates 3% survival at five years (Table 5.8). However, this curve was not considered by the company, as they had already seemingly narrowed down their choice to the three best performing curves in terms of statistical fit. The difference in fit between the log-logistic selected by the company

and the generalised gamma was just 1.74 for AIC and 4.42 for BIC. Given the immaturity of the data, the similarity of the fit statistics across the models and the similar performance in terms of visual fit, the ERG would agree that clinical plausibility should have priority. Therefore, the ERG would argue that the generalised gamma should be considered in the base-case for the extrapolation of OS for pemigatinib rather than the loglogistic as the latter leads to a 5-year survival estimate that is 6 %-point higher than the estimate from the experts, whereas with the generalised gamma the 5-year survival is only 2 %-point lower. However, the ERG acknowledges that this choice leads to a small underestimation of the suggested survival by the experts.

As detailed at the beginning of Section 5.2.6 as well as in Section 4.4, the MAIC indirect comparison leads to substantial uncertainty in the estimate of relative treatment effect in the population described in the scope. Additionally, the MAIC is also based on digitised pseudo patient-level data, which adds additional uncertainty. The company state that the KM data for both comparator treatments is mature, however this does not eliminate the uncertainty caused by the population mismatch and unanchored comparison.

The HRs estimated from the MAIC analysis of the KM data from FIGHT-202 and ABC-06 were applied over the entire extrapolation to estimate relative treatment efficacy. This implies lifetime relative efficacy for pemigatinib without any waning. There is no evidence available for the efficacy of pemigatinib beyond approximately 20 months.

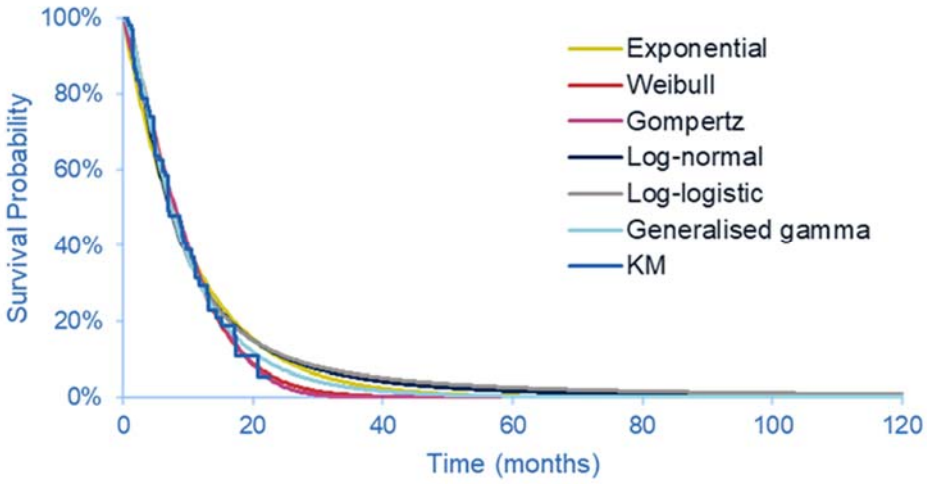
5.2.6.2 Progression free survival

The same approach was used to estimate PFS as for OS. PFS as per the independent review committee analysis was used in the base case, as this was a key secondary outcome of the FIGHT-202 study and also matched the analysis used in the ABC-06 study.[23]

Pemigatinib

PFS for patients treated with pemigatinib was informed by parametric survival models fitted to the FIGHT-202 PFS KM data for Cohort A patients, as shown in Figure 5.7. Only marginal differences in statistical fit were observed between models, with Weibull and log-normal performing the best. Some models, demonstrated good visual fit for the initial follow-up period but provided an overly optimistic extrapolation and relatively poor fit to the tail of the KM data, shown in Table 5.9. Although one of the clinicians interviewed for model validation could not choose between any of the PFS curves of patients treated with pemigatinib, the other suggested that they would expect approximately 10% of patients to be progression-free at two years.[41] Therefore, the company chose the log-normal distribution as it has the better statistical fit and closely aligned with clinical expert opinion.

Figure 5.7: Pemigatinib PFS KM data and fitted PSM models



Source: Figure 25 from the CS.[2]
KM = Kaplan–Meier; PFS = progression-free survival; PSM = parametric survival model.

Table 5.9: Pemigatinib PFS - AIC, BIC and 2-year survival estimates

Model	AIC	AIC Rank	BIC	BIC Rank	2-year PFS estimates	PFS estimate rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 38 of the CS.[2]
AIC = Akaike information criterion; BIC = Bayesian information criterion; PFS = progression free survival.

Active symptom control

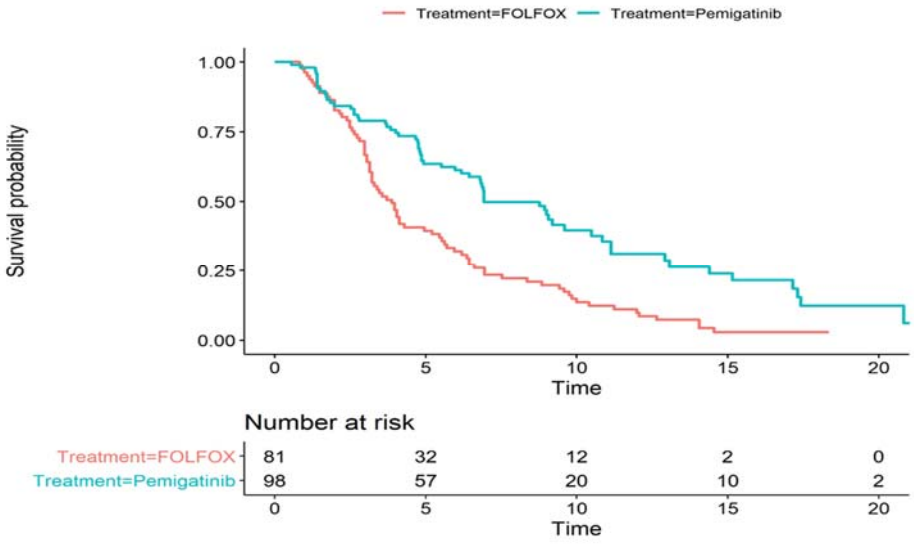
In the absence of any PFS data reported for ASC alone in the ABC-06 publication, PFS for the ASC arm was assumed to be equal to that of the mFOLFOX+ASC arm.[23] The company consider this a conservative assumption, as it is likely the OS benefit for mFOLFOX+ASC in the ABC-06 study would translate into a PFS benefit too.

mFOLFOX+ASC

PFS for patients treated with mFOLFOX+ASC was informed by a relative treatment effect derived from the MAIC analysis using digitised pseudo-PLD from the ABC-06 study displayed in Figure 5.8.[23] The HR derived from the MAIC, of [redacted] was applied to the base case PSM fitted for pemigatinib. Assessment of the log-cumulative hazards plot shows the hazards for the treatments coming together initially and then following a parallel path for the remainder of the follow-

up period. The company claim that proportional hazards assumption is not clearly violated in this case, but they acknowledge the subjective nature of the assessment.

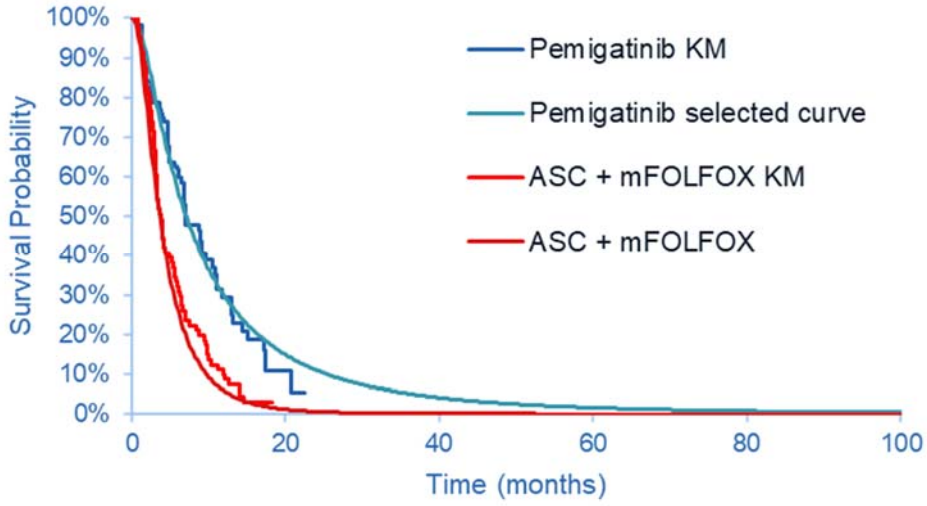
Figure 5.8: Unadjusted PFS KM – Pemigatinib versus mFOLFOX+ASC (ABC 06)



Source: Figure 26 from the CS.[2]
ASC = active symptom control; KM = Kaplan-Meier; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; PFS = progression-free survival.

Figure 5.9 shows the extrapolated PFS for pemigatinib compared with mFOLFOX+ASC informed by the MAIC adjusted HR. Alternative options for modelling comparator PFS include relative treatment effects derived by naïve comparison using a Cox proportional hazards model, as shown in Table 39 of the CS as well as independently fitted PSMs to observed KM data from the ABC-06 study.[2]

Figure 5.9: mFOLFOX+ASC PFS compared with pemigatinib PFS



Source: Figure 27 from the CS.[2]
ASC, active symptom control; KM, Kaplan–Meier; mFOLFOX+ASC, oxaliplatin, L-folinic acid and fluorouracil; PFS, progression-free survival.

ERG comment: The ERG agrees with the company that the log-normal and Weibull extrapolations of pemigatinib PFS have the best statistical fit. In terms of visual fit, the log-normal appears to

overestimate the end of the tail, with Weibull and Gompertz performing best. However, the curves which fit the KM tail underestimate the clinical validity estimate of 10% PFS at two years. In terms of clinical validity, the exponential, followed by log-normal and log-logistic perform best. Given all these elements, the ERG understands the company's choice of the log-normal in the base-case. Alternatives, such as the Weibull which exhibits superior visual fit as well as good statistical fit to the KM curve, could be tested in scenarios.

The company had to assume that PFS was equal for ASC and mFOLFOX+ASC, due to lack of PFS data for ASC. It is unclear how much impact this assumption had on the relative efficacy of ASC in terms of PFS.

5.2.6.3 Background mortality

General population mortality was estimated from the ONS national life tables for England and Wales 2019.[72] General population mortality was included to ensure that the modelled mortality risk did not fall below the general population mortality risk at any given age. To do so, the hazards of PFS and OS events were always equal to or exceeded the general population mortality hazard.

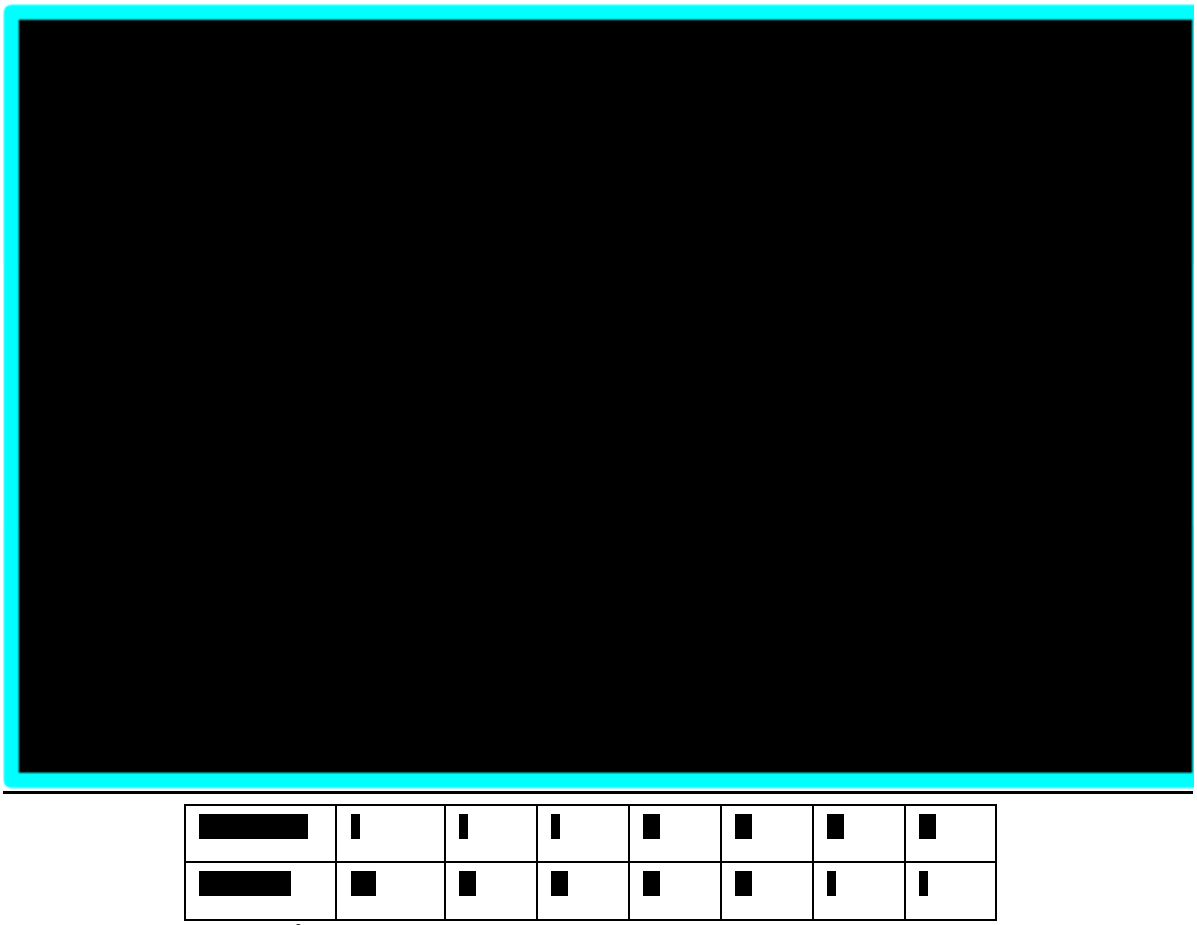
ERG comment: The ERG agrees with this approach.

5.2.6.4 Time on treatment

In the base-case for pemigatinib, ToT was modelled using PSMs fitted to observed data from Cohort A of the FIGHT-202 study.[2] There was a lack of published ToT data for the relevant comparators from any sources, including ABC-06. For simplicity, the company assumed that ToT for ASC alone and mFOLFOX+ASC would be equivalent to PFS. mFOLFOX was assumed limited to a maximum of 24 weeks, consistent with its use in the ABC-06 study.[23]Additional adjustments were made so that ToT could not exceed PFS for any modelled treatment arm. Therefore, all patients discontinued treatment prior to or at the point of disease progression, in line with UK clinical practice as well as the current anticipated license for pemigatinib.

ToT for pemigatinib was extrapolated from the FIGHT-202 KM data, as shown below in Figure 5.10. Visual fit of the PSMs to the observed KM data was relatively good for all distributions, as was the statistical fit (Table 5.10), with the exponential and log-logistic models performing the best, although differences in AIC and BIC were small. The log-normal and log-logistic distributions had long-extended tails not thought to be appropriate for modelling ToT for CCA patients [redacted].[41] Therefore, the exponential model was used in the company base case as it represents the simplest approach, has good visual and statistical fit and a close alignment with clinical expert estimates (Table 5.10).

Figure 5.10: Pemigatinib unadjusted ToT KM data and models



Source: Figure 28 of the CS.[2]
KM, Kaplan–Meier; ToT, time on treatment.

Table 5.10: Pemigatinib unadjusted ToT AIC and BIC scores

Model	AIC	AIC rank	BIC	BIC rank	2-year ToT estimates	ToT estimate rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 40 of the CS.[2]
AIC, Akaike information criterion; BIC, Bayesian information criterion; ToT, time on treatment.

ERG comment: In terms of clinical validity, the Weibull curve performs best, and only performs slightly worse than the company's preferred exponential in terms of statistical fit. Given the rule that ToT should not extend beyond progression, the ERG would argue that clinical plausibility should be prioritised in this choice and therefore the ERG would select the Weibull for their base-case.

Given a lack of ToT data for the comparators, the company had to assume that ToT equalled PFS, with an assumed maximum of 24 weeks of treatment for mFOLFOX. This assumption may have overestimated ToT for these comparators if patients withdraw from these treatments prior to progression.

5.2.6.5 FGFR2+/ iCCA prognostic effect

The company did not identify any prospective high-quality studies investigating the prognostic and predictive impact of FGFR2 genetic aberrations. However, several retrospective studies have investigated this topic, including a study by Jain *et al* (2018), identified by clinical experts as the most robust evidence to support the potential prognostic effect of FGFR.[21, 41]

The study by Jain *et al* reported survival outcomes for CCA patients by FGFR genetic aberration status and showed that these patients had greater OS than those without the mutation. Patients with FGFR genetic aberrations were younger, more likely to be women, presented at an earlier stage of the disease (TNM I/II vs III/IV 35.8% vs 22%, respectively), and had more intrahepatic disease (87.4% vs 67%, respectively). Additionally, these patients had a range of prior lines of therapy across different stages of disease. This makes it challenging to discern whether patients confer a survival advantage due to presenting at an earlier stage of disease, thus being more likely to be successfully resected and receive adjuvant therapy (43% of patients had been resected and received adjuvant therapy).[21] Clinical experts agreed that it is unknown whether the prognostic effect is due to the genetic aberration itself or other associated characteristics of this molecularly selected population such as intrahepatic disease.

While acknowledging the considerable limitations of the study described above an approach was investigated by the company in scenario analyses to re-weight comparator OS based on the estimated prognostic effect of, and the estimated proportion of, patients with FGFR2 fusions/rearrangements in the ABC-06 study.[2] As the proportion of patients with FGFR2 fusions/rearrangements within the key comparator study (ABC-06) was not reported, this was estimated to be 8.6% based on the published literature.

The FGFR2 prognostic effect was calculated as a HR informed by a Cox-proportional hazards model fitted to pseudo-patient level data derived from digitised KM curves for the whole population of the Jain *et al* (2018) study.[21] Patients of all stages from the study were included as it represents the only analysis that reported outcomes excluding patients treated with FGFR-targeted therapies (Table 5.11). The company note that using analyses from the advanced population may overestimate any true effect of the FGFR2 genetic alteration by also including the added benefit of treatment of this cohort with a targeted therapy. The inputs described above and tested in scenario analyses are considered exploratory, but are presented to inform decision makers of the potential impact on results of an unobserved prognostic effect. Base-case settings included no adjustment for FGFR2 status.

Table 5.11: Estimates of FGFR2+ prognostic effect used in the economic model

Population	OS (months)	HR using naïve medians	HR using Cox PH model
All stages of CCA without FGFR GA	20.0		
All stages with FGFR GA	30.0	0.67	0.65
Advanced CCA without FGFR GA	17.0		
Advanced CCA with FGFR GA	24.0	0.71	0.57

Source: Table 34 of the CS.[2]
CCA = cholangiocarcinoma; FGFR = fibroblast growth factor receptor; GA = genetic aberration; HR = hazard ratio; OS = overall survival; PH = proportional hazards.
Notes: HRs presented as without FGFR GA as reference level. HR indicative of prognostic effect

ERG comment: The proportion of patients with FGFR2 fusions/rearrangements within the key comparator study (ABC-06) was not reported and had to be estimated from the literature. This makes the results of this adjustment for FGFR2 prognostic effect very uncertain. It was not used in either base-case.

5.2.7 Adverse events

Adverse events (AEs) were included in the model if treatment-related grade ≥3 events occurred in ≥5% of patients for any relevant comparator in their respective clinical trial. If an AE was included based on these criteria, but AEs occurred in <5% of patients for another treatment, these events were still included where possible. For ASC and mFOLFOX+ASC, where AE incidence data were not publicly available, AE incidence was assumed to be zero as a conservative assumption. Additional AEs were also included if clinical experts deemed them to have a significant clinical impact. The list of AEs included in the model is shown in Table 5.12 below. For inclusion in the model, the frequency of each event was used to calculate an annual rate, adjusted for the number of patients treated [redacted]

Table 5.12: Adverse event annual rates

Adverse event	Pemigatinib[25]	ASC[23]	mFOLFOX+ASC[23]
Abdominal pain	[redacted]		
Alanine aminotransferase increased	[redacted]		
Anaemia	[redacted]	[redacted]	[redacted]
Anorexia		[redacted]	[redacted]
Arthralgia	[redacted]		
Aspartate aminotransferase increased	[redacted]		
Biliary event	[redacted]	[redacted]	[redacted]
Cholangitis	[redacted]		
Decreased serum albumin level			
Fatigue	[redacted]	[redacted]	[redacted]
Hypophosphataemia	[redacted]		
Infection (lung/urinary/fever/not specified)	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]		
Neutropenia			[redacted]

Adverse event	Pemigatinib[25]	ASC[23]	mFOLFOX+ASC[23]
Palmar-plantar erythrodysaesthesia syndrome	[redacted]		
Thromboembolic events	[redacted]	[redacted]	
Hyperphosphataemia (Grade 2+)	[redacted]		

Source: Table 41 of the CS.[2]
ASC, active symptom control; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil.

ERG comment: There was no attempt by the company to conduct a MAIC analysis for AEs. Therefore, the rates of AEs across the studies and their relevant populations remain unadjusted.

In the model the ERG observed that, in calculating the yearly event rate for the AEs, the number of observed events was divided by the number of patient-years. This number of patient-years was derived from the model by estimating the area under the ToT-curve for pemigatinib and the area under the PFS-curve for the comparators. At clarification, the ERG queried why the area under the extrapolated curve was used for the number of patient-years rather than the area under the KM curve, given that the later represents the observed number of patient-years.[78] The company agreed that using the area under the KM curve was more appropriate to capture the observed AE rates and amended this in the model, using the area under the time to treatment discontinuation KM for pemigatinib and the area under the PFS KM ABC-06 mFOLFOX+ASC arm for mFOLFOX+ASC and ASC alone, due to the absence of comparator data on time to treatment discontinuation.[1] This change was made during the clarification stage.

Additionally, the ERG noted an error in the calculation of the annual AE rate, due to confusion between patient-months and patient-weeks in different model sheets. The company corrected this error at clarification.[1]

5.2.8 Health-related quality of life

5.2.8.1 Mapping and modelling of trial HRQoL data

Health related quality of life data was collected from patients in Cohort A of the FIGHT-202 study using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30). HRQoL observations were scheduled at screening and then every three cycles, while patients were on treatment. Patients also had one end of treatment observation upon discontinuation.[2]

These EORTC-QLQ-C30 data were mapped to EQ-5D-3L utilities using a published mapping algorithm. Four potentially relevant mapping algorithms were reviewed based on the use of the UK tariff for EQ-5D-3L and the type of cancer the mapping algorithm was derived from.[69, 79-81] No algorithms were identified which were estimated in patients with BTC. The company identified a review by Doble & Lorgelly et al. (2016) which found that although most published algorithms were not fit for purpose, the Longworth algorithm was found to accurately predict EQ-5D-3L utilities.[82] For this reason, the mapping algorithm by Longworth et al., 2014 was used in the base-case.[69] This algorithm was estimated in patients with a range of cancers.

The company conducted a visual validation of the Longworth algorithm using graphical methods, comparing results to one of the alternative identified algorithms published by Kontodimopoulos et al., 2009.[80] This basic validation exercise showed that both algorithms predicted similar utility values. However as shown in Figure 29 of the CS, the Kontodimopoulos et al., 2009 algorithm resulted in a

high proportion of utilities predicted as >1.[80] Therefore, the Longworth algorithm was used to map the FIGHT-202 HRQoL data to EQ-5D-3L utilities in the economic model. The Longworth algorithm uses a 'response mapping' technique that predicts the probability of a patient scoring 1, 2 or 3 for each of the five EQ-5D-3L dimensions using multinomial logistic regression models applied to the EORTC-QLQ-C30 responses from each patient.[69] To estimate the utility score in the observed EQ-5D data, the coefficients for each domain score from the standard UK utility tariff were multiplied by the corresponding probability derived from the Longworth algorithm.

A series of linear mixed effects regression models were then fitted to the mapped EQ-5D-3L utility data to quantify the impact of potential explanatory variables and events on utility. An exploratory analysis was carried out which included all patients with at least one utility observation. Observations with unknown progression status were removed due to the importance of progression status in informing the health states of the economic model. The following linear mixed effects models were explored:

- Model 1: Utility = treatment + baseline utility
- Model 2: Utility = treatment + baseline utility + treatment state
- Model 3: Utility = treatment + baseline utility + health state
- Model 4: Utility = treatment + baseline utility + treatment state + health state
- Model 5: Utility = treatment + baseline utility + treatment state*health state (interaction) + treatment state + health state

A random effect for patient was included to adjust for the correlation between multiple observations from the same patient.

One hundred and seven patients from Cohort A provided 496 observations. Of the post-screening observations, 282 (71%) were observed prior to disease progression and 91 (19%) after disease progression. Observations with unknown progression status (26 observations from 24 patients), were subsequently removed from the analysis. The descriptive statistics indicated lower utility for patients post-progression and off treatment compared to patients pre-progression and on-treatment respectively, as shown in Table 5.13 below. Furthermore, it appeared that the impact of treatment status on utility was independent of progression status.

Table 5.13: CS Summary of utility observations by progression and treatment status

	Category	Mean (SD)	Median (range)	N Subjects (N utility observations)
All observations	All	[redacted]	[redacted]	[redacted]
	Screening	[redacted]	[redacted]	[redacted]
	Post-screening	[redacted]	[redacted]	[redacted]
Progression-status	Pre-progression	[redacted]	[redacted]	[redacted]
	Post-progression	[redacted]	[redacted]	[redacted]
	Unknown	[redacted]	[redacted]	[redacted]
Treatment-status	On-treatment	[redacted]	[redacted]	[redacted]

	Off-treatment	[redacted]	[redacted]	[redacted]
Pre-progression	On-treatment	[redacted]	[redacted]	[redacted]
	Off-treatment	[redacted]	[redacted]	[redacted]
Post-progression	On-treatment	[redacted]	[redacted]	[redacted]
	Off-treatment	[redacted]	[redacted]	[redacted]

Source: Table 42 of the CS.[2] SD = standard deviation.

The company noted some important potential limitations in their data. Mean utilities increased over the follow up period, as shown in Table 43 of the CS.[2] This suggests potential selection bias as unhealthier patients discontinue treatment and stop providing HRQoL data. This was accounted for in regression analyses, using a random effect for patient. Furthermore, by only including a single observation post treatment discontinuation and with progression being so closely linked to treatment discontinuation, there is a significant risk that post-progression observations failed to capture the full impact of disease progression on patients' HRQoL. Lastly, patients had an average of two months between HRQoL observations, meaning it is unlikely that the results are sensitive to AEs.

Regression coefficients for each utility model are shown in Table 5.14. Models were similar in terms of statistical fit, with Models 1 and 2 performing best, followed by 5, 3 and 4 performing worst. The company report that the AIC was higher for Model 5 than Model 1 as models with more covariates were penalised more for the AIC criterion. When included in isolation in Models 2 and 3, treatment status and disease progression were both associated with a utility decrement, but only treatment status was statistically significant. When included in combination in Model 4, the effect of treatment status remained significant, whereas the impact of progression independent of treatment status was negligible and insignificant. Model 5 was shown to have significant coefficients for both treatment status and an interaction term for treatment and progression status. However, the company acknowledge that these results are highly uncertain, as there were only five observations available for patients who were pre-progression and off-treatment.

Table 5.14: Linear mixed effects regression model coefficients and statistical fit

	Coefficient (p-value)				
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Off-treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interaction: post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

***off-treatment**					
Fit statistic					
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source: Table 44 of the CS.[2] AIC; Akaike information criterion.					

ERG comment: Firstly, the ERG would like to note that it would have been preferable to have EQ-5D data from the trial in order to estimate utilities without the need for mapping which introduces additional uncertainties into the analysis. However, given that EQ-5D data was unavailable, mapping is an appropriate alternative and the ERG agree with the company's selection of the Longworth et al. algorithm.

The ERG agrees with the company's concerns surrounding the potential biases within their trial data. By only including a single observation post treatment discontinuation and with progression being so closely linked to treatment discontinuation, there is a significant risk that post-progression observations failed to capture the full impact of disease progression on patients' HRQoL. However, in Table 5.13 it can be seen that [redacted] patients provided [redacted] observations post-progression. In an attempt to further understand the potential biases in post-progression HRQoL data, the ERG requested more information from the company about these post-progression observations, which the company provided in their response to clarification and is displayed in Table 5.15 below.[1] The data shows that the vast majority of post-progression utility observations came within a mean of [redacted] days from progression. There was no clear pattern in the utilities observed at first, second, third and fourth observation after progression, with the only notable difference being that the three participants who provided a fifth observation after a mean of [redacted] days of progression provided a notably lower mean utility of [redacted] versus approximately [redacted] for the earlier observations. This may suggest that utility worsens the longer spent in progression and that the post-progression utility value estimated from data may underestimate the impact of progression, but it is difficult to say given the substantial drop out.

Table 5.15: Post-progression utility observations

Number utility observation post-progression	Number of patients who provided a first, second etc. observation	Mean number of days between progression and observation	Mean utility by observation number post-progression
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
Source: Response to clarification.[1]			

Table 5.13 shows the summary of utility values by treatment and progression status as well as the number of patients and observations available for each estimate. These values seem generally plausible, at the level of progression status and treatment status independently, with an acceptable sample size within each category. However, when treatment and progression status are combined within categories, sample sizes are reduced, sample size across categories becomes more uneven and resulting utility values appear less plausible. At this level the vast majority of observations fall into the pre-progression on treatment category which contains [redacted] observations from [redacted] patients, while for post-progression on

treatment and off treatment there are only [redacted] and [redacted] observations available respectively and worse of all only [redacted] observations available to estimate utility for patients pre-progression off treatment. The utility value of [redacted] estimated from these [redacted] observations for pre-progression off treatment seems to be fairly implausible, as it is substantially lower than both post-progression values ([redacted] and [redacted] for on and off treatment respectively). Both health economists and one of the clinicians consulted by the company raised concerns about the plausibility of the pre-progression off treatment utility value.[41]

When asked to comment on the plausibility that utility in the PFS off treatment state is substantially lower than the utility in the progressed state off treatment, the company responded that: "*the plausibility and face validity of the PFS off treatment health state utility derived from Model 5 is unclear. Clinical experts suggested that the substantial decrease seen could be explained if the HRQL questionnaire was completed while experiencing the AEs that led to treatment discontinuation.[41] Otherwise, the HRQL of patients in the PFS off-treatment state would be expected to improve rather than decline. Consequently, Model 3 was investigated in scenario analyses as an appropriate alternative and model 5 was used in the base case as it was shown to have the best statistical fit."*[1] Given that AEs are accounted for separately in the model, if this value was indeed due to what would have to be a very severe AE, this would be double counting. This limits the ERGs confidence in the results of models requiring both progression status and treatment status.

Additionally the ERG note that the post-progression on treatment state is not used in the base-case, given that scheduling rules do not allow for pemigatinib or its comparators to be used post-progression.[2] Given that the pre-progression utilities separated by treatment status are not clinically plausible and the post-progression utilities separated by treatment status are not used within the model, the ERG questions how appropriate it is to include this distinction of treatment status within the model, particularly given the reduction in sample size for each estimate and the concerning results. The ERG will use Model 3, with no distinction of utility by treatment status, in their base-case.

5.2.8.2 Utilities from the literature

No studies were identified in the original searches for HRQoL studies in patients consistent with the setting considered in this appraisal. Updated searches found a small number of studies in patients treated with earlier stages of disease, prior to the use of systemic therapies, the majority of which were in patients from Thailand, using the country's corresponding EQ-5D value set. The company therefore did not consider the utilities identified from the SLR to be appropriate for inclusion in the model.

To investigate utilities from a source other than FIGHT-202, the utilities used in NICE appraisal TA474 for sorafenib in advanced hepatocellular carcinoma were used in the model for scenario analysis [redacted]

ERG comment: The utility values from the NICE appraisal for sorafenib in advanced hepatocellular carcinoma do not appear to follow the pattern of utility values obtained from FIGHT-202, likely because of the [redacted]. Therefore, the ERG retains their use in scenario analyses but does not consider them an appropriate source for the base-case.

5.2.8.3 Health state utility values used in the cost effectiveness analysis

The company found that HRQoL data are scarce for patients previously treated, unresectable, locally advanced, or metastatic CCA, likely due to the rarity of the condition and lack of previously approved treatment options and corresponding clinical trial data. The same is true for the specific population of patients with an *FGFR2* fusion/rearrangement who are considered in this model, although there is no evidence to suggest that FGFR2 status is predictive of HRQoL. The only robust HRQoL evidence available is from the single-arm FIGHT-202 pemigatinib study. In the base-case, patients' baseline utility, treatment and progression status were considered. This model demonstrated the best statistical fit to the available data and resulted in the HSUVs shown in Table 5.16 below. Health state utilities were applied consistently across all treatment arms, as there was no evidence to support an alternative assumption. However, treatment specific administration and AE disutilities were included, as described in the next section.

Acknowledging the uncertainty of these estimates, alternative inputs were tested in scenario analyses. These included an alternative specification of the FIGHT-202 regression analysis in addition to utility estimates from a clinically comparable indication, advanced hepatocellular carcinoma. Scenario 1 removed the impact on utility associated with treatment discontinuation, independent of progression. Utility estimates from advanced hepatocellular carcinoma appear to lack a degree of clinical validity with progressed disease utility exceeding progression-free utility. However, they provided the best available comparison to utilities derived from FIGHT-202 and demonstrated that utilities from the two sources were comparable. Table 5.16 summarises the utilities for the two scenarios.

Table 5.16: Health state utility values used in the cost effectiveness analysis

	Health state utility value		
Health state	**Base-case**	**Scenario 1[25]**	**Scenario 2[83]**
Progression-free on treatment	[redacted]	[redacted]	[redacted]
Progression-free off-treatment	[redacted]	[redacted]	[redacted]
Progressive disease on-treatment	[redacted]	[redacted]	[redacted]
Progressive disease off-treatment	[redacted]	[redacted]	[redacted]
Source: Table 45 of the CS.[2]			

ERG comment: Given the previously detailed concerns surrounding the plausibility of the utility values produced by the company's base-case utility model (Model 5), for the pre-progression off treatment state, the ERG prefers to use the utility values produced by the company's scenario 1 (Model 3) in their base-case. Alternatives will be explored in scenarios.

The company did not include adjustment for age over time in the utilities in the model submitted alongside their submission. This was included in the model at the request of the ERG during clarification.[1] Estimates of age-related decline in utility were sourced from Ara & Brazier 2010 and applied to the economic model.[84]

5.2.8.4 Adverse reactions

The impact on HRQoL of those treatment-related, grade ≥3 AEs included in the economic model as well as Grade ≥2 hyperphosphataemia were captured using disutilities and durations identified from the literature, as shown in Table 5.17 below. The company considered the inclusion of AE disutilities appropriate as the scheduled frequency of HRQoL observations in the FIGHT 202 study was unlikely to be sensitive to short-term changes in utility. In the absence of published data, assumptions were made

based on clinical expert opinion. QALY decrements were applied to pemigatinib and the relevant comparators while patients remained on treatment, based on the frequency of AEs shown in Table 5.12.

Table 5.17: Adverse event disutilities

Event	AE duration (days)	Disutility per AE	Source/assumption
Abdominal pain	11.8[25]	-0.069	Assumed same as arthralgia
Alanine aminotransferase increased	8.3[25]	0	Assumed to have limited impact on HRQoL[41]
Anaemia	9.9[25]	-0.085	TA439: cetuximab and panitumumab for previously untreated metastatic colorectal cancer[85]
Anorexia	17[86]	-0.069	Assumed same as for decreased appetite; TA307: aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy[87]
Arthralgia	18.7[25]	-0.069	Assumed same as SAE for bone pain; TA391: cabazitaxel for the second-line treatment of hormone-refractory metastatic prostate cancer[88]
Aspartate aminotransferase increased	6.8[25]	0	Assumed to have limited impact on HRQoL[41]
Biliary event	2.625	-0.085	Assumed same as anaemia
Cholangitis	4.7[25]	-0.085	Assumed same as anaemia
Decreased serum albumin level	7[25]	-0.085	Assumed same as anaemia
Fatigue	2.625	-0.085	Assumed same as anaemia
Hypophosphataemia	29.3[25]	0	Assumed to have limited impact on HRQoL[41]
Infection (lung/urinary/ fever/not specified)	8.3[25]	-0.085	Assumed same as anaemia
Stomatitis	9.8[25]	-0.0375	TA439: cetuximab and panitumumab for previously untreated metastatic colorectal cancer[85]
Neutropenia	7	-0.0607	TA439: cetuximab and panitumumab for previously untreated metastatic colorectal cancer[85]
Palmar-plantar erythrodysaesthesia syndrome	17.3[25]	-0.085	Assumed same as anaemia

Event	AE duration (days)	Disutility per AE	Source/assumption
Thromboembolic events	14	-0.085	Assumed same as anaemia, with duration longer than seven days as per clinical opinion[41]
Hyperphosphataemia (Grade 2+)	15.5[25]	0	Assumed to have limited impact on HRQoL[41]

Source: Table 45 of the CS.[2]
HRQoL = health related quality of life; SAE = serious adverse event.

The company also included an additional treatment administration disutility, due to the patient burden of IV treatment administration. Clinician interviews confirmed that treatment with the mFOLFOX regimen typically requires an implantable port, particularly given the 46 hours continuous infusion time with 5-FU.[41] Comparative HRQoL data that capture the differential administration disutility of an IV therapy versus an oral therapy such as pemigatinib in BTC are not currently available. Therefore, administration disutilities were searched from the literature.

NICE technology appraisal TA427 (pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib) used a disutility of 0.025 for patients receiving either subcutaneous or IV therapies.[89] In addition, a separate UK study used a time trade-off approach to derive disutilities for different modes of treatment administration, finding a disutility of 0.037 for an infusion at hospital every four weeks versus SC injection at home every 12 weeks.[90] Finally, an SLR in non-small cell lung cancer identified a paper reporting disutilities of 0.014 for oral therapy and 0.043 for IV therapy (a difference of 0.029).[91] Acknowledging the uncertainty of treatment administration disutilities for patients with advanced CCA, a value of 0.025 was used to estimate the administration disutility value of mFOLFOX+ASC in the model and applied while patients were on treatment. This is considered to be an estimate within the range reported by the studies listed above, and is included in one-way and probabilistic sensitivity analyses.

ERG comment: The ERG agrees that the collection of data in the trial is likely to have missed the impact of AEs as patients had an average of two months between HRQoL observations and therefore the inclusion of separate disutilities for AEs is appropriate.[2]

Many of the disutilities were taken from previous appraisals in colorectal cancer. The lack of disutility evidence in the population of interest in this appraisal increases the uncertainty in their value, particularly where assumptions have been made regarding the equivalence of AEs in the complete absence of evidence. However, AEs disutilities have a very limited impact on results and therefore this is not a major issue.

The ERG agrees with the inclusion of the administration disutility for mFOLFOX+ASC. The ERG agrees that there is uncertainty as to the exact disutility which would reflect the administration of mFOLFOX+ASC in this population, but given the previous use in TA427 and very limited impact on results, the ERG consider the value of 0.025 appropriate.

5.2.9 Resources and costs

The following costs are included in the analysis: drug acquisition costs, drug administration costs, other health care resource use (i.e. clinical examination, computed tomography (CT) scans, blood tests and pain management), costs associated with grade ≥ 3 treatment-related adverse events (AEs), costs for FGFR genetic testing, and end-of-life costs. The details to each of these cost categories are provided below.

5.2.9.1 Drug acquisition costs

The list price for pemigatinib as provided by the company is £511.36 per tablet, with the same price applying to tablets of either 4.5 mg, 9 mg, or 13.5 mg. After applying the Patient Access Scheme (PAS) discount of [redacted], the cost price of pemigatinib as used in the analysis is [redacted] per tablet. Pemigatinib acquisition costs were adjusted to account for dose interruptions by applying the relative dose intensity (RDI), which was calculated as the percentage of doses received in Cohort A of FIGHT-202 as a proportion of the expected number of doses without any interruptions. This resulted in an RDI of [redacted]. No wastage costs were assumed in the original CS,[2] for pemigatinib. The company justified this with reference to an assumed packaging that corresponds to a single treatment cycle consisting of 14 tablets. At the ERG's request during the clarification phase, the company provided the option to include wastage costs for pemigatinib. This was implemented as an alternative to applying the weekly average treatment costs per model cycle by applying the costs of a full treatment cycle (i.e. 14 tablets) every three weeks in the model, both with and without accounting for the RDI.

For the components of the mFOLFOX regimen drug acquisition costs were sourced from the electronic Market Information Tool (eMIT) 2020,[92] and weighted averages were calculated for each component based on their various pack sizes and dosages in combination with the estimates of NHS hospital-sector annual usage from English trusts. This resulted in the following weighted average costs: £0.001/mg for fluorouracil, £0.10/mg for oxaliplatin, £0.05/mg for calcium folinate. In addition, the electronic model provides the option to run the analysis using the minimum costs for each component: £0.001/mg for fluorouracil, £0.087/mg for oxaliplatin, £0.006/mg for calcium folinate. For chemotherapy drugs with dosing based on patient body surface area (BSA), the mean BSA from the FIGHT-202 population was applied. No wastage costs were assumed for chemotherapy, which was justified with reference to the low acquisition costs implying that wastage costs were expected to be negligible. No drug acquisition costs were applied for ASC. An overview of the drug acquisition costs is provided in Table 5.18, and an overview of the dosing and administration schedule for each drug is provided in Table 5.19.

Table 5.18: Drug acquisition costs

Drug and pack size	Pack cost (£)	Cost per mg (£)	Source
Pemigatinib			
List price per tablet (4.5, 9 or 13.5 mg)	511.36	113.64 (4.5 mg tablet), 56.82 (9 mg tablet), 37.88 (13.5 mg tablet)	Incyte Corporation
PAS price per tablet (4.5, 9 or 13.5 mg)	[redacted]	[redacted] (4.5 mg tablet), [redacted] (9 mg tablet), [redacted] (13.5 mg tablet)	
Fluorouracil			
1 x 1g	1.13	0.001	eMIT[92]
1 x 2.5 g (100 ml)	2.84	0.001	
1 x 2.5 g (50 ml)	1.88	0.001	
1 x 500 mg (10 ml)	0.96	0.002	
10 x 500 mg (20 ml)	66.00	0.013	
1 x 5 g	4.82	0.001	

Oxaliplatin			
1 x 100 mg	8.67	0.087	eMIT[92]
1 x 200 mg	18.78	0.094	
1 x 50 mg	7.19	0.144	
Calcium folinate			
1 x 100 mg	2.23	0.022	eMIT[92]
10 x 100 mg	5.97	0.006	
1 x 300 mg	9.97	0.033	
1 x 350 mg	5.96	0.017	
10 x 350 mg	54.96	0.016	
1 x 50 mg	4.50	0.090	
10 x 50 mg	14.66	0.029	
1 x 10 mg	21.37	2.137	
1 x 20 mg	39.94	1.997	
1 x 40 mg	79.88	1.997	

Source: Table 48 in the CS.[2]
CS = company submission; eMIT = electronic market information tool; mg = milligram; PAS = patient access scheme.

Table 5.19: Drug dosing and administration schedule

Drug	Administration route	Dosing and administration schedule	Source
Pemigatinib	Oral	One tablet (of 4.5, 9 or 13.5 mg) daily	FIGHT-202[25]
Fluorouracil	IV	Once every 14 days for up to 12 cycles, 400 mg/m2 bolus injection + 2400 mg/m2 continuous infusion over 46 hours	Lamarca et al., 2019[23]
Oxaliplatin	IV	Once every 14 days for up to 12 cycles, 85 mg/m2	
Calcium folinate	IV	Once every 14 days for up to 12 cycles, 350 mg	

Source: Table 49 in the CS.[2]
CS = company submission; IV = intravenous; mg = milligram.

5.2.9.2 Drug administration costs

Drug administration was costed using 2018/2019 NHS reference costs.[93] Chemotherapy administration costs were £370.68 for each intravenous infusion for the delivery of complex chemotherapy including a prolonged infusion treatment at first attendance.[93] Since fluorouracil is administered over a 46 hour time period, an additional cost of £147.38 per visit was applied for patients returning to the hospital to have their infusion removed by a nurse.[93] This was in line with the costing methodology in TA476.[94]. This resulted in average weekly chemotherapy administration costs of £259.03 for up to a maximum of 24 weeks (i.e. 12 treatment cycles of 2 weeks). No drug administration costs were included for the oral administration of pemigatinib, nor were any drug administration costs included for ASC. An overview of drug administration costs is provided in Table 5.20.

Table 5.20: 2018/2019 NHS reference costs for chemotherapy administration

HRG code	Description	Cost
SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusion Treatment, at First Attendance, total HRG data	£370.68
WF01A	Non-consultant led, Non-Admitted Face-to-Face Attendance, Follow-up, Medical Oncology (370)	£147.38
Average weekly chemotherapy administration cost (i.e. up to a maximum of 24 weeks)		£259.03

Based on the CS.[2]
CS = company submission; HRG = healthcare resource group.

5.2.9.3 Other health care resource use

Other than drug acquisition and administration costs, the costs for a monitoring strategy consisting of clinical examinations, computed tomography (CT) scans and blood tests were included. This was in accordance with the ESMO guidelines for biliary cancer follow-up, which suggest a follow-up visit once every three months during which a CT scan and blood test is performed .[32] Although the ESMO guidelines recommend this frequency only for the first two years after therapy,[32] it was applied to all patients in the model who are progression-free. The same frequency was assumed for follow-up visits including blood tests for progressed patients, except that CT scans were assumed to be performed once every 12 months after progression. The latter assumption was based on clinician feedback, which, based on documents provided during the clarification phase at the ERG's request, consisted of one clinician noting that *"few patients would be scanned following progression*" and a second clinician noting that "*following progression, patients on treatment for advanced disease would likely have CT scans every 3 months but for patients receiving best supportive care alone, scanning would not be performed*".[41] For progressed patients the model furthermore included the cost of pain medication consisting of daily morphine sulphate at a cost of £5.78,[95] which was in line with clinician feedback and TA581.[41, 96] This resulted in annual monitoring costs of £1,208.08 for progression-free patients, and £3,003.55 for progressed patients. An overview of the unit costs for monitoring and pain medication is provided in Table 5.21, and their monthly frequencies and annual costs are provided, for progression-free and progressed patients separately, in Table 5.22.

Table 5.21: Monitoring and pain medication costs

Health care resource	HRG code	Description	Unit cost	Source
Clinical examination	WF01A	Consultant led, Non-Admitted Face-to-Face Attendance, Follow-up 370 Medical Oncology	£194.17	2018/2019 NHS reference costs[93]
CT scan	RD22Z	IMAG Diagnostic imaging: Outpatient, Computerised Tomography Scan of One Area, with Pre- and Post-Contrast	£105.37	
Blood test	DAPS05	DAPS: Directly accessed pathology services - Haematology	£2.79	
Pain medication	-	Morphine sulfate 50mg/50ml solution for infusion vials (Martindale Pharmaceuticals Ltd)	£5.78	BNF 2020[95]

Based on the electronic model and CS.[2]
BNF = British national formulary; CS = company submission; CT = computed tomography; NHS = national health service.

Table 5.22: Monitoring and pain medication frequencies and costs

Health care resource	Monthly frequency		Annual costs	
	PF	PD	PF	PD
Clinical examination	0.333	0.333	£775.91	£775.91
CT scan	0.333	0.083	£421.04	£105.37
Blood test	0.333	0.333	£11.14	£11.14
Pain medication	-	30.4	-	£2,111.15
Total annual costs			£1,208.08	£3,003.55

Based on the electronic model and CS.[2]
CS = company submission; CT = computed tomography; PD = progressed disease; PF = progression-free.

5.2.9.4 Adverse events costs

The model includes the costs associated with each grade ≥ 3 treatment-related AE since these were the AEs considered to be the greatest cost burden. In addition, costs for grade ≥ 2 hyperphosphataemia was included due to their frequency in patients treated with FGFR inhibitors. AEs that were reported in FIGHT-202 and ABC-06 but were not reported explicitly in the reference costs were assumed to have the same cost as a similar AE. For the AEs increased alanine aminotransferase and aspartate aminotransferase it was assumed that these were managed with watchful waiting at no additional costs. Annual AE costs per treated patient year were £4,334 for pemigatinib, £4,265 for ASC alone and £7,925 for mFOLFOX+ASC. An overview of the unit costs and assumptions that were applied to AEs is provided in Table 5.23.

Table 5.23: Adverse event costs

Adverse event	Description/HRG code[1]	Unit cost (£)
Abdominal pain	Assumed same as arthralgia	990
Alanine aminotransferase increased	Watchful waiting (and thus no cost) assumed	0
Anaemia	Non-elective short stay weighted average SA04G-SA04L, Iron deficiency anaemia	691
Anorexia	Non-elective short stay weighted average FD04C-FD04E, Nutritional Disorders without Interventions	1,256
Arthralgia	Non-elective short stay average HD26D-HD26G, Musculoskeletal Signs or Symptoms	990
Aspartate aminotransferase increased	Watchful waiting (and thus no cost) assumed	0
Biliary event	Assumed equal to cholangitis	1,256
Cholangitis	Assumed equal to infection	1,256
Decreased serum albumin level	Non-elective short stay average SA08G-SA08J, Other Haematological or Splenic Disorders	1,077
Fatigue	Assumed equal to anorexia	1,256
Hypophosphataemia	One pack of oral phosphate supplements - Phosphate Sandoz effervescent tablet[97]	19

Infection (lung/urinary/fever/not specified)	Assumed equal to fatigue	1,256
Stomatitis	Non-elective short stay average FD10E-FD10H, Non-malignant Gastrointestinal Tract Disorders with Single Intervention	3,346
Neutropenia	Non-elective short stay average SA08G-SA08J, Other Haematological or Splenic Disorders	1,077
Palmar-plantar erythrodysaesthesia syndrome	Assumed equal to infection	1,256
Thromboembolic events	Non-elective short stay average SA12G-SA12JK Thrombocytopenia	640
Hyperphosphataemia (Grade 2+)	One pack of phosphate binders - Renacet 950 mg tablets[98]	18

[1]All AE costs were based on 2018/2019 NHS reference costs, unless indicated otherwise.
Source: Table 50 in the CS.[2] CS = company submission; HRG = healthcare resource group; mg = milligram.

5.2.9.5 FGFR genetic testing costs

The company did not include the costs for FGFR genetic testing in their base case analysis, due to it not being a part of routine clinical practice until recently. Since it is likely that FGFR genetic testing will be incorporated into standard clinical practice, the company included the corresponding costs in a scenario analysis. Next generation sequencing was assumed to be the gold standard technique for genetic testing, with the cost for a test that can detect FGFR2 fusions varying between £500 and £750, based on consultation with several providers including NHS laboratories (i.e. no reference was provided for this consultation). The company assumed a unit cost of £550, based on "*factors specific to the processing of CCA samples*". The cost of testing one patient as FGFR2-fusion positive included the costs for the negative tests of other patients and was calculated by dividing the unit cost for testing by the prevalence of FGFR2 fusions of 8.6%. This resulted in a unit cost of £6,395 per additional FGFR2-fusion positive patient.

5.2.9.6 End of life costs

The base case model included end of life costs based on Round *et al* 2015,[99] which were updated to 2019 using the Personal Social Services Research Unit (PSSRU) inflation indices.[100] This included healthcare costs (i.e. £5,203) and social care costs (i.e. £1,596), with a total of £6,799. End of life costs were applied to all patients upon entering the death state in the model.

ERG comment: The ERG agrees that the costing of drug acquisition, drug administration, and other health care resource use was generally appropriate, being in accordance with clinician feedback,[41] ESMO guidelines for monitoring costs,[32] the methodology of TA476 for costing of prolonged fluorouracil infusion,[94] and the inclusion of pain medication costs for progressed patients based on TA581.[96] However, the validation document also notes that following a second progression, patients may incur additional costs for palliative care (MacMillan nursing support), nausea management and treatments to deal with previous platinum-based therapies adverse effects (cisplatin, carboplatin and oxaliplatin) may be administered. These are not included in the model. Based on the results of exploratory analysis, the ERG notes that the impact of increasing the health state costs of progressed disease on the cost effectiveness results is small.

As described in section 5.2.4, patients receiving ASC alone may have received biliary drainage, antibiotics, analgesia, steroids and anti-emetics as well as palliative radiotherapy and blood

transfusions. The costs for these drugs and procedures are not explicitly included in the model, because the company expects these to apply to all treatment arms equally. The ERG asked the company to provide justification for this assumption during the clarification phase, and the company responded by referring to the advanced stage of the disease in the target population making it likely that ASC is expected to remain unchanged despite treatment. Furthermore, the company explained that no clinical opinion was available regarding this matter at the time of submission. Based on the results of exploratory analysis, the ERG notes that the impact of increasing the costs of ASC alone on the cost effectiveness results is small.

In the validation document, clinical opinion seemed to challenge some of the assumptions made by the company regarding the inclusion, definition, and associated costs of treatment-related AEs.[41] Clinical opinion indicated that the definition of a biliary event in the ABC-06 trial was questionable and it being odd that there was no abdominal pain or cholangitis in the active symptom control or mFOLFOX arms. It furthermore indicated that potentially costly, treatment-related AEs may be missing including nausea, ascites, thrombocytopenia, hypercalcemia, bone pain, diarrhoea, cardiac toxicity and neuropathy. Also, it indicated that the assumed cost of a biliary event and cholangitis are likely to be higher given that the patient is likely to be hospitalized for a week and will require radiology time plus antibiotics. The cost of thromboembolic events was deemed as low by clinical opinion given that patients would require subcutaneous anticoagulants. AE costs that are higher than indicated by clinical opinion include those for stomatitis, neutropenia and palmar-plantar erythrodysaesthesia syndrome. Since the validation document was only made available to the ERG in response to the ERG's request to do so during the clarification phase, the ERG did not have opportunity to ask the company to provide additional information and justification of the assumptions that were challenged by clinicians in this document. Based on the results of exploratory analysis, the ERG notes that the impact of increasing total AE costs on the cost effectiveness results is small.

The ERG did not agree with the exclusion of genetic testing costs in the base-case, and therefore have included these costs for the pemigatinib arm in the ERG preferred base-case. The ERG also explored a scenario in which the genetic testing costs are excluded from the analysis. In addition, the ERG prefers to include wastage costs for pemigatinib for the ERG preferred base-case, in combination with the observed RDI.

6. Cost effectiveness results

6.1 Company's cost effectiveness results

The company base-case fully incremental deterministic results, shown in Table 6.1, indicate that mFOLFOX+ASC is extendedly dominated by pemigatinib due to its higher incremental cost effectiveness ratio (ICER) and lower effectiveness. Pemigatinib is more costly and more effective than ASC, with incremental costs of £[redacted] and [redacted] QALYs gained resulting in an ICER of £61,084 per QALY gained. The results from the pairwise comparison between pemigatinib and mFOLFOX+ASC, shown in Table 6.2, indicate that pemigatinib is more costly and more effective than mFOLFOX+ASC, with incremental costs of £[redacted] and [redacted] QALYs gained resulting in an incremental cost effectiveness ratio (ICER) of £57,315 per QALY gained. These results are based on the PAS price of pemigatinib, that includes a [redacted] discount on the list price of £511.36.

Table 6.1: Company base-case fully incremental deterministic results (PAS price, discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ASC	[redacted]	0.51	[redacted]				
mFOLFOX+ASC	[redacted]	0.60	[redacted]	[redacted]	0.09	[redacted]	298,132 / Extendedly dominated
Pemigatinib	[redacted]	2.34	[redacted]	[redacted]	1.82	[redacted]	61,084

Source: Table 55 in the CS.[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).

Table 6.2: Company base-case pairwise deterministic results (PAS price, discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
mFOLFOX+ASC	[redacted]	0.60	[redacted]				
Pemigatinib	[redacted]	2.34	[redacted]	[redacted]	1.73	[redacted]	57,315

Source: Table 56 in the CS.[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).

6.2 Company's sensitivity analyses

6.2.1 Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) that involved simultaneously drawing random samples from the assigned probability distribution for each model parameter. The probability distributions were based on the 95% confidence intervals surrounding the parameter's mean estimates, and a standard error (SE) representing 10% of the mean estimate was assumed when no measure of uncertainty was reported. The probabilistic results, shown as incremental results in Table 6.3 and as a pairwise comparison of pemigatinib versus mFOLFOX+ASC in Table 6.4, represent the

mean results for a set of 1,000 iterations. The PSA results are well in agreement with the deterministic results, with ICERs slightly lower than the deterministic results.

Figures 6.1 and 6.2 show the 1,000 pairs of incremental costs and incremental QALYs from the PSA for the comparison of pemigatinib versus ASC and the comparison of pemigatinib versus mFOLFOX+ASC, respectively. The cost effectiveness acceptability curve (CEAC) is shown in Figure 6.3, which indicates that the probability of cost effectiveness for pemigatinib is [redacted] at a threshold of £50,000.

Table 6.3: Company base-case fully incremental probabilistic results (PAS price, discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ASC	[redacted]	0.51	[redacted]				
mFOLFOX+ASC	[redacted]	0.60	[redacted]	[redacted]	0.09	[redacted]	284,012 / Extendedly dominated
Pemigatinib	[redacted]	2.38	[redacted]	[redacted]	1.86	[redacted]	58,856

Source: Table 57 in the CS.[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).

Table 6.4: Company base-case pairwise probabilistic results (PAS price, discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
mFOLFOX+ASC	[redacted]	0.60	[redacted]				
Pemigatinib	[redacted]	2.38	[redacted]	[redacted]	1.77	[redacted]	55,161

Source: Table 58 in the CS.[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 6.1: Company base-case cost effectiveness plane: pemigatinib versus ASC

Source: The electronic model, updated from the response to the clarification letter.[1]
ASC = active symptom control; QALYs = quality adjusted life years.

Figure 6.2: Company base-case cost effectiveness plane: pemigatinib versus mFOLFOX+ASC

Source: The electronic model, updated from the response to the clarification letter.[1]

ASC = active symptom control; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; QALYs = quality adjusted life years.

Figure 6.3: Company base-case cost effectiveness acceptability curve

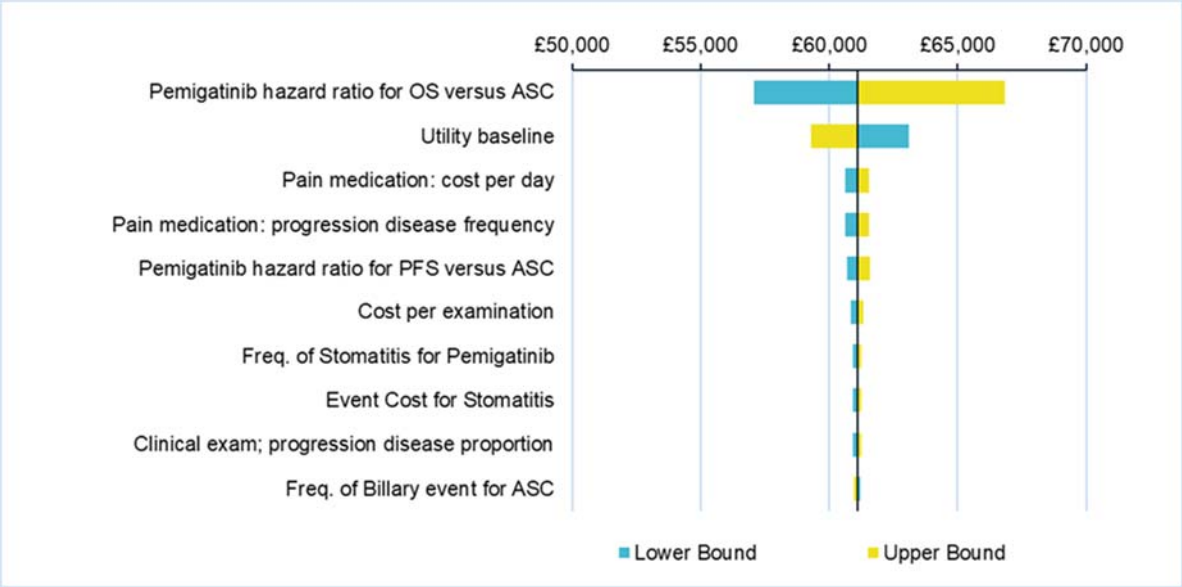
Source: The electronic model, updated from the response to the clarification letter.[1]
ASC = active symptom control; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; QALYs = quality adjusted life years.

6.2.2 Deterministic sensitivity analysis

The company performed a one-way sensitivity analysis (OWSA) to assess the impact of uncertainty surrounding the individual model input parameters. Each parameter was varied independently at both the upper and lower bounds of the 95% confidence interval that surrounds a parameter's mean estimate. Similar to the PSA, an SE that represents 10% of the mean estimate was assumed when a measure of uncertainty was not reported. The tornado plots, presented in Figures 6.4 and 6.5, show the deviations from the base-case ICER for the 10 parameters of which the impact of their uncertainty was the largest for the comparison of pemigatinib versus ASC and the comparison of pemigatinib versus mFOLFOX+ASC, respectively.

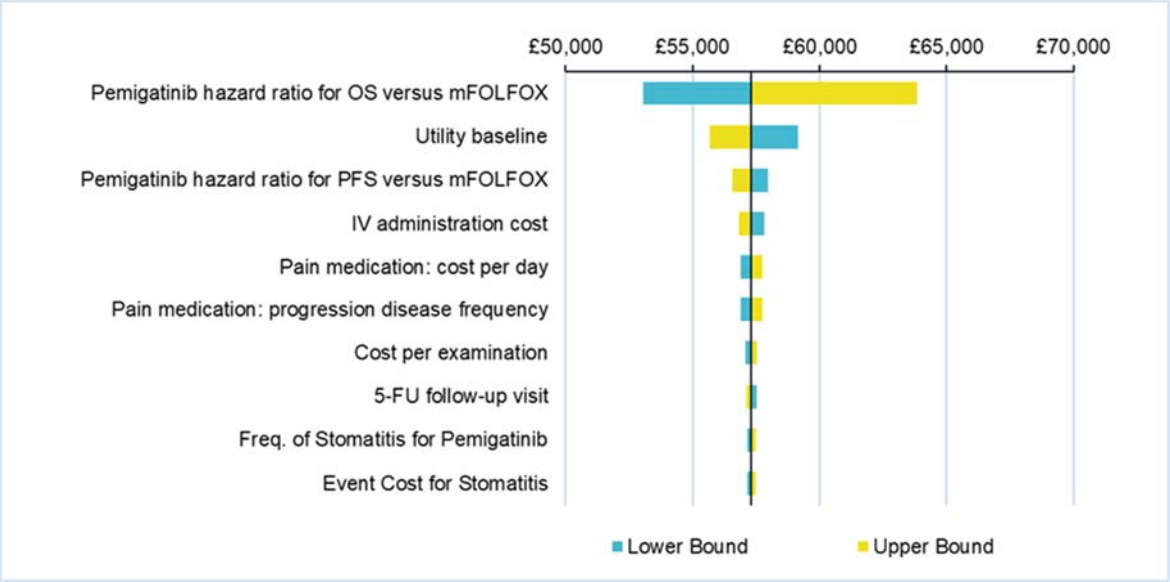
For both comparisons, pemigatinib versus ASC and pemigatinib versus mFOLFOX+ASC, the most influential parameter was the pemigatinib OS HR versus the comparator derived from the MAIC. The HR for PFS also had a noticeable but less substantial impact. These parameters reflect the key area of uncertainty in the economic model: the relative treatment effect using the single-arm FIGHT-202 study and the MAIC analysis informed by the ABC-06 trial. Utility at baseline also had a considerable impact on the ICER as a higher baseline utility value was associated with a lower ICER for pemigatinib due to a greater QALY gain. Differences between the tornado diagrams for both comparisons are related to differences in the inclusion of costly resource use items.

Figure 6.4: Tornado diagram: pemigatinib versus ASC (company's preferred assumptions)



Source: Figure 39 in the CS.[2]
ASC = active symptom control; OS = overall survival; PFS = progression-free survival.

Figure 6.5: Tornado diagram: pemigatinib versus mFOLFOX+ASC (company's preferred assumptions)



Source: Figure 40 in the CS.[2]
5-FU = fluorouracil; ASC = active symptom control; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; OS = overall survival; PFS = progression-free survival.

6.2.3 Scenario analyses

The company performed a series of scenario analyses to address uncertainty regarding the structural assumptions underlying the cost effectiveness model. The results of these analyses are shown in Table 6.5, alongside a description of the rationale for exploring each scenario.

Table 6.5: Company's scenario analyses results

Scenario		ICER of pemigatinib vs		Change from base-case pemigatinib vs		Rationale
		ASC (£)	mFOLFOX +ASC (£)	ASC (£)	mFOLFOX +ASC (£)	
1	Base case	61,084	57,315	0	0	
2	A longer time horizon of 50 years	61,065	57,297	-19	-18	Exploration of the impact of longer model duration
3	Costs and benefits are not discounted	54,709	51,401	-6,375	-5,914	Undiscounted results
4	A higher discounting rate of 6% is assumed	64,869	60,810	3,785	3,495	Explore impact of alternative higher discount rate
5	Exclude adverse event utilities	60,891	57,125	-193	-190	Explore impact of AE disutilities
6	Use a utility model excluding treatment	59,598	57,495	-1,486	180	Explore model sensitivity to utility regression analyses used
7	Remove treatment admin disutilities	61,084	57,702	0	387	Explore impact of treatment administration disutility applied to mFOLFOX
8	Use literature values for progression-based utilities	57,172	55,223	-3,912	-2,092	Explore alternative source of health state utilities.
9	Assume FGFR2+ HR adjustment for comparators (all stages Cox model)	66,146	63,410	5,062	6,095	Explore structural assumptions relating to potential prognostic effect of FGFR2
10	Assume FGFR2+ HR adjustment for comparators (all stages Cox model) using prevalence from source (Jain et al)	65,261	62,305	4,177	4,990	Explore structural assumptions relating to potential prognostic effect of FGFR2, varying the prevalence of FGFR2 genetic alteration
11	Comparator efficacy informed by naïve HRs	63,230	60,131	2,146	2,816	Test estimates of treatment effect unadjusted for prognostic effect
12	Comparator efficacy informed by MAIC HRs, using a Weibull extrapolation for pemigatinib OS	[redacted]	[redacted]	[redacted]	[redacted]	Explore impact on results of using MAIC HRs with alternative more pessimistic extrapolation of pemigatinib OS (Weibull)

Scenario		ICER of pemigatinib vs		Change from base-case pemigatinib vs		Rationale
		ASC (£)	mFOLFOX +ASC (£)	ASC (£)	mFOLFOX +ASC (£)	
13	Comparator efficacy informed by independent PSMs fitted to unadjusted KM	63,100	63,297	2,016	5,982	Explore impact on results of using independent curve fits to unadjusted comparator survival data
14	Survival informed by independent curve fits. Pemigatinib PSMs fitted to KM function adjusted to ASC population (ABC-06)	64,004	64,291	2,920	6,976	Same as Scenario 12, but using pemigatinib survival adjusted to match ASC arm of ABC-06 study
15	Survival informed by independent curve fits. Pemigatinib PSMs fitted to KM function adjusted to mFOLFOX+ASC population (ABC-06)	62,456	62,591	1,372	5,276	Same as Scenario 12, but using pemigatinib survival adjusted to match mFOLFOX arm of ABC-06 study
16	Extrapolate PFS for all treatments using Weibull (unadjusted KM)	55,385	54,852	-5,699	-2,463	Test alternative parameterisations of the PFS curves
17	Extrapolate OS for all treatments using Weibull (unadjusted KM)	100,395	97,124	39,311	39,809	Test alternative parameterisations of the OS curve
18	Extrapolate ToT for pemigatinib using log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	Test alternative parameterisations of the pemigatinib ToT curve
19	Include FGFR2+ testing costs only for pemigatinib	66,416	62,731	5,332	5,417	Explore impact of including FGFR testing costs only for patients treated with pemigatinib

Source: Table 61 in the CS.[2]
AE = adverse event; ASC = active symptom control; CS = company submission; FGFR2+ = fibroblast growth factor receptor 2-positive; HR = hazard ratio; ICER = incremental cost effectiveness ratio; KM = Kaplan-Meier; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; PSM = parametric survival model; ToT = time on treatment.

The scenarios with the greatest influence on the results related to the choice of methods used to model survival outcomes (i.e. OS and PFS) for both intervention and comparators. In the base-case, MAIC adjusted HRs were applied to PSMs fitted to unadjusted pemigatinib survival. Scenario 17 used independent curves fitted to both intervention and comparator OS, using a Weibull distribution in all cases. This increased the ICER by more than £39,000 for both comparisons. A similar result was seen in Scenario 12 when continuing to use the MAIC HRs for comparator efficacy while switching to the Weibull extrapolation for pemigatinib OS (an increase of [redacted] for the comparison with ASC, and £[redacted] for the comparison with mFOLFOX+ASC), although the company noted that this extrapolation was considered to be implausible by clinical experts. Including an adjustment for the potential prognostic effect of FGFR2 increased the ICER by £5,062 for the comparison with ASC, and by £6,095 for the comparison with mFOLFOX+ASC. The magnitude of the impact on the ICER for FGFR2 was dependent on the FGFR2 prevalence estimate used, as shown in Scenarios 9 and 10. Using Weibull independent curve fits for PFS in isolation (i.e. Scenario 16) reduced the ICER noticeably, as did using the utility values from published literature (i.e. Scenario 8).

6.3 Model validation and face validity check

The company consulted two practising UK clinicians and two health economic experts to externally validate the model in terms of model structure, current clinical practice, survival extrapolations for pemigatinib, relative treatment effect assumptions, the impact of FGFR2 fusions or rearrangements, monitoring and resource use, safety assumptions and HRQoL inputs.[41]

Both health economists validated the model structure, with one expressing concern that, in comparison to a three-health state model, the choice for five health states means that the model is populated with limited data. Both clinicians also validated the model as being representative of the natural history of the disease and it not missing important clinical outcomes.

Both clinicians confirmed that mFOLFOX can be regarded as current standard clinical practice for previously treated patients with CCA, although one noted that CAPOX may be preferred by some clinicians for some patients who are not suitable for a chemotherapy port (also see ERG comment in Section 5.2.4).Regarding the survival extrapolations for pemigatinib, both health economists noted that alternative distributions to the ones preferred by the company for OS and PFS based on best statistical fit also provided a good visual and/or statistical fit to the data. One health economist queried why the generalised gamma curve was not considered a good statistical fit, as the visual fit closely matched that of the Weibull curve. It was suggested that this was likely due to the fact that the generalised gamma curve has more parameters, and therefore is penalised regarding statistical fit. They furthermore noted the importance of clinical validation of survival extrapolations in addition to an assessment of statistical fit and that, given the different lines of previous treatment in this patient population, subgroup analyses may be appropriate to demonstrate the efficacy of pemigatinib in later lines of therapy. Both clinicians expected 5% of patients to be alive after five years. One clinician indicated the same estimate for patients on treatment and would see a survival of two to three years as significant, the other clinician expected that 10% of patients would be progression-free and on treatment after two years and estimated median survival for patients with general CCA around 11.7 months. Both clinicians confirmed that patients would not be treated beyond progression.

In light of the assessment of relative treatment effect, one health economist emphasised the importance of face validity of the analysis, support by other evidence, and understandable outcomes. The other health economist confirmed the advantage of using MAICs over naïve analyses in the base case by being able to adjust for confounders, but also emphasised the importance of considering the uncertainty in MAIC outcomes and change in patient characteristics before and after MAIC adjustment. It was

furthermore confirmed by the company that an indefinite treatment effect was modelled in their base case, which would later be a subject of clinical validation. Other points raised were the importance of including both the Cox proportional hazards method and individual extrapolations as options in the model to facilitate the testing of these assumptions, and a change in steepness of the OS curve from FIGHT-202 that was observed after adjustment for comparator trial characteristics.

The clinicians as well as health economists acknowledged the large uncertainty that surrounds the influence of FGFR2 fusions or rearrangements on patient survival. This pertains to it being uncertain whether the influence is caused by the genetic aberration versus a younger age and more female population, whether it is caused by associated differences in extra- versus intrahepatic CCA, unavailability of data on the prevalence of FGFR2 fusions or rearrangements in the comparator trial, and the difficulty in interpreting the limited data that is available on the influence of prior second-line systemic therapy on PFS in patients with FGFR2 fusions or rearrangements .

Both clinicians confirmed the assumptions made regarding health care resource use for monitoring, with one also noting that progressed patients may incur additional costs that are not included in the model (also see the ERG comment in Section 5.2.9).

Both clinicians indicated some concerns regarding the definition, inclusion and costing of some specific AEs (also see the ERG comment in Section 5.2.9).

Both health economists expressed concerns about the plausibility of the utility values produced by the company's preferred Utility Model 5, which resulted in a drop in utility score between on treatment (0.71) and off treatment (0.39). One of the clinicians was surprised by these results given that patients stopping treatment due to intolerance would usually experience better quality of life when coming off treatment. It was discussed whether this could be due to the possibility of the questionnaire being administered when patients were experiencing AEs that had led to treatment discontinuation. The other clinician confirmed that this was a reasonable hypothesis. One of the health economists suggested that this may not reflect true clinical outcomes and was not likely to be considered by a review committee and therefore it was important to include a switch in the model to assume no impact of being off treatment. Aside from the PFS off treatment issue, one clinician believed the utility scores were sensible and represented the average cholangiocarcinoma patient experience. One clinician agreed that the slight decrease in utilities seen between progression-free and progressed disease on treatment reflects the slight decrease in quality of life seen in clinical practice. Both clinicians expressed several concerns about AE disutility and duration assumptions.

As final comments in the validation document, one health economist indicated the overall approach as being a sensible one considering the limited availability of data and emphasised the importance of demonstrating that the available data has been explored fully. The other health economist acknowledged the technical soundness of the model and emphasised the importance of including genetic testing costs in the model, justifying why the absence of FGFR2 would not invalidate the MAIC analysis, clinical validation of survival extrapolation beyond trial data, and conducting appropriate sensitivity analyses.

The above summary of the results of the validation efforts that were done by the company were not described in the CS,[2] and therefore provided by the ERG based on the validation document that the ERG requested to be made available during the clarification phase.

Internal validation

In the CS,[2] the company provided internal validation of their base case survival extrapolations by comparing them against reported medians from the trial publications. These are shown in Tables 6.6

and 6.7. The company notes an underestimation of OS in pemigatinib in the model, that is explained as being due to the plateau in the KM function between 16.53 and 21.06 months, with reference to the modelled survival being a longer-term view that is based on the most clinically plausible extrapolations.

Table 6.6: Validation of OS modelling

Treatment	Median (months)		
	Literature	Source	Model
Pemigatinib	21.06	FIGHT-202[25]	17.94
mFOLFOX+ASC	6.2	ABC-06[23]	5.98
ASC	5.3		5.06

Source: Table 62 in the CS.[2]
ASC = active symptom control; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; OS, = overall survival.

Table 6.7: Validation of PFS modelling

Treatment	Median (months)		
	Literature	Source	Model
Pemigatinib	6.93	FIGHT-202[25]	6.90
mFOLFOX+ASC	4	ABC-06[23]	3.68
ASC	NR		3.68

Source: Table 63 in the CS.[2]
ASC = active symptom control; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; PFS, = progression-free survival.

Lastly, the cost effectiveness model underwent a quality check by its builders and was reviewed using a checklist of known modelling errors. An independent economist reviewed the model for coding errors, inconsistencies and input and assumption plausibility.

7. Evidence review group's additional analyses

7.1 Exploratory and sensitivity analyses undertaken by the ERG

7.1.1 Explanation of the company adjustments after the request for clarification

In response to the clarification letter, the company supplied an updated version of the model with the following changes:

- The company corrected the error in the calculation of the annual AE rate in the model, due to confusion between patient-months and patient-weeks.
- The company updated their calculation of AE rates in the model by using the area under the KM curves to capture the observed AE rates rather than the area under the extrapolated curves.
- The company incorporated age-adjustment of utilities into the model.

7.1.2 Explanation of the ERG adjustments

The changes made by the ERG (to the model received with the response to the clarification letter) were subdivided into the following three categories (according to Kaltenthaler et al. 2016)[101]:

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong).
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice has not been adhered to).
- Matters of judgement (amending the model where the ERG considered that reasonable alternative assumptions are preferred).

After these changes were implemented in the company's model, additional scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the cost effectiveness results.

7.1.2.1 Fixing errors

After clarification no further errors were identified.

7.1.2.2 Fixing violations

After clarification no further violations were identified.

7.1.2.3 Matters of judgement

The ERG made the following changes to the company model as the ERG considered that reasonable alternative assumptions are preferred:

- Extrapolation of pemigatinib OS using the generalised gamma curve instead of the company's preferred log-logistic curve.
- Extrapolation of pemigatinib ToT using the Weibull curve instead of the company's preferred exponential curve.
- Use of the HRQoL utility estimates from Model 3, which does not include treatment status, instead of the company's preferred Model 5 in which treatment status is included.
- Application of pemigatinib drug costs per the designated three-week prescription and account for wastage.
- Apply the RDI for pemigatinib in drug wastage calculation
- Inclusion of costs of genetic testing in the base-case

The overview of the changes and the bookmarks for the justification of the ERG changes are presented in Table 7.1.

Table 7.1: Company and ERG base-case preferred assumptions

Base-case preferred assumptions	Company	ERG	Justification for change
Extrapolation of pemigatinib OS	Log-logistic	Generalised gamma	Section 5.2.6.1
Extrapolation of pemigatinib ToT	Exponential	Weibull	Section 5.2.6.4
Utility estimates	From Model 5, including progression and treatment status	From Model 3, including progression status but without treatment status	Section 5.2.8
Application of pemigatinib drug costs	Per week	Per the designated 3-week prescription to account for potential wastage	Section 5.2.9
Inclusion of costs of genetic testing	Costs of genetic testing not included	Costs of genetic testing included	Section 5.2.9

Abbreviations: ERG = evidence review group; OS = overall survival; ToT = time on treatment.

7.1.3 Additional scenarios conducted by the ERG

The ERG conducted a series of scenario analyses to explore the impact of key assumptions and uncertainties within the cost effectiveness analyses. These uncertainties were related to the extrapolation of treatment effectiveness outcomes for pemigatinib, the methods of estimating relative treatment effectiveness, the methods used and source of values used in the estimation of health state utility values,

7.1.3.1 Scenario set 1: Extrapolation of pemigatinib efficacy outcomes

In this set of scenarios, the parametric survival model that was used to extrapolate OS, PFS and ToT for patients in the pemigatinib arm of Cohort A of FIGHT-202 were varied. For OS, the company used a log-logistic as it had good statistical fit, was among the curves which better aligned with clinical validity estimates and did not cause OS and PFS to cross. However, the generalised gamma was closest aligned with the clinical validation estimate and was used in the ERG base-case. Weibull and Gompertz were the next closest aligned with clinical validation and therefore these curves were also explored in scenarios.

For PFS, the log-normal was used in both the company and ERG base-case but two other well performing curves, the exponential and lognormal were tested in scenarios. For ToT, the company preferred to use the exponential curve, however the Weibull (used in the ERG base-case), the generalised gamma and the Gompertz all provided extrapolations which were equivalently or better aligned with the clinical validation estimate. Therefore, all these curves were tested in scenarios.

7.1.3.2 Scenario set 2: Estimation of relative treatment effect

The CS provided several methods through which the relative treatment effect could be estimated. In the base-case, unanchored MAICs were used to adjust for observed prognostic factors. The model also included the possibility to estimate unadjusted naïve relative treatment effect using Cox proportional hazards models as well as an option to simply extrapolate the KM curves of the comparators independently of the extrapolations for pemigatinib. None of these options included an adjustment for FGFR2 prognostic effect, however an option was available in the model. This option was explored in combination with the MAIC estimation of relative treatment effect for OS in the last scenario.

7.1.3.3 Scenario set 3: HRQoL

The company preferred to use the HRQoL data from the trial to estimate separate utility values according to treatment and progression status. However due to issues in the plausibility of the results, the ERG preferred to estimate utilities according to progression status only. Both models were tested in scenarios as well as using the alternative utility values obtained from the literature.

7.1.3.4 Scenario set 4: Genetic testing costs excluded

In line with the decision problem as defined in the final scope by NICE, the ERG preferred their base-case to include the costs of genetic testing for the pemigatinib arm. In addition, the ERG performed a scenario analysis that excludes these costs.

7.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

7.2.1 Results of the ERG preferred base-case scenario

The deterministic results of the ERG base-case are shown in Table 7.2. They show that mFOLFOX+ASC compared to ASC provides a small additional QALY of [redacted] at an incremental cost of [redacted], resulting in an ICER of £97,523. However, when pemigatinib is considered in a fully incremental analysis, mFOLFOX+ASC is extendedly dominated as the ICER for pemigatinib versus ASC is slightly lower at £91,883, thus rendering the comparison of pemigatinib to mFOLFOX+ASC irrelevant. However, for completeness sake, the ICER of pemigatinib versus mFOLFOX+ASC can be estimated to be £91,508.

Table 7.2: ERG base-case deterministic results (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£) versus ASC	Incr. LYGs versus ASC	Incr. QALYs versus ASC	ICER versus ASC (£/QALY)	Full incr. ICER (£/QALY)	ICER versus mFOLFOX +ASC (£/QALY)
ASC	[redacted]	0.51	[redacted]						
mFOLFOX + ASC	[redacted]	0.60	[redacted]	[redacted]	0.09	[redacted]	£97,523	Extendedly dominated	
Pemigatinib	[redacted]	1.73	[redacted]	[redacted]	1.22	[redacted]	£91,883	£91,883	£91,508

Based on the model provided with the clarification response.[1]
ASC = active symptom control; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, Incr. = incremental, LYGs = life years gained, mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; QALYs = quality-adjusted life years.

The PSA results in Table 7.3 are similar to the deterministic results, with the exception of the total QALYs gained on pemigatinib treatment, which are slightly higher in the probabilistic analysis, resulting in lower ICERs across all analyses. However, mFOLFOX+ASC is still extendedly dominated. This higher number of QALYs for pemigatinib is a result of the skewed uncertainty around the generalised gamma distribution for OS, leading to some PSA iterations where the OS curve has a heavy tail.

Figures 7.1 and 7.2 display the cost effectiveness planes for pemigatinib versus ASC and versus mFOLFOX+ASC respectively. In both comparisons, all simulations fall in the north-east quadrant, with the majority falling above the £50,000 per QALY gained threshold line. Figure 7.3 shows the CEACs for all three treatments. At a threshold of £50,000 pemigatinib, ASC and mFOLFOX+ASC have approximately a [redacted] [redacted] and [redacted] chance of being considered cost effective, respectively.

Table 7.3: ERG base-case probabilistic results (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£) versus ASC	Incr. LYGs versus ASC	Incr. QALYs versus ASC	ICER versus ASC (£/QALY)	Full incr. ICER (£/QALY)	ICER versus mFOLFOX +ASC (£/QALY)
ASC	[redacted]	0.51	[redacted]						
mFOLFOX + ASC	[redacted]	0.61	[redacted]	[redacted]	0.09	[redacted]	£89,282	Extendedly dominated	
Pemigatinib	[redacted]	2.04	[redacted]	[redacted]	1.53	[redacted]	£73,976	£73,976	£73,096

Based on the model provided with the clarification response.[1]
ASC = active symptom control; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, Incr. = incremental, LYGs = life years gained, mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; QALYs = quality-adjusted life years.

Figure 7.1: ERG preferred cost effectiveness plane pemigatinib vs. ASC

Based on the model provided with the clarification response.[1]
ASC = active symptom control; ERG = evidence review group; QALYs = quality adjusted life years.

Figure 7.2: ERG preferred cost effectiveness plane pemigatinib vs. mFOLFOX+ASC

Based on the model provided with the clarification response.[1]
ASC = active symptom control; ERG = evidence review group; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; QALYs = quality adjusted life years.

Figure 7.3: ERG preferred cost effectiveness acceptability curve

Based on the model provided with the clarification response.[1]
ASC = active symptom control; ERG = evidence review group; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil.

7.2.2 Results of the ERG additional exploratory scenario analyses

7.2.2.1 Scenario set 1: Extrapolation of pemigatinib efficacy outcomes

As can be seen from Table 7.4, the extrapolation scenario which had the largest impact on results was using the log-logistic curve to extrapolate OS, as in the company base-case, which reduced the ICER from £91,508 to £62,347 for the comparison of pemigatinib to ASC and had a similar impact on the pemigatinib mFOLFOX+ASC comparison. Using the alternative PFS curves had a minimal impact on the ICER while the use of alternative ToT curves had up to a £7,000 impact on the ICER.

Table 7.4: Extrapolation of pemigatinib efficacy outcomes scenarios

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 (£)
OS extrapolation												
Log-logistic (Company)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	62,347	[redacted]	[redacted]	63,800
Generalised Gamma (ERG)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	91,508	[redacted]	[redacted]	91,883
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	97,684	[redacted]	[redacted]	97,644
PFS extrapolation												
Log-normal (BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	91,508	[redacted]	[redacted]	91,883
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	92,923	[redacted]	[redacted]	92,407
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	91,685	[redacted]	[redacted]	92,218
ToT extrapolation												
Weibull (ERG)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	91,508	[redacted]	[redacted]	91,883
Exponential (Company)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	94,738	[redacted]	[redacted]	94,912
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	92,531	[redacted]	[redacted]	92,843
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	98,227	[redacted]	[redacted]	98,183

Based on the model provided with the clarification response.[1]
ASC = active symptom control; BC = base-case (both ERG and company) ERG = evidence review group; ICER = incremental cost effectiveness ratio; Incr. = incremental; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; OS = overall survival; PFS = progression free survival; QALY = quality-adjusted life year; ToT = time on treatment.

7.2.2.2 Scenario set 2: Estimation of relative treatment effect

Use of the naïve HRs or independently extrapolated curves instead of the MAIC adjusted HRs increased the ICER comparing pemigatinib to ASC by approximately £4,500 and £6,000 respectively, with somewhat larger differences observed in the comparison between pemigatinib and mFOLFOX, as shown in Table 7.5. Adjusting for FGFR2 status for OS using the MAIC analysis increased the ICER by approximately £11,500 in the pemigatinib ASC comparison and £15,000 in the pemigatinib mFOLFOX comparison. Therefore, the MAIC analysis, not including the adjustment for FGFR2 status, provided the most optimistic estimate of relative treatment effect and cost effectiveness.

Table 7.5: Estimation of relative treatment effect scenarios

Treatment effect	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 (£)
MAIC adjusted HRs (BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	91,508	[redacted]	[redacted]	91,883
Naïve HRs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	99,366	[redacted]	[redacted]	96,613
Extrapolated curves	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	101,976	[redacted]	[redacted]	98,298
MAIC with FGFR2 adjustment (all stages Cox model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	106,814	[redacted]	[redacted]	103,632

Based on the model provided with the clarification response.[1]

ASC = active symptom control; BC = base-case, FGFR2 = Fibroblast growth factor receptor 2; HR = hazard ratio; ICER = incremental cost effectiveness ratio; Incr. = incremental, MAIC = matched-adjusted indirect comparison; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; QALY = quality-adjusted life year.

7.2.2.3 Scenario set 3: HRQoL

Table 7.6 shows that use of the ERG preferred utility values, estimated according to progression status without treatment status, reduced the ICER by approximately £3,500 in the comparison with ASC alone and increased the ICER by approximately £380 in the comparison with mFOLFOX+ASC.

Table 7.6: HRQoL scenarios

HRQoL	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 (£)
Model no treatment status [redacted] (ERG)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	91,508	[redacted]	[redacted]	91,883
Model with treatment status [redacted] (Company)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	91,120	[redacted]	[redacted]	95,334
Literature values TA474[83] [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	89,012	[redacted]	[redacted]	89,143
Based on the model provided with the clarification response.[1]												

ASC = active symptom control; BC = base-case, ERG = evidence review group; ICER = incremental cost effectiveness ratio; Incr. = incremental, mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; PD = progressed disease; PF = progression free; PFnoTx = progression free no treatment; PFonTx = progression free on treatment; QALY = quality-adjusted life year.

7.2.2.4 Scenario set 4: Genetic testing costs excluded

As shown in Table 7.7, after excluding the genetic testing costs, the ICER is reduced by £7,780 in the comparison with ASC alone and by £8,297 in the comparison with mFOLFOX+ASC.

Table 7.7: Scenario with genetic testing costs excluded

HRQoL	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 (£)
Including genetic testing costs (ERG)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	91,508	[redacted]	[redacted]	91,883
No genetic testing costs included (company)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	83,211	[redacted]	[redacted]	84,103

Based on the model provided with the clarification response.[1]

ASC = active symptom control; ERG = evidence review group; ICER = incremental cost effectiveness ratio; Incr. = incremental, mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; QALY = quality-adjusted life year.

7.3 ERG's preferred assumptions

Table 7.8 below displays the step-by-step changes which the ERG made to the company base-case alongside the cumulative impact of each change added to the previous changes on results. The change which had the largest impact on results was extrapolating the OS of pemigatinib using the generalised gamma curve instead of the log-logistic, which added approximately £16,500 to the ICER comparing pemigatinib to ASC and approximately £26,000 to the ICER comparing pemigatinib to mFOLFOX+ ASC. The change which had the next largest impact was including the cost of genetic testing for pemigatinib which added approximately £8,000 to each ICER. The rest of the changes affected the ICER by less than £5,000 each.

Table 7.8: ERG's preferred model assumptions

Preferred assumption	Section in ERG report	Pemigatinib		mFOLFOX+ASC		ASC		Cumulative ICER pemigatinib vs mFOLFOX+ASC	Cumulative ICER pemigatinib vs ASC
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs		
Company original base-case	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	57,315	61,084
Company post-clarification base-case	7.1.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	57,467	60,806
Extrapolation of OS using generalised gamma	5.2.6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	83,073	87,417
Extrapolation of ToT using Weibull	5.2.6.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	80,943	85,391
HRQoL utility values from Model 3 (HSUVs independent of treatment status)	5.2.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	81,288	82,300
Application of pemigatinib drug costs per 3-week subscription	5.2.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	85,253	86,019
Application of the RDI for pemigatinib in drug wastage calculation	5.2.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	83,211	84,103
Inclusion of costs of genetic testing for pemigatinib	5.2.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	91,508	91,883

Based on the model provided with the clarification response.[1]

ASC = active symptom control; ERG = evidence review group; HRQoL = health related quality of life; HSUV = health state utility values; ICER = incremental cost effectiveness ratio; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; OS= overall survival ; ToT = time on treatment; RDI = relative dose intensity; QALY = quality-adjusted life year

7.4 Conclusions of the cost effectiveness section

The main issue in the cost effectiveness analysis is the uncertainties in the estimates of relative treatment effectiveness. These uncertainties stem from the mismatches in patient population and the weakness of MAIC analyses. The population in the ABC-06 study, from which comparator efficacy is estimated, does not match the scope population as this study was not restricted to patients with FGFR2 mutations nor to patients with iCCA. The proportion of patients in ABC-06 with FGFR2 fusions or rearrangements was not report, but estimated to be low based on the FIHGT-202 study which identified 8.6% of UK patients to have FGFR2+ fusions or rearrangements at screening. Additionally, only 47% of patients in ABC-06 were iCCA, while the vast majority of patients with FGFR2 fusions or rearrangements are iCCA (98% in Cohort A of FIGHT-202)

The estimate of relative treatment effect in the model was based on an unanchored MAIC analysis between these two mismatched trials. The prognostic factors included in the MAIC were [redacted]

However, FGFR2+ status could not be included, and neither were type of BTC or site of tumour, both of which would have adjusted for important difference in patient population across the studies. Therefore, it is unclear if any difference in survival observed between the two studies can be attributed to the effect of the treatment with pemigatinib. Thus, the ERG would argue that the estimate of treatment effect in the model is highly uncertain and likely to be biased.

Additionally, the HRs estimated from the MAIC were applied over the entire extrapolation to estimate relative treatment efficacy. This implies lifetime relative efficacy for pemigatinib without any waning. There is no evidence available for the efficacy of pemigatinib beyond approximately 20 months.

Other issues were also identified within the cost effectiveness analyses which are still important to note, although secondary to the key issues of the extent to which the analyses conducted are able to reflect the relative efficacy in that population.

Treatment with pemigatinib was compared to active symptom control and mFOLFOX with active symptom control. The ERG feel that it is likely that other treatments are also given in clinical practice, especially given that other comparators were used in other trials identified by the company. However, given the uncertainty in the guidelines and in the absence of real-world prescribing data in this population it is difficult for the ERG to ascertain whether the important comparators have been included or whether commonly prescribed comparators have been missed. However, the ERG would like to emphasise that given the weaknesses in the estimates of relative treatment effectiveness which drive model results, the addition of more comparators (unless a key comparator has been missed) would not resolve the inherent uncertainties within the cost effectiveness analyses.

In the selection of the parametric curve for OS for pemigatinib the company state that clinical validity was given priority in the selection given the immaturity of data. Two clinicians suggested that they may expect to observe 5% of patients alive at five years.[41] The curve which provides the closest estimate is the generalised gamma, which estimates 3% survival at five years. However, this curve was not considered by the company, as they had already seemingly narrowed down their choice to the three best performing curves in terms of statistical fit. However, the difference in fit between the log-logistic selected by the company and the generalised gamma was small. Given the immaturity of the data, the similarity of the fit statistics across the models and the similar performance in terms of visual fit, the ERG would agree that clinical plausibility should have priority. Therefore, the ERG would argue that

the generalised gamma should be considered in the base-case for the extrapolation of OS for pemigatinib.

Similarly, in the extrapolation of ToT, clinical validation stated [redacted]. In their base-case the company chose the exponential curve. However, the Weibull better aligned with the estimate of clinical validity and the ERG would argue that this should be used in the base-case.

There was no attempt by the company to conduct a MAIC analysis for AEs. Therefore, the rates of AEs across the studies and their relevant populations remain unadjusted. However, the ICERs are quite insensitive to the costs and disutilities associated with AE, so it is unlikely that including adjusted rates of AEs rather than unadjusted would have a noticeable impact on the ICERs.

HRQoL was not measured using EQ-5D in FIGHT-202 and had to be mapped from EORTC-QLQ-C30 data to EQ-5D-3L utilities using a published mapping algorithm. The company's preferred regression equation included coefficients for treatment status and progression as well as the interaction between treatment and progression status. This analysis resulted in an implausible value for the progression-free off-treatment state, which had a substantially lower utility than either of the progressed disease utility values. These strange results were likely due to the fact that certain states were left with very few observations for estimation. Given that the inclusion of treatment status in addition to progression resulted in an implausible result for progression free on treatment and that the on-treatment state for progressed disease is not used, the ERG prefers to use a utility value estimation model without treatment status in the base-case.

Regarding health care resource use and costs, the only differences between the company base-case model and the one based on the ERG's preferred assumptions were that the latter included wastage costs for pemigatinib as well as the costs for genetic testing in the pemigatinib arm. The wastage costs were included for completeness, the genetic testing costs were included to be in line with the decision problem as formulated in the final scope by NICE.

The company base-case incremental deterministic results indicate that pemigatinib is more costly and more effective than ASC, with incremental costs of £[redacted] and an incremental QALY of [redacted] resulting in an ICER of £61,084 per QALY gained. The results from the pairwise comparison between pemigatinib and mFOLFOX+ASC indicate that pemigatinib is also more costly and more effective than mFOLFOX+ASC, with incremental costs of £[redacted] and an incremental QALY of [redacted] resulting in an ICER of £57,315 per QALY gained. The fully incremental results indicate that mFOLFOX+ASC is extendedly dominated by pemigatinib due to its higher ICER and lower effectiveness. The CEAC indicates that the probability of cost-effectiveness for pemigatinib is [redacted] at a threshold of £50,000.

In the ERG base-case, when pemigatinib is considered in a fully incremental analysis, mFOLFOX+ASC is again extendedly dominated. The ICER for pemigatinib versus ASC is £91,883 per QALY gained and the ICER of pemigatinib versus mFOLFOX+ASC is £91,508.

The PSA results were similar to the deterministic results, with the exception of the total QALYs gained on pemigatinib treatment, which are slightly higher in the probabilistic analysis, resulting in lower ICERs across all analyses i.e. the probabilistic ICER for pemigatinib versus ASC is £73,976 per QALY gained and the probabilistic ICER of pemigatinib versus mFOLFOX+ASC is £73,096. However, mFOLFOX+ASC is still extendedly dominated.

In both comparisons, all simulations fall in the north-east quadrant, with the majority falling above the £50,000 per QALY gained threshold line. At a threshold of £50,000 pemigatinib, ASC and mFOLFOX+ASC have approximately a [redacted], [redacted] and [redacted] chance of being considered cost effective, respectively.

The ERG scenario which had the largest impact on results was modelling OS on pemigatinib using the log-logistic curve, as in the company base-case, which reduced the ICER by approximately £28,000 in each comparison. The next most influential scenario was including an adjustment for FGFR2 status in the MAIC analysis, which increased the ICER by approximately £15,000 compared to mFOLFOX+ASC and approximately £11,500 compared to ASC.

Nevertheless, given the problems with the estimation of the effect of treatment with pemigatinib based on only a single-arm study, all ICERs mentioned are potentially biased, reflecting a level of uncertainty much larger than that indicated by all sensitivity and scenario analyses. Unfortunately, given the data available, these uncertainties cannot be resolved.

8. End of life

The CS, section B.2.13.3,[2] states that pemigatinib meets the NICE end-of-life criteria and provides a summary table of supporting evidence (Table 8.1).

Table 8.1. End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• The median OS for patients treated with systemic chemotherapy (mFOLFOX+ASC) was 6.2 months[23]
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• Median OS differences between pemigatinib and the source used for OS exceeds 3 months (21.1 months[53] vs 6.2 months; unadjusted)[23] • Results of a MAIC analysis presented in Section B.2.9 of the CS[2] and in section 4.3 of this report*

Source: Table CS[2]
MAIC = matching-adjusted indirect comparison; NE = not estimated; NHS = National Health Service; OS = overall survival
*The results of additional MAICs, provided in response to clarification questions, are also included

ERG comment: The model results suggest that pemigatinib meets the end of life criteria as mean survival in the ERG base-case (life expectancy) is approximately 6.1 months for patients receiving ASC and approximately 7.2 months for those receiving mFOLFOX+ASC and the incremental life years are approximately 1.2 and 1.1 for these comparators respectively versus pemigatinib in the company base-case.

However the ERG considers that, given the high level of uncertainty about the results of the MAICs (see Section 4.4 of this report) and the uncertainty about the outcomes of people with advanced CCA with FGFR2 fusion or rearrangement treated with second-line systemic chemotherapy (none of the comparator studies used in the MAICs provided data specific to this population), it is not clear that pemigatinib meets the NICE end-of-life criteria. The ERG notes that OS data were not mature at the 22 March 2019 cut-off.

9. References

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

Addendum after new PAS 22 March 2021

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Introduction

This addendum contains the ERGs critique of the company's updated survival analyses and related base-case assumptions, provided in the company's response to technical engagement.[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. The results presented have been updated to reflect the new PAS of [redacted], submitted to NICE in March 2021.

1. Updated survival analyses for key issues 8 and 9

Key Issue 8 - The selection of the parametric curve for overall survival (OS) for pemigatinib.

The company provided updated survival analyses in patients receiving pemigatinib from a later data cut of the FIGHT-202 study ([redacted] versus March 2019 in the original submission).[1, 2] The updated extrapolations of OS for pemigatinib are shown in Figure 1.1, while updated statistical fit and clinical validity estimates are displayed in Table 1.1. The company continue to prefer the log-logistic curve for their base-case, reporting that it is supported by further clinical validation since it predicts a decline in the predicted hazard over time that is consistent with the published literature, shown in Figure 1.2.[1]

Figure 1.1: Pemigatinib OS KM data and fitted PSM models

Source: Figure 3 of the Company's Technical Engagement Response Appendix.[3]
KM = Kaplan Meier, OS = overall survival; PSM = parametric survival model.

Table 1.1: Pemigatinib OS – AIC, BIC and five-year survival estimates

Model	AIC	BIC	5-year survival estimate
Exponential	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]

Source: Table 2 of the Company's Technical Engagement Response Appendix.[3]
AIC = Akaike information criterion; BIC = Bayesian information criterion; OS = overall survival.

Figure 1.2: Smoothed hazard plots for overall survival showing the empirical hazard vs. each parametric distribution

Source: Figure 4 of the Company's Technical Engagement Response Appendix.[3]

The company refer to two estimates of long-term clinical validity: the existing estimate of 10% survival at 5-years provided by clinical experts in the company submission and literature sources which report that approximately 70% of patients are diagnosed late with unresectable, locally advanced, or metastatic disease and that these patients have an estimated 5-year survival rate of ≤ 10% when receiving current SoC.[4-9] Given that all curves estimate a survival rate of below 10% at 5-years for patients receiving either comparator, this additional evidence does not help to narrow down the range of extrapolations to a plausible selection. Therefore, while the ERG acknowledge the company's argument that the uncertainty associated with these estimates is high as long term survival data for this rare condition are sparse, and long-term survival data specifically for patients receiving pemigatinib are not yet available, the estimate of 10% survival at 5-years for patients receiving pemigatinib remains the only long-term estimate of clinical validity.

In their technical engagement response, the company argue for the use of the loglogistic as it predicts a decline in the mortality hazard over time that is consistent with statements made during additional clinical validation that published evidence suggests that the probability of death conditional on survival until certain landmarks decreased over time.[10, 11] The ERG note from Figure 1.2 that the loglogistic, lognormal and generalised gamma all predict a decline in the mean predicted hazard over time and in fact the clinical validation report provided by the company shows that the clinician recognises that these three curves all represent this feature.[11] No further preference within these three curves was stated.

Given that the three curves which meet the clinical validation of the long-term decline in the hazard of mortality have very similar statistical fit, the ERG prefer to continue to use the generalised gamma curve which best fits the long-term validity estimate of 10% survival at 5-years. They acknowledge the uncertainty within this estimate and provide scenarios using the alternative OS extrapolation curves which also show a decline in long-term hazards.

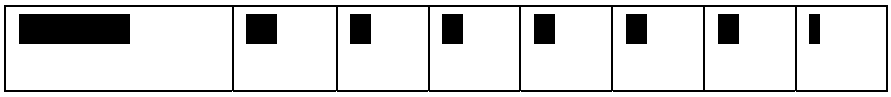
Key Issue 9 - The method used to extrapolate time on treatment (ToT).

In the original CS the exponential curve was selected to extrapolate ToT, whilst the ERG considered the Weibull curve a better choice.[12] Now, during technical engagement, the company also presented updated survival analyses for ToT from the updated data cut.[1] Extrapolations are shown in Figure 1.3, with statistical fit indices and clinical validation estimates shown in Table 1.2. The company reported that previous clinical expert opinion suggested that ToT should closely align with PFS, expecting approximately 10% remaining on treatment at 2 years.[4] This estimate is broadly consistent with the observed data in the updated FIGHT-202 data cut with [redacted] of patients remaining on treatment at [redacted]. In updated expert elicitation conducted for the technical engagement response, the clinician was unable to select between any of the curves due to their similarity.[11] Given that the Weibull curve still provides the closest alignment with the clinical validation estimate, as shown in Table 1.2 and the observed data in the updated data cut, the ERG still considers the Weibull curve the best option and welcome the decision of the company to select the Weibull for the base case as well.

Figure 1.3: Pemigatinib unadjusted ToT KM data and models

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



Source: Figure 6 of the Company's Technical Engagement Response Appendix.[3]
KM = Kaplan–Meier; ToT = time on treatment.

Table 1.2: Pemigatinib ToT – AIC, BIC and two-year survival estimates

Model	AIC	BIC	2-year ToT estimate
Exponential	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]

Source: Table 4 of the Company's Technical Engagement Response Appendix.[3]
AIC = Akaike information criterion; BIC = Bayesian information criterion; ToT = time on treatment.

2. Company's updated cost effectiveness results

2.1 Company's updated deterministic results

The company base-case results presented here are based on the same assumptions as those produced at Technical Engagement and differ only due to the updated PAS ([redacted]).

At technical engagement, the company provided updated cost effectiveness results using the updated survival analysis and matched-adjusted indirect comparison (MAIC) from the [redacted] data cut. Their base-case assumptions were the same as their base-case in the original company submission with the exception of:

- Correction of the method used to calculate adverse event (AE) rates and application of age-adjustment for health state utility values (HSUVs) (which were included in the company's post-clarification base-case)
- HSUVs were estimated using model 3 (excluding treatment status) instead of model 5 (including treatment status)
- Wastage costs were included, consistent with patients receiving a pack of 14 tablets every 3 weeks
- ToT was extrapolated using the ERG preferred Weibull curve

The updated survival analyses did not cause the company to change their preferred extrapolation curve 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 £51,952 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]	154,493 / Extendedly dominated
Pemigatinib	[redacted]	2.44	[redacted]	[redacted]	1.84	[redacted]	51,952

Based on the model provided with the company's Technical Engagement Response. [1]
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).

1.2 Company scenario and threshold analyses

The company scenario and threshold analyses are shown in Table 2.2 and 2.3 respectively. The company scenario which had the largest impact on results was extrapolating OS using the generalised gamma curve as in the ERG preferred base-case which increased the ICERs by approximately £9,000 in both comparisons.

Table 2.2: Results of the company's scenario analyses (PAS [redacted])

Scenario	ICER of pemigatinib vs		Change from base case pemigatinib vs	
	ASC (£/QALY)	mFOLFOX+ ASC (£/QALY)	ASC (£/QALY)	mFOLFOX+ ASC (£/QALY)
Updated company base case	51,952	49,186	0	0
Use generalised gamma to extrapolate FIGHT-202 OS	61,184	58,167	+9,232	+8,982
Comparative efficacy using a HR calculated using unadjusted ABC-06 data	52,860	51,183	+908	+1,997
Comparative efficacy using unadjusted ABC-06 data extrapolations	51,223	52,848	-729	+3,663
200% comparator AE frequency	51,603	48,707	-349	-479
0% comparator AE frequency	52,302	49,665	+349	+479

Based on the model provided with the company's Technical Engagement Response. [1]

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.

Table 2.3: Results of the company's threshold analyses (PAS [redacted])

Scenario	ICER		Incremental QALYs		Incremental LYs	
HR (WT versus FGFR2 rearrangement OS)	Pemigatinib Vs ASC	Pem. Vs mFOLFOX+ASC	Pemigatinib Vs ASC	Pem. Vs mFOLFOX+ASC	ASC	mFOLFOX +ASC
0.2	£43,545	£41,286	2.21	2.20	0.22	0.24
0.22	£43,795	£41,425	2.20	2.18	0.24	0.26
0.26	£44,281	£41,715	2.18	2.15	0.26	0.28
0.32	£44,982	£42,176	2.14	2.12	0.30	0.32
0.4	£45,879	£42,857	2.10	2.07	0.34	0.37
0.5	£46,953	£43,911	2.05	2.02	0.39	0.42
0.62	£48,182	£45,178	2.00	1.95	0.44	0.48
0.76	£49,575	£46,638	1.94	1.89	0.50	0.55
0.92	£51,156	£48,324	1.87	1.82	0.57	0.62
1.1	£52,958	£50,287	1.80	1.74	0.63	0.70
1.3	£55,024	£52,594	1.73	1.66	0.71	0.78
1.52	£57,408	£55,323	1.65	1.57	0.79	0.87
1.76	£60,177	£58,586	1.57	1.47	0.87	0.97
2.02	£63,422	£62,542	1.49	1.37	0.95	1.07
2.3	£67,261	£67,413	1.39	1.26	1.04	1.17
2.6	£71,859	£73,529	1.30	1.15	1.14	1.29
2.92	£77,442	£81,387	1.20	1.03	1.24	1.41
3.26	£84,332	£91,784	1.10	0.90	1.34	1.53
3.62	£93,001	£106,075	0.99	0.77	1.45	1.66
4	£104,177	£126,775	0.88	0.64	1.56	1.80

Based on the model provided with the company's Technical Engagement Response. [1]

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; WT = wild-type.

3. Exploratory and scenario analyses undertaken by the ERG

Assumptions in the ERG base-case are consistent with their Addendum submitted in response to Technical Engagement with the exception of the updated PAS. The ERG's base-case differs from the company's Technical Engagement base-case in the following two assumptions:

- Extrapolation of OS using the generalised gamma curve
- Inclusion of genetic testing costs for pemigatinib

The deterministic results of the ERG base-case are displayed in Table 3.1. In the ERG base-case, mFOLFOX+ASC is still extendedly dominated by pemigatinib. In the comparison between pemigatinib and ASC, the ERG base-case results in higher incremental costs and lower incremental QALYs than the company base-case, resulting in a higher ICER of £67,448 per QALY gained versus the company's ICER of £51,952 per QALY gained.

Table 3.1: ERG 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]	0.59	[redacted]				
mFOLFOX+ASC	[redacted]	0.66	[redacted]	[redacted]	0.06	[redacted]	153,707/ Extendedly dominated
Pemigatinib	[redacted]	2.12	[redacted]	[redacted]	1.52	[redacted]	67,448

Based on the model provided with the company's Technical Engagement Response. [1]
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 ERGs probabilistic sensitivity analysis (PSA) results in an ICER of £63,122 when comparing pemigatinib versus ASC, which is lower than the deterministic ICER of £67,448 per QALY gained (Table 3.2). The cost effectiveness plane in Figure 3.1 shows that the majority of simulations fall above the willingness to pay threshold line of £50,000 per QALY shown in the figure and would therefore not be considered cost effective at the higher end of life threshold. Even fewer simulations would be considered cost effective at the top end of the standard threshold range of £30,000 and none at the lower threshold of £20,000 per QALY gained. The cost effectiveness acceptability curve (CEAC) in Figure 3.2 shows that at thresholds of £20,000, £30,000 and £50,000 per QALY gained, pemigatinib would have a [redacted]%, [redacted]% and [redacted]% probability of being considered cost effective respectively, while at the same thresholds ASC would have a [redacted]%, [redacted]% and [redacted]% probability of being considered cost effective.

Table 3.2: ERG base-case probabilistic results (PAS [redacted], discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incr. costs	Incr. LYG	Incr. QALYs	ICER (£/QALY)
ASC	[redacted]	0.59	[redacted]				
mFOLFOX+ASC	[redacted]	0.65	[redacted]	[redacted]	0.06	[redacted]	147,786/ Extendedly dominated
Pemigatinib	[redacted]	2.22	[redacted]	[redacted]	1.63	[redacted]	63,122

Based on the model provided with the company's Technical Engagement Response. [1]
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 3.1: ERG base-case cost effectiveness plane (PAS [redacted])

Based on the model provided with the company's Technical Engagement Response. [1]
ERG = Evidence Review Group; QALY = quality-adjusted life year.

Figure 3.2: ERG base-case CEAC (PAS [redacted])

Based on the model provided with the company's Technical Engagement Response. [1]
ASC = active symptom control; CEAC = cost effectiveness acceptability curve; ERG = Evidence Review Group; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil.

3.1 Additional scenarios conducted by the ERG

The ERG conducted scenarios on the two remaining key issues which can be tested in the model: overall survival extrapolation (Table 3.3) and genetic testing costs (Table 3.4). The results show that the choice of OS curve has a substantial impact on the ICER, with the use of the ERGs preferred generalised gamma curve increasing the ICER by approximately £10,000 in the comparison between pemigatinib and ASC. The inclusion of genetic testing costs for pemigatinib also has a substantial, albeit smaller impact on results, increasing the ICER by approximately £6,000 in the pemigatinib ASC comparison.

2.1.1 Scenario set 1: Overall survival extrapolation

Table 3.3: Extrapolation of pemigatinib OS (PAS [redacted])

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 (£)
OS extrapolation												
Log-logistic (Company)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54,571	[redacted]	[redacted]	57,197
Generalised Gamma (ERG)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	64,635	[redacted]	[redacted]	67,448
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	53,730	[redacted]	[redacted]	56,321

Based on the model provided with the company's Technical Engagement Response. [1]

ASC = active symptom control; BC = base-case (both ERG and company) ERG = evidence review group; ICER = incremental cost effectiveness ratio; Incr. = incremental; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; OS = overall survival; PFS = progression free survival; QALY = quality-adjusted life year; ToT = time on treatment.

2.1.2 Scenario set 2: Genetic testing costs

Table 3.4: Genetic testing cost for pemigatinib scenarios (PAS [redacted])

Genetic testing costs	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 (£)
Genetic testing cost excluded (Company)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	58,167	[redacted]	[redacted]	61,184
Genetic testing costs included (ERG)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	64,635	[redacted]	[redacted]	67,448

Based on the model provided with the company's Technical Engagement Response. [1]

ASC = active symptom control; BC = base-case (both ERG and company) ERG = evidence review group; ICER = incremental cost effectiveness ratio; Incr. = incremental; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; OS = overall survival; PFS = progression free survival; QALY = quality-adjusted life year; ToT = time on treatment.

References

[1] Incyte Biosiences UK. *Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations [ID3740]: Technical engagement response*, 2020. 16p.

[2] Incyte Biosiences UK. *Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations [ID3740]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA)*, 2020

[3] Incyte Biosiences UK. *Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations [ID3740]: Technical engagement new company evidence appendix*, 2020. 21p.

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

Updated genetic testing cost scenario (New PAS, [redacted])

Authors: Hannah Penton, Pim Wetzelaer, Nigel Amstrong and Maiwenn Al

Date 22 March 2021

In their ERG report, the ERG had included the costs of genetic testing in their base case analysis, whereas the company did not include it in their base case but in a scenario analysis instead. The ERG had used the same estimates for the unit cost per NGS genetic test and prevalence of FGFR2 fusions as the company: £550 per NGS genetic test (which was based on a consultation by the company with several providers including NHS laboratories whilst taking into consideration factors specific to the processing of CCA samples; see page 120 of the CS) and a prevalence of 8.6% (based on Hollebecque et al., 2019). This resulted in a cost estimate of £6,395 per eligible (i.e. FGFR2 fusion-positive) patient.

In preparation for the PMB meeting, the ERG was asked to assess the impact on the cost-effectiveness results of alternative assumptions on the cost of genetic testing, as expressed in an email from NICE on 4th March 2021: "…that is £340 per eligible patient with FGFR2 based on 10% FGFR2 prevalence of the whole CCA population (i.e. £340 genetic testing cost per patient with FGFR2 mutation)." It was unclear to the ERG how the £340 was derived, including both the cost per test and how the figure for the prevalence was incorporated. The ERG requested clarification on the same day and so far none has been provided.

In addition, the ERG assessed the impact of using a recent estimate of the unit cost of NGS testing as provided by Schwarze et al., 2020 (which the ERG had identified in a technology appraisal they performed subsequent to the one for pemigatinib), indicating a NGS genetic testing unit cost of £6,841 per cancer case. Combining this estimate with a prevalence of 8.6% gives a cost estimate of £79,547 per eligible patient.

The cost-effectiveness results using this set of alternative estimates for the unit cost per NGS genetic test and prevalence of FGFR2 fusions are shown in Table 1 below.

Table 1. Scenarios: Alternative assumptions for the unit cost of NGS genetic testing and prevalence of FGFR2 fusions (PAS [redacted])

Genetic testing costs	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 (£)
Genetic testing cost excluded (Company)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	58,167	[redacted]	[redacted]	61,184
Genetic testing costs included (ERG)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	64,635	[redacted]	[redacted]	67,448
Genetic testing costs included (at £340 per eligible patient with FGFR2, based on 10% FGFR2 prevalence)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	58,511	[redacted]	[redacted]	61,517
Genetic testing costs included (at £79,547 per eligible patient with FGFR2, based on 8.6% FGFR2 prevalence)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	138,616	[redacted]	[redacted]	139,092

Based on the model provided with the company's Technical Engagement Response. [1]

ASC = active symptom control; BC = base-case (both ERG and company) ERG = evidence review group; ICER = incremental cost effectiveness ratio; Incr. = incremental; mFOLFOX = oxaliplatin, L-folinic acid and fluorouracil; OS = overall survival; PFS = progression free survival; QALY = quality-adjusted life year; ToT = time on treatment.

References

[1] Incyte Biosiences UK. *Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations [ID3740]: Technical engagement response*, 2020. 16p.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

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

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm** on **Wednesday 28 October 2020** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18, Table 1.6 of the ERG report: The ERG state "The MAICs did not include adverse events (AEs) and the CS did not include any information about AEs associated with any of the comparator chemotherapy regimens considered ." Page 64 of the ERG report: "No safety data were provided for any of the comparator treatments considered." "no conclusions can be drawn about the safety profile of pemigatinib, relative to second-line systemic chemotherapy regimens" Page 70 of ERG report: "However, even though MAICs were not performed they could still have provided information about AE rates for the comparator trial ABC-06." Page 72 of ERG report: "…the CS did not include any information about AEs associated	The company submission included available AE data for comparator regimens mFOLFOX+ASC and ASC as reported by Lamarca et al. and observed in the ABC-06 trial (calculated annual rates for AEs from ABC-06 are presented in Table 41 of Document B). These data were also included in the base case economic analysis. It is factually inaccurate to suggest that the CS did not include any information about AEs associated with any of the comparator chemotherapy regimens considered Proposed amendments: "The MAICs did not include adverse events (AEs) as an outcome adjusted for potential prognostic factors. AE data for patients treated with comparator therapies were sourced from ABC-06 and were therefore observed in a molecularly unselected patient population." "Conclusion of pemigatinib's safety profile can only be drawn from the unadjusted comparison between FIGHT-202 and ABC-06 outcomes"	Factual inaccuracy.	Page 18, Table 1.6 of the ERG report: Text has been amended to: "There is a lack of evidence about the comparative safety of pemigatinib vs SOC, in the specified population. Adverse events (AEs) data for comparator regimens mFOLFOX+ASC and ASC, from the ABC-06 trial, were included in the cost effectiveness section of the CS and in the company's base case. The MAICs did not include AEs." Page 64 of the ERG report: The text has been amended to: "Adverse events (AEs) data for comparator regimens mFOLFOX+ASC and ASC, from the ABC-06 trial, were included in the cost effectiveness section of the CS, but no safety data were provided for any other comparators."

with any of the comparator chemotherapy regimens considered.”			and “The ERG notes that this omission means that no conclusions can be drawn about the safety profile of pemigatinib, relative to second-line systemic chemotherapy regimens, in the specified population.” Page 70 of ERG report: The sentence “However, even though MAICs were not performed they could still have provided information about AE rates for the comparator trial ABC-06” has been deleted. Page 72 of ERG report: The text has been amended to: “The MAICs also did not include AEs and the CS only included information about comparator regimens mFOLFOX+ASC and ASC; no AE data were reported for any other comparator.”

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 25 and 72 of the ERG report "The company have failed to demonstrate that this assumption has been met in any of the MAICs ""	"It is not possible to demonstrate that this assumption has been met in any of the MAICs"	All potential prognostic factors and effect modifiers that were reported in the comparator trial have been used in the MAICs. It is not possible to adjust for covariates that are not reported. Furthermore, where 100% (or close to 100%) of the patients in the trial with PLD have a characteristic, it is not possible to match to that covariates (such as FGFR2 (100%) and intrahepatic CCA (98%). Given the data available in the comparator trials, it would not be possible to demonstrate that this assumption had been met and there is no further analysis that can be performed to demonstrate this assumption.	Not a factual inaccuracy. The ERG do not believe that they could assert that, because such evidence has not been provided, it cannot be under any circumstances. The ERG could only state with certainty that this assumption has not been met. It is, however, informative that the company believe that the assumption cannot be demonstrated to have been met at all.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 86 of the ERG report: "clinical expert opinion consulted by the company indicated that oxaliplatin (administered	It is misleading and factually inaccurate to suggest that clinical experts indicated that CAPOX is part of the SoC for these patients in the UK. Both clinical experts consulted by the company confirmed that mFOLFOX is considered SoC in the UK. One clinician indicated that CAPOX may be considered	Misleading representation of clinical expert opinion and factually	The ERG agrees that the amendments as proposed by the company provide a more accurate representation of clinical

intravenously, in combination with oral capecitabine; together referred to as CAPOX)) and mFOLFOX+ASC are considered to be the current SOC therapy for these patients in the UK" Page 119 of the ERG report: "Both clinicians confirmed that mFOLFOX can be regarded as current standard clinical practice for previously treated patients with CCA, although one noted that CAPOX may be preferred by some clinicians (also see ERG comment in Section 5.2.4)."	for patients who are unsuitable for a chemotherapy port, but that CAPOX is also associated with additional toxicity when compared to mFOLFOX. It is noted that later on page 87, the ERG provide a more accurate representation of the clinical expert opinion. Proposed amendment page 86: "clinical expert opinion consulted by the company indicated that mFOLFOX + ASC is considered to be the current SOC therapy for these patients in the UK. However, one clinician did indicate that as these patients have been previously treated, they may be unsuitable for a chemotherapy port – in which case oxaliplatin (administered intravenously, in combination with oral capecitabine; together referred to as CAPOX) is preferred, despite this regimen being more toxic than mFOLFOX." Proposed amendment page 119: Both clinicians confirmed that mFOLFOX can be regarded as current standard clinical practice for previously treated patients with CCA, although one noted that CAPOX may be preferred by some clinicians for some patients who are not suitable for a chemotherapy port (also see ERG comment in Section 5.2.4)."	inaccurate.	expert opinion, and has made the amendments as proposed by the company on page 86 and page 119 of the ERG report.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 81, Table 5.5 of the ERG report: "The company deviated from the decision problem as stated in the final scope by NICE by not including the costs for genetic	The company explicitly included the cost of genetic testing in the submission and the economic analysis. The cost was not included in the base case economic analysis and justification was provided in Table 1 and Table 2 of Document B of the company submission.	Factual inaccuracy.	The ERG agrees to include the company's justification for deviating from the final scope by NICE for completeness. The ERG has amended the indicated sentence in Table

testing.”	Proposed amendment: “The company did not include the cost of genetic testing in the base case economic analysis, providing justification suggesting that patients will be tested routinely according to NHS plans. The impact of genetic testing costs for pemigatinib were explored in scenario analyses.”		5.5. on page 81 of the ERG report as proposed by the company.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 92 of the ERG report: “Therefore, the ERG would argue that the generalised gamma should be considered in the base-case for the extrapolation of OS for pemigatinib.”	While the company acknowledge that neither the log-logistic or generalised gamma curves match clinical expert opinion, the ERG’s proposed distribution to model pemigatinib OS is lower than the expected long-term OS for these patients and therefore should be considered a lower plausible bound for pemigatinib OS rather than the preferred base case. Proposed amendment: Clarifying text that the proposed generalised gamma distribution may underestimate pemigatinib OS based on existing clinical expert opinion.	Clarification required.	The ERG has amended the text on page 92, which now reads: “Therefore, the ERG would argue that the generalised gamma should be considered in the base-case for the extrapolation of OS for pemigatinib rather than the loglogistic as the latter leads to a 5-year survival estimate that is 6 %-point higher than the estimate from the experts, whereas with the generalised gamma the 5-year survival is only 2 %-point lower. However, the ERG acknowledges that this choice leads to a small underestimation of the

			suggested survival by the experts.”

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 129, Table 7.4 of the ERG report: Extrapolation of pemigatinib efficacy outcomes scenarios	By investigating the following scenario, the ERG makes several assumptions regarding the choice of parametric distributions used to extrapolate comparator OS and PFS, in some cases choosing distributions with considerably worse statistical and visual fit, without also considering the clinical plausibility of the chosen curves. Proposed amendment: Additional clarification is required to inform the reader of the assumptions made for the chosen scenario, and why these are informative for decision making.	Clarification required.	Not a factual inaccuracy. These scenarios are already explained in section 7.1.3.1.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 131, Table 7.6 of the ERG report: Literature values TA474. ERG results report ICERs for pemigatinib vs. ASC alone and pemigatinib vs. mFOLFOX + ASC of £89,142 and £89,002, respectively.	The ERG present results for literature values taken from TA474 in Table 7.6 but do not refer to these results in the text and it is unclear which utility values were tested by the ERG. The company were unable to replicate results presented by the ERG, as ICERs for pemigatinib vs. ASC alone and pemigatinib vs. mFOLFOX + ASC were found instead to be £89,143 and £89,012 respectively.	Clarification of scenario tested and potential correction of error in results table.	The results of this scenario have been updated following the correction of the utility controls noted by the company in Issue 12. The relevant utility values have been added in Table 7.6 for clarification.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23, Table 1.14 of the ERG report	Within this table, we believe the ERG preferred assumptions are applied each in isolation to the company base case post-clarification. An almost identical table later in the document (Table 7.8) then reports results with preferred assumptions applied cumulatively. Proposed amendment: Additional clarifying text of the approach used when applying ERG assumptions would avoid any confusion by the reader and allow easier interpretation by decision makers of the impact of each assumption on cost-effectiveness results.	Clarification required.	Not a factual inaccuracy. These tables are intended to show the assumptions applied in insolation in Table 1.14 and cumulatively in Table 7.3 as per the ERG report template. The fact that the impact is cumulative is already clarified in the text in section 7.3. For clarification, the in-text description of Table 1.14 has been amended to "The ERG preferred assumptions are described in detail in section 7.1.2 of this report and summarised in Table 1.14, with the impact on results of each assumption applied in isolation also shown"

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 42 of the ERG report: *'The relevant extracted data from these studies in the 2L+ treatment of FGFR2+ CCA can be found in Tables 15 (Response rate of non-randomised controlled trials [RCT] and observational studies) and 16 (Survival outcomes of non-RCT and observational studies) of the*	N/A	We acknowledge that this information was missing from the clarification responses. The tables have now been provided alongside this factual accuracy check.	Not a factual inaccuracy, no amendments suggested by the company.

SLR.' However, these tables were not included in the submission: *'Data from these studies were not included in the NICE appendices, which only included studies relevant from a MAIC perspective.'*			

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 77 of the ERG report: "The ERG is unable to comment on the cost and resource use SLR or the studies included/excluded as these details were not provided."	N/A	We acknowledge that this information was missing from Appendix I. This was not brought to our attention in the ERG clarification questions, but have provided a revised Appendix I alongside this factual accuracy check form.	This is not a factual inaccuracy, as the required information was not provided by the company. However, for completeness for the committee, the ERG has summarised and critiqued the now provided information.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 36 of the ERG report, Page 50, Table 3.3 of ERG report: "This study included 146 patients with histologically or cytologically confirmed CCA who had failed one prior treatment."	This study included 146 patients with histologically or cytologically confirmed CCA who had failed <u>at least</u> one prior treatment	Factual inaccuracy	Corrected.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 102 of the ERG report: "The ERG will use Model 3, with no distinction of utility by treatment status, in their base-case." Page 123, Table 7.1 of the ERG report: ERG preferred assumption: "From Model 3, including progression status but without treatment status" Page 131, Table 7.6 of the ERG report. Page 133, Table 7.8 of the ERG report. Page 135 of the ERG report: "Given that the inclusion of treatment status in addition to progression resulted in an implausible result for progression free on treatment and that the on-treatment state for progressed disease is not used, the ERG prefers to use a utility value estimation model without treatment status in the base-case."	There appears to be a discrepancy between the ERG preferred base case results and their preferences stated in the text. The ERG state that their preferred assumption would be to use model 3, which includes only covariates for baseline utility and progression status. Instead what the ERG appear to have done and reported for their preferred assumptions is to continue to use model 5 but apply the in-built model switch so that off-treatment health states are assumed to be equal to the on-treatment health states (progression-free off treatment = progression-free on treatment, progressive disease off treatment = progressive disease on treatment). Proposed amendment: We propose that the ERG clarify their preferred base case for utility analysis.	Factual inaccuracy and inconsistency.	The ERG thanks the company for noting this error in the use of controls. The ERG prefers the use of utilities estimated from Model 3 and therefore the ERG base-case and scenario results have been updated.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 123, Table 7.1 of the ERG report: When referring to the company	The company did not include wastage calculations in its base case and therefore did not make an assumption about whether to include RDI with respect to wastage	Factual inaccuracy.	The ERG agrees with the company that this is not accurately stated and removed the corresponding line in the

base case assumption for application of the RDI for pemigatinib in drug wastage calculation: "RDI not applied"	calculations. Proposed amendment: "N/A"		Table due to it being redundant.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21, Table 1.13 of the ERG report: "However the ERG considers that, given the high level of uncertainty about the results of the and the uncertainty about the outcomes of people with advanced CCA with FGFR2 fusion or rearrangement treated with second-line systemic chemotherapy (none of the comparator studies used in the MAICs provided data specific to this population), it is not clear that pemigatinib meets the NICE end-of-life criteria."	From the current wording, it is unclear which results the ERG is referring.	Missing text or typographical error.	Corrected.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 133, Table 7.8 of the ERG report Application of pemigatinib drug costs per 3-week subscription -	There appears to be a typographical error, the ICER was found instead to be £83,708	Factual inaccuracy.	The ERG thanks the company for noting this typographical error. However, it no longer applies as the results of this scenario have been updated

ICER for pemigatinib vs mFOLFOX+ASC, £83, 703			following the correction of the utility controls noted by the company in Issue 12.

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 137 of the ERG report "The model results suggest that pemigatinib meets the end of life criteria as mean survival in the EGR base-case (life expectancy)"	"The model results suggest that pemigatinib meets the end of life criteria as mean survival in the ERG base-case (life expectancy)"	Typographical error	The ERG thanks the company for noticing this and have corrected the error

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **by 5pm on Tuesday 8 December 2020**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement 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.

About you

Your name	[redacted]
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.	**N/A**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: There is a lack of direct evidence about the comparative efficacy and safety of pemigatinib vs standard of care (SOC), defined as systemic chemotherapy or BSC, in the specified population.	**No**	The company acknowledges the concerns raised by the evidence review group regarding the comparative efficacy and safety of pemigatinib versus standard of care in the specified patient population. However, the available evidence base has been systematically reviewed and the evidence supporting this appraisal reflects the best available evidence at the time the company dossier was submitted. The company has strived to provide robust data for pemigatinib in the context of a clinical setting where current treatments provide limited benefit, for patients with a rare disease (cholangiocarcinoma) and an infrequent molecular alteration (FGFR2 fusions/rearrangements), and hence, only limited data are available for other treatment options. The uncertainty that results from the lack of direct evidence for comparative efficacy is directly linked to the rarity of the disease being considered. Current estimates suggest that approximately 25 patients will be eligible for treatment in 2020. Therefore, the level of uncertainty and challenges associated with evidence generation should be viewed within the context of the prevalence of the disease. If a confirmatory trial were to be conducted in the same setting, the study population of the confirmatory trial would have to be restricted to ≥ third-line due to these patients having access to pemigatinib as a commercially available treatment, and this would greatly impact accrual of the trial (Pemazyre™ received FDA

		approval in the same indication on 17 APR 2020). Fewer than 50% of patients get second-line therapy due to the dismal prognosis. In a first-line trial, 100% of patients will have the chance to be treated with a targeted drug. Of note, in ABC-06 only 14% of patients received ≥ third line of therapies, which only reinforces the difficulties in accrual that this study would face. [4] Furthermore, other FGFR inhibitors are conducting compassionate use programs in the same previously treated population and their confirmatory studies in the first-line setting (futibatinib [NCT04093362] and infigratinib [NCT03773302]), which would also impact accrual of a confirmatory study in the second-line setting. FIGHT-302, a phase III trial investigating pemigatinib versus chemotherapy in patients with unresectable or metastatic cholangiocarcinoma with FGFR2 rearrangement, is expected to provide evidence on the comparative efficacy and safety of pemigatinib versus standard of care in previously untreated patients.[1] This will help support the evidence in previously treated patients, resolving this uncertainty, and is expected to read out in 2026.
Key issue 2: The evidence about the efficacy of pemigatinib is for a subset of the specified population.	**No**	The company agrees that the evidence for efficacy of pemigatinib is for a subset of the specified population (those with FGFR2 fusions/rearrangements) as pemigatinib is a potent and selective FGFR1, 2 and 3 inhibitor. However, it should be considered that FGFR2 fusions and rearrangements are found almost exclusively in cholangiocarcinoma (CCA) with the intrahepatic anatomical subtype.[2] This was also acknowledged by the ERG. In FIGHT-202, patients with non-intrahepatic disease were not excluded and one patient in the FGFR2 positive cohort (cohort A; n=107) had extrahepatic disease. There is no biological rationale that pemigatinib would not provide benefit to non-intrahepatic CCA patients with FGFR 2 fusion/rearrangements. It is important from an equity perspective that patients with other anatomical classifications of CCA (i.e. perihilar or distal, both of which are classified as

		extrahepatic CCA) are not excluded from receiving pemigatinib if they have a FGFR2 fusion or rearrangement. When consulted on molecular profiling, stakeholders (including health care professionals and patient groups) recommend that all CCA patients be molecularly assessed and not just those patients with intrahepatic disease.[3] Thus, the suitability of treatment with pemigatinib should be decided based on FGFR2 status and not anatomical subtype. Any consideration to the contrary could disadvantage patients who already have very limited treatment options available to them.
Key issue 3: There is a lack of any kind of evidence about the efficacy and safety of the comparator (systemic chemotherapy or BSC), in the specified population: a) The proportion of patients in, the main comparator study, with FGFR2 fusions/rearrangements was not reported, but estimated to be low. b) There were relatively few patients in the comparator studies who had intrahepatic cholangiocarcinoma (iCCA), compared to the pemigatinib study (FIGHT-202) where 98% of patients had iCCA.	**No**	The company acknowledges the concerns raised by the evidence review group regarding the lack of evidence of efficacy and safety for the comparator in the specified patient population. The available evidence base has been systematically reviewed and the dossier supporting this appraisal reflects the best available evidence at this time. In this context, the phase 3, randomized, second-line study in biliary tract cancer showed a median OS of 6.2 months with mFOLFOX (oxaliplatin/5-FU chemotherapy) vs 5.3 months for active symptom control (ABC-06).[4] Following recent clinical consultation, this study was still assessed as an appropriate and robust representation of standard of care in the UK in the absence of formalised treatment guidelines.[5, 6] At the time of this appraisal, the proportion of patients in the ABC-06 study with FGFR2 fusions/arrangements was not reported but Incyte understands that translational research (including molecular profiling) was a secondary endpoint of this study and this data would be made available in the future. The evidence review group acknowledged that ABC-06 included 44% of participants with intrahepatic cholangiocarcinoma making this study a relevant source for comparator data. Additionally, sub-group analyses by primary tumour site (intrahepatic, extrahepatic, gallbladder and cyst duct, ampulla) showed no significant differences in the primary outcome of overall survival.

		Additional studies were assessed to inform comparative effectiveness during the clarification process. Following review the ERG agreed that all the identified studies had limitations in matching the FIGHT 202 population. As highlighted in issue 1 there are significant hurdles in delivery a confirmatory trial in the same setting. Issue 2 also gives context for the high proportion of patients with intrahepatic cholangiocarcinoma included in the FIGHT-202 study in comparison to studies of non-molecularly selected patients. FIGHT-302, a phase III trial investigating pemigatinib versus chemotherapy in patients with unresectable or metastatic cholangiocarcinoma with FGFR2 rearrangement, is expected to provide evidence on the comparative efficacy and safety of pemigatinib versus standard of care in previously untreated patients.[1] This will help support the evidence in previously treated patients, resolving this uncertainty, and is expected to read out in 2026.
Key issue 4: The indirect evidence about the comparative efficacy of pemigatinib vs SOC is weak; the estimate of relative treatment effect in the model was based on an unanchored matched adjusted indirect comparison (MAIC) analysis between these two mismatched trials.	**Yes**	The company acknowledges that there are limitations to the use of a MAIC. However, based on the current data available (FIGHT-202, a single arm trial for the intervention), the most appropriate method of indirect treatment comparison has been performed and has followed the guidance set out NICE TSD 18.[7] The MAICs using ABC-06 have also been updated to reflect the latest FIGHT-202 data ([redacted], see company additional evidence appendix). We believe there are no alternative methods that could be applied without additional data (rationale for the limited data is discussed in issue 1), and there were no suggestions of alternative methods given in the evidence review group report. As such, we agree that the uncertainty surrounding this method of comparison is unresolvable at this time. Regarding the choice of trials, although we acknowledge there are differences between FIGHT 202 and ABC-06, we believe this is the most appropriate study and treatment for comparison based on the current evidence base, for this decision problem. Alternative studies were considered in response to the evidence

		review group questions, but these are subject to the same unresolvable limitations and additional differences. However, when further comparative efficacy data for the selected population become available in the future (such as that from FIGHT-302), the uncertainty in the relative efficacy of pemigatinib versus chemotherapy in FGFR2-selected patients can be reduced.
Key issue 5: There is a lack of evidence about the comparative safety of pemigatinib vs SOC.	**Yes**	The company acknowledges the uncertainty of current estimates of comparative safety between pemigatinib and standard of care. However, as mentioned in issue 1, this is due to a lack of available evidence. In addition to the updated efficacy data from FIGHT 202 ([redacted]), safety data was also provided [redacted]. The safety profile of pemigatinib in FIGHT 202 continues to be consistent with that reported in the first analysis and maintains a positive benefit/risk ratio. In order to demonstrate that cost-effectiveness estimates are insensitive to comparative safety data, extreme value testing has been conducted, varying the modelled adverse events for the comparator to extreme lower and upper bounds. Using the updated company base case and increasing mFOLFOX+ASC (oxaliplatin/5-FU+active symptom control) and ASC adverse event rates by 100% resulted in a decrease to the incremental cost-effectiveness ratio of £352 and £482 for pemigatinib vs. mFOLFOX+ASC and ASC, respectively. By setting adverse event rates for mFOLFOX+ASC to 0 and keeping pemigatinib rates the same, a £353 and £482 increase in the incremental cost-effectiveness ratio was observed for pemigatinib vs. mFOLFOX+ASC and ASC, respectively (see Table 13 in the company additional evidence appendix).

		This clearly demonstrates that while the comparative safety of treatments remains an important consideration, given that there are no other safety concerns associated with pemigatinib and that it does not influence the cost-effectiveness estimates, it should not be considered a key issue for decision making.
Key issue 6: It is not clear that pemigatinib meets the NICE end-of-life criteria	**Yes**	There are no approved therapies for patients with advanced/metastatic cholangiocarcinoma who have progressed on at least 1 line of prior therapy. Chemotherapy, locoregional therapy, and targeted therapies have limited clinical activity in molecularly unselected populations. Overall survival estimates for comparators in the model are taken from molecularly unselected patients observed in the ABC-06 study. Since overall survival for the current standard of care in the target population is uncertain, it is argued that it is unclear whether pemigatinib meets the end-of-life criteria. An updated data cut from [redacted] for the FIGHT-202 study has been provided, which aims to reduce the uncertainty associated with long-term survival outcomes of patients treated with pemigatinib, but the uncertainty for comparator long-term survival remains. [redacted] Although there is no conclusive answer regarding prognosis of FGFR2-rerranged cholangiocarcinoma, if there were any prognosis impact of this alteration, it is not expected that the overall response rate, duration of response, progression free survival, and median overall survival observed in this population with pemigatinib could be due to good prognosis of the disease alone. While further evidence generation is not possible to resolve this issue currently, the company has tested existing modelling assumptions using extreme values to help

		support decision makers in assessing whether pemigatinib meets the requisite end of life criteria. The economic model has a functionality to apply a hazard ratio to the comparator overall survival extrapolations, demonstrating the differences in any potential prognostic effects between FIGHT-202 and ABC-06, such as the prevalence of FGFR2 rearrangements. No adjustment was applied in the company base case, which is consistent with applying a hazard ratio of 1. A threshold analysis was conducted, with HR estimates (for wild-type patients versus FGFR2 rearrangements) varied between 0.2 and 4 – considered to be far outside the plausible limits of any required adjustment (this was estimated as 1.54 and 1.77 from Jain et al.[8] data [inverse presented in Table 34, Section B.3.3.3 of the company submission]). At all levels, the mean total life years for comparators active symptom control (ASC) alone or oxaliplatin/5-FU (mFOLFOX) +ASC never rose above 24 months, rising to a maximum mean life expectancy of 21.61 months for mFOLFOX+ASC. In the same manner, mean incremental life year gains for pemigatinib versus mFOLFOX+ASC fell to a minimum value of 7.64 months at a hazard ratio of 4 (see Table 13 of the company additional evidence appendix). In addition, clinical opinion elicited at a recent clinical validation meeting was that pemigatinib in this indication clearly meets the NICE end-of-life criteria, despite uncertainty in comparative efficacy between pemigatinib and mFOLFOX+ASC.[5] By conducting the aforementioned analysis, it is clear that the end of life criteria for normal life expectancy less than 24 months and extension to life of greater than 3 months are consistently met, even when modelling assumptions and uncertainty are tested at their extreme limits.
Key issue 7: It is not clear that all relevant comparators have been included in the cost effectiveness model.	**No**	The clinical experts consulted by the company stated that oxaliplatin/5-FU+active symptom control (mFOLFOX+ASC) is considered the standard of care for patients with previously treated cholangiocarcinoma, and in some circumstances clinicians may offer alternative regimens, which are better suited for patients who are not suitable for intravenous therapies. These alternative therapies are associated with

		worse outcomes, including additional safety concerns, with minimal cost savings due to the reduced need for IV administration. The clinical systematic literature review also failed to identify any published evidence for the alternative regimens suggested by clinicians (CAPOX – oxaliplatin/capecitabine) and therefore it was not feasible to include these regimens within the economic analysis. In response to evidence review group clarification questions, the evidence review group requested several additional MAIC analyses for comparators not considered to be standard of care by UK clinicians. These were completed and provided to the evidence review group at the clarification stage but have not been considered further. While clinical expert opinion sought by the company has stated that mFOLFOX+ASC is currently considered the UK standard of care for this indication[5, 6], the company would welcome further clinical input on this issue from any clinicians advising NICE.
Key issue 8: The selection of the parametric curve for overall survival (OS) for pemigatinib.	**Yes**	Additional follow up for pemigatinib overall survival data is provided in response to technical engagement, consisting of an updated datacut from the FIGHT-202 study ([redacted]). Details of the data-cut and updated survival analysis are provided separately in the company additional evidence appendix. The additional follow up reduces uncertainty of long-term survival outcomes for patients treated with pemigatinib, and further clinical validation supports the use of the log-logistic distribution in the base case analysis since it predicts a decline in the predicted hazard over time that is consistent with the published literature.[5, 9] Based on the updated FIGHT-202 data survival analysis, the company consider the log-logistic extrapolation to be the most appropriate for overall survival, considering the visual and statistical fit and clinical plausibility of the shape and pattern of long-term hazards.

Key issue 9: The method used to extrapolate time on treatment (ToT).	**Yes**	Similarly to issue 8, updated analysis of time on treatment extrapolations has been provided using the updated data cut from FIGHT-202, presented in the company additional evidence appendix. Extrapolations are consistent with previously provided clinical expert opinion. Due to the similarity between extrapolations and their visual and statistical fit, the company base has been revised to use the distribution preferred by the evidence review group (Weibull), due to its proximity to estimates from clinical opinion.[5, 6]
Key issue 10: There was no attempt by the company to conduct a MAIC analysis for adverse events (AEs). Therefore, the rates of AEs across the studies and their relevant populations remain unadjusted.	**No**	The company acknowledges that a MAIC analysis for AEs may have provided more accurate estimates of comparative safety between pemigatinib and standard of care. However, as discussed for efficacy, MAIC analyses are not without limitations. The company has presented a naïve comparison of treatment safety, using the publicly available data from ABC-06, and in response to issue 5, additional scenario analyses have been conducted to demonstrate the negligible impact of AE rates on the incremental cost-effectiveness ratios for pemigatinib versus standard of care.
Key issue 11: Health-related quality of life (HRQoL) was not measured using the EQ-5D in FIGHT-202 and had to be mapped from EORTC-QLQ-C30 data to EQ-5D-3L utilities using a published mapping algorithm.	**No**	In response to the approach used in the company's economic analysis, the evidence review group (ERG) responded with the following*: "However, given that EQ-5D data was unavailable, mapping is an appropriate alternative and the ERG agree with the company's selection of the Longworth et al. algorithm."* As such, it is the company's understanding that the mapping methods used are not a key issue for this appraisal. Regarding the regression model used to inform health state utilities, in scenario analyses in the original submission, the impact of including a covariate for treatment state was tested and shown to have a limited impact on the ICER. In response to some of the ERGs comments, considering the implausible utility values and limited number of observations for the progression-free off-treatment health state, the company base case has been altered to reflect the ERG's

		preference for using “model 3”, including covariates for baseline utility and progression status only. The company agree that having EQ-5D data would reduce uncertainty further and should this remain as an issue, EQ-5D data is being collected as part of the FIGHT-302 trial[1], reading out in 2026 albeit for previously untreated patients.
Key issue 12: The company base case model did not include wastage costs or the costs of genetic testing.	**No**	The revised base presented in response to technical engagement includes wastage costs, as preferred by the evidence review group. The impact of the corresponding changes on the updated base case incremental cost-effectiveness ratio are described below. The company considered the issue of testing and has worked to understand the current landscape in the NHS. The cost of genetic testing has not been included in the company base case because Incyte believes that testing is being integrated into routine care for specific cancers like cholangiocarcinoma (CCA). Molecular testing in cancer is becoming commonplace in the NHS and is currently carried out extensively in tumours such as non-small cell lung cancer and melanoma. The 2020/2021 National Genomic Test Directory specifies which genomic tests are commissioned by the NHS in England, the technology available to carry out the test, and the patients eligible to have access. CCA is already included in the Test Directory for the detection of a neurotrophic tyrosine receptor kinase (NTRK) rearrangement. This means treating oncologists can request this test if they wish to determine their patients’ eligibility of an NTRK inhibitor. Indeed the guidance from NICE regarding entrectinib and larotrectinib state that they are recommended as an option for patients if ‘they have no satisfactory treatment options’.[10, 11] There are no approved therapies for patients with advanced/metastatic CCA who have progressed on at least 1 line of prior therapy. Patients may receive chemotherapy or other regimens in second line, but these are not typically associated with meaningful therapeutic outcomes and are generally regarded as having significant safety concerns. One would argue that

		these treatment options are less than 'satisfactory'. Therefore, given the recommendation for the NTRK inhibitors, metastatic CCA patients are likely to be eligible for the test to assess NTRK rearrangements. Genomic testing is not carried out in isolation for one target. Instead, a multi-gene panel is used to identify alterations across a range of genes of interest. Thus, when a biopsy sample is tested for the presence an NTRK rearrangement, the presence of alterations in other genes such as FGFR will automatically be identified. Incyte has not included the cost of genetic testing in the base case model because, as demonstrated above, genetic testing is not specific to the identification of FGFR2. Furthermore, it is already being carried out in the NHS for CCA patients to identify the presence of NTRK rearrangements and this process is likely to become routine clinical practice.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
No additional issues	N/A	N/A	N/A

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER vs.	
			mFOLFOX + ASC	ASC
Changes following ERG clarification	Following ERG clarification the company made two changes. Correction of the method used to calculate AE rates and application of age-adjustment for health state utilities.	NA	Company base case ICER before technical engagement: £57,467	Company base case ICER before technical engagement: £60,806
Key issue 11	The company base case previously used model 5 including covariates for baseline utility, progression status, treatment status and an interaction term progression status*treatment status.	In response to the ERGs suggestions, model 3 is now used which includes only covariates for baseline utility and progression status.	£57,685 + £218	£59,340 -£1,466
Key issue 12	The base case previously did not include the cost of wastage	The model now includes the cost of wastage consistent with patients receiving a pack of 14 tablets every 3 weeks.	£58,478 + £1,281	£62,067 +£1,261

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER vs.	
			mFOLFOX + ASC	ASC
Key issues 1, 8 and 9	The base case used FIGHT-202 data from the original (March-2019) data cut	Updated survival analysis for overall survival, progression-free survival and time on treatment have been conducted using an additional data cut with follow-up until [redacted]. In addition, MAIC analyses informing estimates of comparative efficacy have also been updated using the updated FIGHT-202 data. Parametric curves used in the updated based case remain consistent with the previous base case with the exception that the ERGs preference of the Weibull distribution for time on treatment is now used.	£55,852 -£1,615	£60,340 -£466
Company's preferred base case following technical engagement	The company's preferred base case includes the combined changes listed above.		**£56,386** **-£1,081**	**£58,963** **-£1,843**

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Technical engagement new company evidence appendix

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

Updated FIGHT-202 data

In order to provide updated data on efficacy and more mature overall survival (OS), progression free survival (PFS) and time on treatment (TOT) data, we conducted another data cut for FIGHT-202 on [redacted]Note that one additional patient has been included in Cohort A (this cohort originally included 107 patients in the April 2019 data cut). This additional patient was included in the analysis as the study is still recruiting in Japan. [redacted]

Table 1: Summary of Best Overall Response and Objective Response Rate in Participants With FGFR2-Rearranged Cholangiocarcinoma in Study INCB 54828-202 ([redacted])

Variable	Pemigatinib 13.5 mg QD, 2-Weeks-On/1-Week-Off Schedule Cohort A, (N=108)
Objective response[a], n (%)	[redacted]
95% CI[b]	[redacted]
Best overall response, n (%)	
Confirmed complete response	[redacted]
Confirmed partial response	[redacted]
Stable disease	[redacted]
Progressive disease	[redacted]
Not evaluable[c]	[redacted]

[a] Participants who have best overall response of complete response or partial response according to RECIST v1.1
[b] The CI was calculated based on the exact method for binomial distribution
[c] Postbaseline tumor assessment was not performed due to study discontinuation (2 participants) or was performed prior to the minimum interval of 39 days for an assessment of stable disease (1 participant).

The complete and partial responses and long duration of responses can only be explained by the activity of pemigatinib.

[redacted]

Figure 1: Updated datacut ([redacted]) progression-free survival data, Study INCB 54828-202

[redacted]

Figure 2: Updated datacut ([redacted]) overall survival data, Study INCB 54828-202

In addition to the updated efficacy data, safety data was also analysed based on follow-up of [redacted] for the overall population. The safety profile of pemigatinib in FIGHT 202 continues to be consistent

with that reported in first analysis of the study and aligns with the summary of evidence provided in the company submission (section B.2.10).

Updated survival analysis

In order for the cost-effectiveness results to reflect the most recent data available from the FIGHT-202 study, updated survival analyses were conducted using the [redacted] data cut. The methods used to conduct the survival analyses, as well as implementation of those inputs within the cost-effectiveness model have remained consistent with the original submission. This section reports the updated survival analyses for all pemigatinib survival outcomes, including overall survival, progression-free survival and time on treatment.

For survival analysis, standard parametric survival functions were fitted to the observed FIGHT-202 data from the [redacted] data cut. The most appropriate curve was then selected based on visual and statistical fit within the trial period and the clinical plausibility of the extrapolated curves beyond the trial period. Statistical fit was assessed using the Akaike information criterion (AIC) and Bayesian information criterion (BIC) measures.

Overall survival

OS for patients treated with pemigatinib was informed by parametric survival models fitted to the FIGHT-202 OS KM data for Cohort A patients (participants with *FGFR2* fusions/rearrangements). Fitted models extrapolated beyond the observed follow-up period of the trial and predicted survival for the duration of the model time horizon (Xxxxxxxxxxxxxx xxxxxxxxxxxxxxx[redacted]

Figure 3; Table 2).

For the [redacted] data cut, all models again showed acceptable visual fit to the observed KM data, although the log-logistic distribution was shown to have the best statistical fit using both AIC and BIC measures. In addition, upon review of the predicted hazards compared with the empirical hazards (Figure 4), the log-logistic distribution was shown to closely match that of the observed pemigatinib OS hazard function in the first 21 months, after which there is heavy censoring (Figure 2).

In the original submission, a greater weight was placed on the clinical plausibility of OS extrapolations due to the immaturity of the observed data. Although this limitation has to some extent been resolved with the updated data cut, the clinical plausibility of these updated extrapolations using the [redacted] data has been sought.

[redacted]

Figure 3: Pemigatinib OS KM data and fitted PSM models

KM, Kaplan–Meier; OS, overall survival.

Previously, clinical experts had suggested that they may expect to observe approximately 5% of patients alive at 5 years.[1] In addition literature sources also report that approximately 70% of patients are diagnosed late with unresectable, locally advanced, or metastatic disease – with current standard of care, these patients have an estimated 5-year survival rate of ≤ 10%.[2-6] It should be noted that the uncertainty associated with these estimates is high as long term survival data for this rare condition are sparse, and long-term survival data specifically for patients receiving pemigatinib are not yet available.

With this in mind, the log-logistic distribution has been chosen in the updated base case as it represents a clinically plausible estimate of long-term survival specifically for patients treated with pemigatinib. This choice was supported by statements made during additional clinical validation that published evidence suggests that the probability of death conditional on survival until certain landmarks decreased over time.[7, 8] This feature of observed trends in overall survival in this disease area is consistent with the hazards predicted by the log-logistic distribution (Figure 4) as well as other distributions that model a decline in hazard over time. The combination of clinically plausible long-term survival predictions, good visual and statistical fit as well as appropriate modelling of the long-term pemigatinib hazard function suggest the log-logistic distribution is an appropriate and robust choice of curve for the base case cost-effectiveness analysis.

Table 2: Pemigatinib OS – AIC, BIC and 5-year survival estimates

Model	AIC	BIC	5-year survival estimate
Exponential	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]

AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

[redacted]

Figure 4: Smoothed hazard plots for overall survival showing the empirical hazard vs. each parametric distribution

Progression-free survival

Modelling of PFS using the updated data cut was consistent with the approach used in the company submission. PFS for patients treated with pemigatinib was informed by parametric survival models fitted to the FIGHT-202 PFS KM data for Cohort A patients. PFS as per the independent review committee analysis was used in the base case, as this was a key secondary outcome of the FIGHT-202 study and also matched the analysis used in the ABC-06 study.[9] The latest data cut substantially improves the maturity of the observed data for pemigatinib as only [redacted] of patients remain progression-free at the maximum follow up period of just over 3 years.

The comparison here of observed longer term follow up data with initial estimates given by clinicians is insightful. Clinical expert opinion previously suggested that 10% of patients would be expected to remain progression-free at 2 years. This has been shown with the updated data cut to be accurate.[1] Updated extrapolations were presented for further clinical validation, and although the clinician was unable to select between any of the extrapolated curves due to their similarity in long-term estimates, as per the data described for OS, hazards for progression or death would be expected to decrease in the long-term.[7, 8]

The range of fitted curves show very little difference in predicted long-term PFS outcomes and are broadly comparable with the previous data cut with a slight improvement in outcomes consistent with the changes in the observed data. For this reason, and because it remains statistically the best fit, there was no rationale to change the base case PFS curve for pemigatinib from log-normal. As such, the log-normal curve remains as the company base case.

[redacted]

Figure 5: Pemigatinib PFS KM data and fitted PSM models

KM, Kaplan–Meier; PFS, progression-free survival.

Table 3: Pemigatinib PFS - AIC, BIC and 2-year survival estimates

Model	AIC	BIC	2-year PFS estimates
Exponential	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]

AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Time on treatment

As for the other survival outcomes, the same approach was used for the updated data cut. In the base case for pemigatinib, ToT was modelled using PSMs fitted to observed data from Cohort A of the FIGHT-202 study.

Clinical expert opinion [redacted] [1] This has also been shown to be broadly consistent with the observed data in the updated FIGHT 202 datacut with [redacted] of patients remaining on treatment at [redacted]. As per PFS, due to the similarity in long-term extrapolations and visual fit, the clinician interviewed for additional validation was unable to select between any of the curves.[8]

The updated survival curves all show very similar observed visual and statistical fit. The ERG previously suggested that the Weibull curve was a more suitable

distribution to use for ToT than the exponential curve previously used in the company base case, due to its proximity to the original clinician opinion. Considering the similarity in statistical fit between the different curves (Table 4), and as Weibull remains closest to the 2 year estimates of both previously interviewed clinicians and the longer-term FIGHT-202 data, the ERGs preferences have been reflected in the updated base case, which now uses the Weibull distribution from the updated data cut.

[redacted]

Figure 6: Pemigatinib unadjusted ToT KM data and models

KM, Kaplan–Meier; ToT, time on treatment.

Table 4: Pemigatinib unadjusted ToT AIC and BIC scores

Model	AIC	BIC	2-year ToT estimates
Exponential	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]

AIC, Akaike information criterion; BIC, Bayesian information criterion; ToT, time on treatment.

Updated MAIC

The MAICs using ABC-06 data have been updated to incorporate the FIGHT-202 [redacted] data cut and to be consistent with the updated survival analyses. The methodology and comparators used are consistent with the original company submission but have not been updated for the additional comparisons presented for the ERG questions, as these are unlikely to resolve any additional comparator-based uncertainty at this stage, as discussed on the technical engagement call.

Results

Table 5 presents the baseline characteristics of the pemigatinib arm from FIGHT-202 (unadjusted and weighted) and the resulting effective sample size of the comparisons. The MAIC weighting was based on age, sex, ECOG performance

status and albumin. In the analyses performed for the original submission, there were nine patients from FIGHT-202 who had a missing value for albumin and were excluded from the MAIC analyses. However, this information was available for the updated data so these patients were included in the analysis. In addition, there was one additional patient that was enrolled into the trial after the read-out of the previous data-cut, and was included in the analysis (as per the survival analysis update). This additional patient was included in the analysis as the study is still recruiting in Japan. Therefore, the total number of patients included in the updated analysis for FIGHT-202 was 108. After performing the matching to the ABC-06 trial cohort characteristics, the weighted FIGHT-202 patients were approximately 10 years older, a higher proportion were male, a higher proportion had an ECOG performance status of 0–1, and lower albumin levels. Based on these characteristics, it was not clear how the matching would affect the weighted analyses compared to the naïve comparison, as the changes in some characteristics were likely to improve the relative effect when using weighted data (e.g. increase in ECOG 0–1 and decrease in albumin levels) whereas others were likely to decrease the relative effect (e.g. increase in age). The effective sample size was reduced by approximately half of the original sample size.

Table 5: Comparison of baseline characteristics – pemigatinib (FIGHT-202) unadjusted and weighted

Treatment (study)	N/ESS	Mean age (years)	Male %	ECOG PS 0–1 %	Albumin ≥35 g/L %
Pemigatinib unadjusted (FIGHT-202)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemigatinib weighted to mFOLFOX+ASC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemigatinib weighted to ASC only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ASC; active symptom control; ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size.
Sources: Abou-Alfa et al, 2020[10]; Lamarca et al., 2019[9].

FIGHT-202 vs ABC-06 (mFOLFOX+ASC) overall survival

Unadjusted and weighted KM plots, KM summary of number of events and median, and the HRs for OS are presented in Xxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxx [redacted]

Figure 7, Table 6, and

Table 7, respectively. These results show that the patients receiving pemigatinib demonstrated significantly greater improvements in OS compared with patients receiving mFOLFOX+ASC (unweighted [redacted]). Weighting the pemigatinib patients to match the mFOLFOX+ASC arm of ABC-06 resulted in an increase in the relative treatment effect (weighted [redacted]).

[redacted]

Figure 7: KM plot of OS – Pemigatinib (FIGHT-202) vs mFOLFOX+ASC (ABC-06)

ASC, active symptom control; KM, Kaplan-Meier; OS, overall survival; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; Pemi, pemigatinib.

Table 6: KM summary of OS –pemigatinib (FIGHT-202) vs mFOLFOX+ASC (ABC-06)

Treatment (study)	N/ ESS	Events	Median (95% CI)
Pemigatinib unadjusted (FIGHT-202)	[redacted]	[redacted]	[redacted]
Pemigatinib weighted (FIGHT-202)	[redacted]	[redacted]	[redacted]
mFOLFOX+ASC (ABC-06)	[redacted]	[redacted]	[redacted]

ASC, active symptom control; CI, confidence interval; ESS, effective sample size; KM, Kaplan–Meier; mFOLFOX; oxaliplatin, L-folinic acid and fluorouracil; NA, not available; OS, overall survival.

Table 7: Hazard ratios for OS – pemigatinib (FIGHT-202) vs mFOLFOX+ASC (ABC-06)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	Pemigatinib vs mFOLFOX+ASC	[redacted]
Weighted bootstrapped CI	Pemigatinib vs mFOLFOX+ASC	[redacted]

ASC, active symptom control; CI, confidence interval; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; OS, overall survival.

FIGHT-202 vs ABC-06 (mFOLFOX+ASC) progression-free survival

Unadjusted and weighted KM plots, KM summary of number of events and median and the HRs for PFS are presented in Figure 8, Table 8 and Table 9, respectively. These results show that the patients receiving pemigatinib demonstrated significantly greater improvements in PFS compared with patients receiving mFOLFOX+ASC (unweighted HR: [redacted]). Weighting the pemigatinib patients to match the mFOLFOX+ASC arm of ABC-06 resulted in a slight increase in the relative treatment effect (weighted HR: [redacted]).

Figure 8: KM plot of PFS – Pemigatinib (FIGHT-202) vs mFOLFOX+ASC (ABC-06)

ASC, active symptom control; KM, Kaplan-Meier; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; Pemi, pemigatinib; ; Pemi, pemigatinib; PFS, progression-free survival.

Table 8: KM summary of PFS – pemigatinib (FIGHT-202) vs mFOLFOX+ASC (ABC-06)

Treatment (study)	N/ESS	Events	Median (95% CI)
Pemigatinib unadjusted (FIGHT-202)	108.0	81	[redacted]
Pemigatinib weighted (FIGHT-202)	54.4	55	[redacted]
mFOLFOX+ASC (ABC-06)	81.0	78	[redacted]

ASC, active symptom control; CI, confidence interval; KM, Kaplan–Meier; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; PFS, progression-free survival.

Table 9: Hazard ratios for PFS – Pemigatinib (FIGHT-202) vs mFOLFOX+ASC (ABC-06)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	Pemigatinib vs mFOLFOX+ASC	[redacted]
Weighted bootstrapped CI	Pemigatinib vs mFOLFOX+ASC	[redacted]

ASC, active symptom control; CI, confidence interval; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; PFS, progression-free survival.

FIGHT-202 vs ABC-06 (ASC only) overall survival

Unadjusted and weighted KM plots, KM summary of number of events and median, and the HRs for OS are presented in

Xxxxx [redacted]

Figure 9, Table 10 and Table 11, respectively. These results show that the patients receiving pemigatinib demonstrated significantly greater improvements in OS compared with patients receiving ASC (unweighted HR: [redacted]). Weighting the pemigatinib patients to match the ASC arm of ABC-06 resulted in a slight increase in the relative effect (weighted HR: [redacted]).

[redacted]

Figure 9: KM plot of OS – Pemigatinib (FIGHT-202) vs ASC (ABC-06)

ASC, active symptom control; KM, Kaplan-Meier; Pemi, pemigatinib; PFS, progression-free survival.

Table 10: KM summary of OS – Pemigatinib (FIGHT-202) vs ASC (ABC-06)

Treatment (study)	N/ESS	Events	Median (95% CI)
Pemigatinib unadjusted (FIGHT 202)	[redacted]	[redacted]	[redacted]
Pemigatinib weighted (FIGHT 202)	[redacted]	[redacted]	[redacted]
ASC (ABC-06)	[redacted]	[redacted]	[redacted]

ASC, active symptom control; CI, confidence interval; ESS; effective sample size; KM, Kaplan–Meier; NA, not available; OS, overall survival.

Table 11: Hazard ratios for OS – Pemigatinib (FIGHT-202) vs ASC (ABC-06)

Method	Comparison	Hazard ratio (95% CI)
Unadjusted	Pemigatinib vs ASC	[redacted]
Weighted bootstrapped CI	Pemigatinib vs ASC	[redacted]

ASC, active symptom control; CI, confidence interval OS, overall survival.

The KM plot of PFS was not available for ASC, so this comparison was not possible.

Clinical validation

During technical engagement, Incyte conducted an additional clinical validation interview to elicit clinical opinion on the key issues identified by the NICE team as well as to seek clinical validation of parametric survival models fitted to the updated

FIGHT-202 data. A corresponding summary report is provided and the key points described in this document in the text below.[11]

The clinical validation meeting covered the following topics:

- UK standard of care
- FGFR genetic testing
- Updated pemigatinib FIGHT-202 datacut
    - Overall survival
    - Progression-free survival
    - Time on treatment
- End of life criteria

During the meeting it was confirmed that mFOLFOX+ASC represents the current UK SoC for previously-treatment cholangiocarcinoma patients and that no randomised data are available in this indication, other than ABC-06.[9]

On genetic testing for FGFR, clinical feedback was that although FGFR testing is not currently part of standard UK clinical practice (testing is only available either by self-pay or accessed as part of a clinical trial), the local genetics board are aware of FGFR as a target for testing in the future.

At the meeting, during discussion of extrapolated curves for overall survival and progression-free survival, a recent publication was shared that demonstrates a decline in overall survival and progression-free survival hazards over time.[7] The paper conducted a landmark survival analysis showing that the one-year event rate declined over time for both PFS and OS between time points of 1 year and 4 years. By evaluating the overall survival smoothed hazards plots it was concluded that distributions that predicted the same trend in predicted hazards were the most clinically plausible.

For the choice of progression-free survival curve, clinical opinion was that due to the small differences between fitted curves, it was not possible to differentiate between them. Clinical opinion was that this was also the case for time on treatment and a single curve could not be chosen out of the available set of extrapolations.

On the final topic of end-of life criteria, clinical opinion was that the criteria were clearly met in the case of pemigatinib, despite uncertainty in comparative efficacy.

Updated company base case

The updated survival analysis and MAIC using the April 2020 datacut of FIGHT-202 has been incorporated into the model, and can be selected using the switch in cell C158 of the 'Controls' sheet.

As described in the company technical engagement responses, Table 12 presents the updated company base case results, reflecting the updated survival analysis and MAICs using the FIGHT-202 April 2020 data, along with utility analysis and drug wastage amendments.

Table 12: Updated base-case fully incremental deterministic results – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ASC	[redacted]	0.60	[redacted]					
mFOLFOX+ASC	[redacted]	0.66	[redacted]	[redacted]	0.06	[redacted]	154,593	**Extendedly dominated**
Pemigatinib	[redacted]	**2.44**	[redacted]	[redacted]	**1.84**	[redacted]	**58,963**	**58,963**

ASC, active symptom control; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; PAS, patient access scheme; QALYs, quality-adjusted life years.

Additional scenario and threshold analyses

Additional functionality has been added to the cost-effectiveness model to allow the user to the amend the frequency of comparator adverse events. This has been added as a switch to cells C160 and C162 of the 'Controls' sheet for the scenario switch and user amendable adjustment, respectively. Scenario results for adverse event adjustment and alternative survival extrapolation assumptions are shown in Table 13. Results of the threshold analysis for the FGFR2 rearrangement OS prognostic factor hazard ratio are presented in Table 14.

Table 13: Additional scenario analyses

	ICER of pemigatinib vs		Change from base case pemigatinib vs	
	ASC (£/QALY)	mFOLFOX+ASC (£/QALY)	ASC (£/QALY)	mFOLFOX+ASC (£/QALY)
Updated company base case	58,963	56,386	0	0
Use generalised gamma to extrapolate FIGHT-202 OS	69,558	66,814	+10,595	+10,428
Comparative efficacy using a HR calculated using unadjusted ABC-06 data	60,001	58,714	+1,037	+2,329
Comparative efficacy using unadjusted ABC-06 data extrapolations	58,121	60,672	-842	+4,286
200% comparator AE frequency	58,611	55,904	-352	-482
0% comparator AE frequency	59,316	56,868	+353	+482

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.

Table 14: FGFR2 rearrangement OS prognostic factor HR threshold analysis

	ICER		Incremental LYs		LYs	
HR (WT versus FGFR2 rearrangement OS)	**Pemigatinib Vs ASC**	**Pemigatinib Vs mFOLFOX+ASC**	**Pemigatinib Vs ASC**	**Pemigatinib Vs mFOLFOX+ASC**	**ASC**	**mFOLFOX +ASC**
0.2	£49,343.46	£47,113.25	2.21	2.20	0.22	0.24
0.22	£49,629.64	£47,290.64	2.20	2.18	0.24	0.26
0.26	£50,184.53	£47,654.87	2.18	2.15	0.26	0.28
0.32	£50,984.12	£48,224.18	2.14	2.12	0.30	0.32
0.4	£52,009.11	£49,045.73	2.10	2.07	0.34	0.37
0.5	£53,236.32	£50,270.44	2.05	2.02	0.39	0.42
0.62	£54,642.22	£51,737.54	2.00	1.95	0.44	0.48
0.76	£56,237.98	£53,430.19	1.94	1.89	0.50	0.55
0.92	£58,050.56	£55,386.17	1.87	1.82	0.57	0.62
1.1	£60,116.80	£57,663.93	1.80	1.74	0.63	0.70
1.3	£62,486.12	£60,339.60	1.73	1.66	0.71	0.78
1.52	£65,219.54	£63,505.18	1.65	1.57	0.79	0.87
1.76	£68,395.09	£67,291.03	1.57	1.47	0.87	0.97
2.02	£72,115.53	£71,879.60	1.49	1.37	0.95	1.07
2.3	£76,518.67	£77,531.19	1.39	1.26	1.04	1.17
2.6	£81,791.57	£84,625.91	1.30	1.15	1.14	1.29
2.92	£88,194.08	£93,742.41	1.20	1.03	1.24	1.41
3.26	£96,095.41	£105,804.45	1.10	0.90	1.34	1.53
3.62	£106,038.42	£122,384.28	0.99	0.77	1.45	1.66
4	£118,855.62	£146,399.86	0.88	0.64	1.56	1.80

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; WT, wild-type.

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Technical engagement new company evidence appendix (updated PAS)

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

Updated analyses using the new patient access scheme

Since the submission of the company responses to technical engagement on 8th December 2020, Incyte have updated the patient access scheme simple discount from [redacted] to [redacted]. The updated deterministic company base case (fully incremental and pairwise versus mFOLFOX+ASC), scenario analyses and FGFR2 rearrangement OS prognostic factor HR threshold analysis are presented in Table 1 and Table 2, Table 3 and Table 4, respectively.

Table 1: Updated base-case fully incremental deterministic results – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ASC	[redacted]	0.60	[redacted]					
mFOLFOX+ASC	[redacted]	0.66	[redacted]	[redacted]	0.06	[redacted]	154,593	**Extendedly dominated**
Pemigatinib	[redacted]	**2.44**	[redacted]	[redacted]	**1.84**	[redacted]	**51,952**	**51,952**

ASC, active symptom control; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 2: Updated base-case pairwise deterministic results versus mFOLFOX+ASC – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
mFOLFOX+ASC	[redacted]	0.66	[redacted]				
Pemigatinib	[redacted]	2.44	[redacted]	[redacted]	1.78	[redacted]	49,186

ASC, active symptom control**;** ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, oxaliplatin, L-folinic acid and fluorouracil; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 3: Additional scenario analyses

	ICER of pemigatinib vs		Change from base case pemigatinib vs	
	ASC (£/QALY)	mFOLFOX+ASC (£/QALY)	ASC (£/QALY)	mFOLFOX+ASC (£/QALY)
Updated company base case	51,952	49,186	0	0
Use generalised gamma to extrapolate FIGHT-202 OS	61,184	58,167	+9,232	+8,982
Comparative efficacy using a HR calculated using unadjusted ABC-06 data	52,860	51,183	+908	+1,997
Comparative efficacy using unadjusted ABC-06 data extrapolations	51,223	52,848	-729	+3,663
200% comparator AE frequency	51,603	48,707	-349	-479
0% comparator AE frequency	52,302	49,665	+349	+479

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.

Table 4: FGFR2 rearrangement OS prognostic factor HR threshold analysis

	ICER		Incremental LYs		LYs	
HR (WT versus FGFR2 rearrangement OS)	**Pemigatinib Vs ASC**	**Pemigatinib Vs mFOLFOX+ASC**	**Pemigatinib Vs ASC**	**Pemigatinib Vs mFOLFOX+ASC**	**ASC**	**mFOLFOX +ASC**
0.2	£43,545	£41,286	2.21	2.20	0.22	0.24
0.22	£43,795	£41,425	2.20	2.18	0.24	0.26
0.26	£44,281	£41,715	2.18	2.15	0.26	0.28
0.32	£44,982	£42,176	2.14	2.12	0.30	0.32
0.4	£45,879	£42,857	2.10	2.07	0.34	0.37
0.5	£46,953	£43,911	2.05	2.02	0.39	0.42
0.62	£48,182	£45,178	2.00	1.95	0.44	0.48
0.76	£49,575	£46,638	1.94	1.89	0.50	0.55
0.92	£51,156	£48,324	1.87	1.82	0.57	0.62
1.1	£52,958	£50,287	1.80	1.74	0.63	0.70
1.3	£55,024	£52,594	1.73	1.66	0.71	0.78
1.52	£57,408	£55,323	1.65	1.57	0.79	0.87
1.76	£60,177	£58,586	1.57	1.47	0.87	0.97
2.02	£63,422	£62,542	1.49	1.37	0.95	1.07
2.3	£67,261	£67,413	1.39	1.26	1.04	1.17
2.6	£71,859	£73,529	1.30	1.15	1.14	1.29
2.92	£77,442	£81,387	1.20	1.03	1.24	1.41
3.26	£84,332	£91,784	1.10	0.90	1.34	1.53
3.62	£93,001	£106,075	0.99	0.77	1.45	1.66
4	£104,177	£126,775	0.88	0.64	1.56	1.80

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; WT, wild-type.

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

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

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Tuesday 8 December 2020**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

NICE National Institute for Health and Care Excellence

PART 1 – Treating a patient with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations and current treatment options	
About you	
1. Your name	**CHIARA BRACONI**
2. Name of organisation	**UNIVERSITY OF GLASGOW / BEATSON WEST OF SCOTLAND CANCER CENTRE**
3. Job title or position	**READER (ASSOCIATE PROFESSOR) / CONSULTANT MEDICAL ONCOOGIST**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NONE**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	This approval concerns the use of Pemigatinib (FGFR2 inhibitor) in chemo-refractory advanced cholangiocarcinoma patients. In this setting the main aims will be to improve symptomatology (usually related to the response rate as symptoms of cholangiocarcinoma are mass-induced), to delay tumour progression (measured by progression free survival), and to extend life expectancy (measured by overall survival).
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	A clinically significant treatment response in this setting includes: -reduction in tumour size greater than 30% in the sum of the longest diameter of the target lesions. This is defined as Partial Response (PR) as per RECIST1.1 criteria which are used in the clinical trial setting. A PR rate greater than 5% is expected for a new treatment to be better than current standard of care in this setting (mFolfox chemotherapy).

or a reduction in disease activity by a certain amount.)	-prolongation of Progression Free Survival (PFS) as time from the starting of a second line treatment to date of tumour progression (date of Progressive Disease). PFS with current standard of care in this setting is utmost 4 months. -extension of overall survival (OS), as time from the first dose of second line treatment to the date of death. A median OS greater than 6 months is expected for a new treatment to be better than the current standard of care.
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Cholangiocarcinoma is a rare tumour with incidence < 5/100,000 in UK. Cholangiocarcinoma is anatomically divided into subtypes: intrahepatic (if originates from bile ducts within the liver), perihilar (if originates from bile ducts at the confluence between left and right bile ducts), distal (if originates in the common bile duct), gallbladder cancer (if originates in the gallbladder). Despite this classification can affect the surgical treatment recommended for early stage resectable cholangiocarcinoma, treatment of advanced cholangiocarcinoma patients does not differ across the subtypes. However, recent genomic profiling has shown that enrichment of different molecular alterations can occur within the subtypes, with enrichment of FGFR2 fusions being prevalent in intrahepatic cholangiocarcinoma. Cholangiocarcinoma treatment represents an unmet need. Median overall survival (from diagnosis to death) ranges between 6 and 24 months with the current standard of care, which includes a first line chemotherapy with Cisplatin-Gemcitabine (or gemcitabine monotherapy) and a second line chemotherapy with mFolfox. Specifically, chemo-refractory cholangiocarcinoma patients (those who have progressed after first line chemotherapy) have a poor prognosis with paucity of effective treatment options. Expected median overall survival of advanced chemo-refractory cholangiocarcinoma patients is 6 months. To date the only recommended therapy is chemotherapy with mFolfox, which however gives marginal benefit with RR 5%, PFS 4 months, median OS of 6 months and grade 3/4 toxicity in 60% of patients.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Chemo-refractory cholangiocarcinoma patients who have progressed to first line chemotherapy do currently receive the following treatment: -***Active Symptomatic Control (ASC) and mFOLFOX chemotherapy*** *(combination of oxaliplatin and fluorouracil) which comprises of intravenous administration of chemotherapy and requires a central venous access (PICC line or PORT-a-CATH) to enable 46-hrs infusion of fluorouracil without need for overnight stay. The chemotherapy is given in*

	hospital every 2 weeks and requires bloods taken every two weeks before each administration of chemotherapy. This treatment has been approved on the bases of the ABC-06 trial (Lamarca, JCO 2019 Vol37;15abstr4003), which has shown clinical benefit over ASC alone in patients with biliary cancers (including cholangiocarcinoma). RR was 5%, PFS was 4 months. Median Overall Survival for ASC+mFolfox was 6.2 months vs 5.3 months for ASC alone. At 1 year 26% were still alive in the ASC+mFolfox while only 11% were alive in the ASC arm. *Expected median OS: 6.2 months* *-**Active Sympotmatic Control (ASC)** if patient's fitness is not satisfactory for second line chemotherapy with mFolfox. In this case the median OS is expected to be < 5.3 months, with <11% being alive at 1 year.* *Expected median OS: <5.3 months* No molecular profiling is currently recommended within the NHS for cholangiocarcinoma as chemotherapy activity is not dependent on the genomic characterization.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ESMO guidelines are international European guidelines that guide treatment of biliary tract cancer (including cholangiocarcinoma). However, the last published guidelines are from 2016 (Valle J, Ann Oncol 2016). A new set of guidelines is in preparation for the update of adjuvant treatment (Bilcap study), and second line treatment (ABC-06 and FIGHT 202 and ClarIDHy trials). While an updated formal guideline is awaited, a general international consensus suggests the use in second line of mFolfox and that of targeted therapies (FGFR2- and IDH- inhibitors) according to the molecular alterations of each tumour. (Banales, Nat Rev Gastroenterol Hepatol. 2020; 17(9): 557–588.)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The current pathway of care is well defined across UK. After failure to first line chemotherapy, patients are offered second line treatment with ASC+mFolfox providing their fitness is appropriate. The judgement of fitness is subjected to medical assessment and scored according to the Eastern Cooperative Oncology Group (ECOG). Patient with performance status ECOG 0-2 are offered ASC+mFolfox. In case of ECOF 3-5 patients are supported with ASC. The same pathway of care is applied across UK, independently on regional areas. I currently work in Scotland, where this approach is taken. I have been working in England from 2014 to 2019 and the same pathway of care was followed.

• What impact would the technology have on the current pathway of care?	Pemigatinib is a FGFR inhibitor that would be considered for patients with advanced FGFR2-fused cholangiocarcinoma, which includes 10-12% of all cholangiocarcinomas, after they have progressed to first line treatment. Thus, it would impact on the recommendation of second line treatment in FGFR-2 fused CCA, where Pemigatinib would be favoured over mFolfox or ASC for patients with good performance status (ECOG 0-2). Pemigatinib would impact on: - **quality of life** by --improving symptom control (as a RR of 36% has been reported, with 3% complete response (no disease visualized on imaging after Pemigatinib treatment). As symptoms from cholangiocarcinoma often are mass-induced, it is expected that a reduction in tumour volume will relieve symptomatology. --delaying tumour progression (as a median PFS of 7 months compares favourably with the historical 2-4 months from other studies) -- reducing neutropenia incidence, that can lead to need for hospital admissions. - **life expectancy** (as median OS of 21.1 months compares very favourably with the historical 6 months) - **reducing costs related to infusional therapy** -- reducing need for hospital visits (as Pemigatinib is an oral treatment) -- no need for central venous accesses (as Pemigatinib is an oral treatment) **- increasing costs related to genomic profiling** Despite it is known that FGFR2-fusion occur prevalently in intrahepatic cholangiocarcinoma, I would suggest performing molecular profiling in all biliary cancers as, conversely to early stage, it is often very difficult to differentiate the primary site (and cholangiocarcinoma subtypes) in advanced cases where large masses incorporates all the hepato-biliary structures.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Pemigatinib is not currently used in NHS clinical practice. As the current standard of care it will be prescribed by the oncologist
• How does healthcare resource use differ between the technology and current care?	• **<u>Current standard of care includes mFolfox</u>** which requires intravenous administration of oxaliplatin (over 2 hours) and fluorouracil (in bolus and over 48 hours). This requires: ***7-10 days before starting treatment:*** central venous access (PICC line or PORT-a-CATH) to be inserted by vascular /radiology department. Risk associated with these devices include infection (2%) and clotting (20%), which may require replacement of the line during the course of chemotherapy. ***Day 0 of each cycle:*** outpatient oncology appointment for pre-chemotherapy assessment and prescription. ***Day 1 of each cycle:*** administration of i.v. mFolfox in hospital in Medical Day Care Units with dedicated trained nurses. ***Day 3 of each cycle***: removal of pump (hospital or district nurse at home). Cycles will be repeated every 14 days • **<u>Treatment with Pemigatinib</u>** will be given as oral administration requiring: ***Day 1 of each cycle:*** outpatient oncology appointment for pre-treatment assessment and prescription. Patients start Pemigatinib per os once per day for two weeks. Cycles will be repeated every 21 days
• In what clinical setting should the technology be used? (For example,	Pemigatinib would be used in secondary care with oncology services.

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Pemigatinib will be given as an oral drug, therefore no equipment or further infrastructures are needed. Toxicity profile is favourable and does not include side effects for which additional training is required. To identify patients suitable for Pemigatinib, a molecular profile will need to be performed in order to select patients with tumours harbouring FGFR-2 fusion. This test can be performed on FFPE (formalin fixed paraffin embedded) tissues from diagnostic histological samples, or alternatively in plasma through the analysis of circulating tumour DNA (even though less sensitive and to be considered as second choice).
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	I expect Pemigatinib to provide a clinically meaningful benefit compared with current standard of care. The FIGHT-202 trial is a phase II single arm study which lacks randomization against a standard of care arm; therefore, a direct comparison cannot be made between Pemigatinib and standard of care (mFolfox or ASC). However, efficacy data are very impressive and compare positively to historic data and in a cross-trial comparison. -Response Rate (RR) for Pemigatinib is 36% vs 5% for mFolfox. Included in this RR are 3% of Complete Responses (tumour not visible on imaging) observed after treatment with Pemigatinib that have never been observed before with other therapies (in first- or second-line setting) in cholangiocarcinoma. -12months Progression Free Survival rate for Pemigatinib (proportion of patients who do not have disease progression at 1 year) is 30% (FIGHT-202) vs 6% for mFolfox (ABC-06) vs 0% for ACS (ABC-06 or ClarIDHy). -Life Expectancy (as median OS from starting of second line) is remarkably longer than the one achieved with current standard of care or in other trials --**median OS in patients with FGFR-2 fused cholangiocarcinoma receiving Pemigatinib = 21.1 months (FIGHT-202)** --median OS in patients with cholangiocarcinoma treated with ASC+mFolfox = 6.2 months (ABC-06 trial) --median OS in patients with cholangiocarcinoma with other FGFR-2 alterations = 4 - 6.7 months (FIGHT-202)

	--median OS in patients with cholangiocarcinoma with IDH1 mutations treated with ASC = 6 months (ClarIDHy trial)
• Do you expect the technology to increase length of life more than current care?	I expect Pemigatinib to increase length of time more than current care, as median OS from starting of second line is 6.2 months in mFolfox and 21.1 months in Pemigatinib treated patients. Overall survival rate at 12 months is 68% for Pemigatinib. It is expected to be 24% for mFolfox.
• Do you expect the technology to increase health-related quality of life more than current care?	As detailed above (question 11) I expect Pemigatinib to improve quality of life for an impact on: -symptoms (due to higher chanced of shrinking tumour size) -extension of life expectancy -less need for intraveneuos infusion -less need to attend hospital for treatment
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Pemigatinib would be effective only in FGFR2-fused cholangiocarcinoma.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any	Pemigatinib is an oral treatment to be taken once a day for two weeks in 3-weeks cycles. This will be easier to use for patients than current standard of care which includes mFolfox chemotherapy (a biweekly intraveneous administration of chemotherapy which requires central venous access - please details explained above in question 12)

practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, Pemgatinib would be indicated only in FGFR2-fused cholangiocarcinoma (which represent 10—12% of all cholangiocarcinoma patients); therefore, it is mandatory a genomic test. Genomic testing is currently evaluated for the introduction in clinical practice in NHS, but to date (8DEC2020) it is not practiced as standard of care in cholangiocarcinoma. In selected centres, it is performed as part of a research programme. Test would be indicated in all cholangiocarcinoma patients to select those which are candidates. I would personally advise to extend the genomic testing to all biliary cancers as at the advanced stage is often difficult to identify the subtype of cholangiocarcinoma, as well as differentiate an intrahepatic cholangiocarcinoma from a gallbladder cancer. It is frequent that the epicentre of the mass is not localized and thus difficult to establish if it developed as intrahepatic cholangiocarcinoma and invaded gallbladder or arose from gallbladder and invaded the liver. Please note the rarity of biliary cancers (as detailed above in question 10) when assessing the impact on the costs.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in	Please consider elements discussed in the questions above.

the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	I believe the use of Pemigatinib in chemorefractory cholangiocarcinoma would make a significant impact on health-related benefits for these patients by improving their quality of life, extending their life expectancy (as discussed above).
• Is the technology a 'step-change' in the management of the condition?	Yes, because it is the first time we observe these remarkable data in the second line setting in cholangiocarcinoma patients with a remarkable response rate of 36% (including complete responses never observed with other therapies), an impressive median overall survival of 21 months in patients who have already progressed to first line treatment. This also represents the first positive example of precision oncology in the treatment of cholangiocarcinoma, underlining the need to rethink the therapeutic strategy of this tumour type, where molecular characterization becomes at the base of an individualized treatment.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, cholangiocarcinoma patients lack effective therapeutic options. Pemigatinib fills this gap by confirming a remarkable value for a subpopulation of patients.
19. How do any side effects or adverse effects of the technology affect the management of the	Pemigatinib is well tolerated with a manageable toxicity profile that mainly includes outpatient treatment without hospitalization. Reported side effects include only one case of grade 4 toxicity (hyponatremia). Most frequent toxicity include:

condition and the patient's quality of life?	-hypophosphatemia occurred in 33% of cases (grade 3 only in 7%). However, it was mild in the majority requiring only oral supplement. No grade 4 hypophosphatemia (with need for prompt intravenous therapy) were recorded. -stomatitis (grade 3 in only 5% of patients). Main side effects of standard of care mFolfox include neutropenia (reduction of neutrophils with increased risk of infection), which caused hospital admission in 12% of patients in the ABC06 trial; infection with admission in 19% of cases and fatigue in 19% of cases.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the population of the trial reflects the population of cholangiocarcinoma patients treated in UK. The ABC-06 is a UK trial which showed median age of this population being 65 years. Median age in the FIGHT-202 trial is similar. The group with FGFR2-fused tumours has a slightly lower median age (56 years) in the FIGHT-202, because FGFR2-fusion tend to occur in younger patients. I expect in UK the median age of cholangiocarcinoma patients with FGF2-fusions being equivalent to the one observed in the FIGHT-202 trial.
• If not, how could the results be extrapolated to the UK setting?	See answer above.
• What, in your view, are the most important outcomes, and were they measured in the trials?	-Response Rate (RR) for Pemigatinib is 36% (It is 5% for mFolfox), with a median duration of response of 7.5 months -Median Progression Free Survival (PFS) is 7 months (It is 4 months for mFolfox) -12months Progression Free Survival rate for Pemigatinib (proportion of patients who do not have disease progression at 1 year) is 30% (FIGHT-202). It is 6% for mFolfox (ABC-06); 0% for Active Symptomatic Control (ABC-06 or ClarIDHy). -Life Expectancy (as median OS from starting of second line) is 21.1 months (It is 6.2 months for mFolfox)

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	They provide long term outcome (median overall survival). No need for consideration of surrogates.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s)?	No, in the current UK clinical practice only mFolfox and ASC are recommended and approved as standard of care in this setting. From a wider perspective data on Ivosidenib (IDH inhibitor) in IDH1 mutated cholangiocarcinoma have been recently published (phase III randomized ClariDHy trial). IDH1 mutated cholangiocarcinoma are mainly intrahepatic. The ClariDHy trial can therefore be used to extrapolate data on overall survival for intrahepatic cholangiocarcinoma only when receiving ASC (placebo group in the ClarIDHy trial), which equals 6 months.

23. How do data on real-world experience compare with the trial data?	Real life data for Pemigatinib are not available yet. However, a retrospective study on the use of FGFR2-inhibitors in cholangiocarcinoma has been performed over 300 patients from multiple American Institutes (Jain et al, JCO Prec Oncol 2018). This study showed that the use of FGFR2 inhibition as second line treatment in FGFR2-fused cholangiocarcinoma (N=36) could provide a statistically significant improvement in overall survival when compared to non FGFR2-targeted treatment in FGFR2-fused cholangiocarcinoma (N=50): Median OS (from diagnosis) of FGFR2-fused cholangiocarcinoma treated with FGFR2-inhibitor = 48 mo Median OS (from diagnosis) of FGFR2-fused cholangiocarcinoma treated with non FGFR2-targeted therapy: 24 mo However, please note that in this study they report survival from diagnosis and therefore extrapolation of survival from second line treatment (as reported in the FIGHT-202) is difficult because we need to consider: - 40% of patient received surgery at diagnosis, thus impacting on overall survival. Median recurrence free survival (time of tumour recurrence after surgery) ranges between 17 and 24 months depending on adjuvant treatment (as per phase III Bilcap trial). - Pemigatinib was given in second line, thus we need to consider the time patients have been on first line chemotherapy. Median PFS to first line chemotherapy is 8.7 mo (from ABC-02 trial) (and was not different between FGFR2-fused and non FGFR-2 fused cholangiocarcinoma), Thus, we can estimate that FGFR2-fused cholangiocarcinoma patients who are treated with standard of care (non-FGFR2 inhibitor) live for around 10 months.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

24b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
25. NICE scope defined the population as 'advanced cholangiocarcinoma with FGFR2 fusion or rearrangement'. In FIGHT-202, majority of the patients (98%) had intrahepatic cholangiocarcinoma. Is the population in FIGHT-202 representative of the population defined in NICE scope?	The selection of patients suitable for Pemigatinib will be identified by the presence of the molecular alteration and not by subtype. We are aware that FGFR2 fusions mainly occur within intrahepatic cholangiocarcinoma. However, 1) FGFR2 fusions have been sporadically detected also in other subtypes; 2) in the advance setting is difficult to differentiate intrahepatic cholangiocarcinoma from the other subtypes (please see details above at question 16). Pemigatinib should be recommended only for FGFR2 fused tumours, independently on the subtyping. The test should be recommended in all cholangiocarcinoma (I would actually suggest all biliary cancers for the reasons explained in question 16).
26. In your opinion: a. Are the comparators included sufficient and appropriate for this appraisal? i.e:	Yes, these are the only recommended treatments per current clinical practice (please see details given above).

• Active symptom control (ASC) • 5-fluorouracil + oxaliplatin + folic acid (mFOLFOX) + ASC b. Are there any other comparators that you consider relevant for this appraisal?	
27. Is FGFR genetic testing part of routine clinical practice? If so, how often is FGFR genetic testing carried out in routine clinical practice. What are the cost implications of FGFR genetic testing?	No, genomic testing is not performed as routine clinical practice in UK.
28a. What is the life expectancy of people with relapsed or refractory advanced	Data on survival of cholangiocarcinoma with FGFR2-fusions are limited. Speculations can be done from the data of a retrospective real-life study published by Jain et al (JCO Prec Oncol 2018).

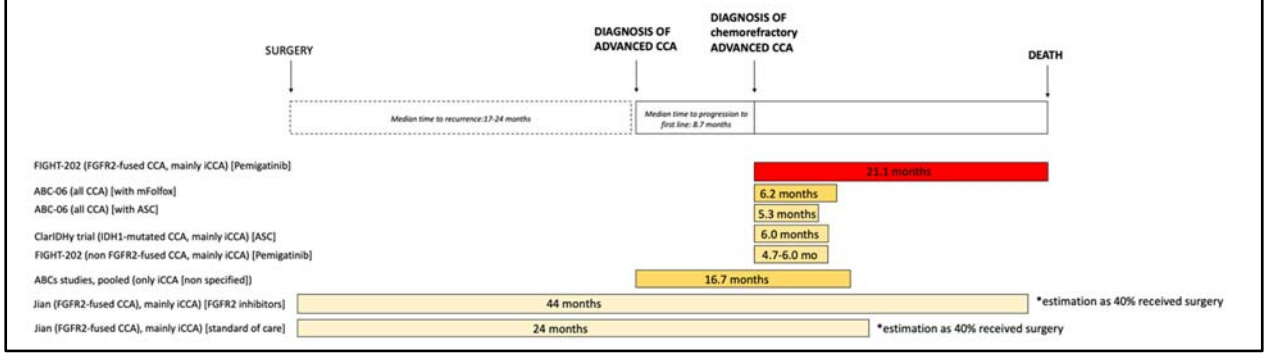
cholangiocarcinoma with FGFR2 alterations in current clinical practice without pemigatinib? 28b. By how long, if any, do you expect pemigatinib to extend life at the end of life compared with current clinical practice without pemigatinib?	Median life expectancy of patients with advanced chemorefractory FGFR2-fused cholangiocarcinoma is expected to be less than 1 year (around 10 months). Please see explanation below along with schematic representation from Figure 1. (PART 2 Key issue 1) From the data in the FIGHT-202 life expectancy can be more than doubled with Pemigatinib (around 21 months).

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: There is a lack of direct evidence about the comparative efficacy and safety of pemigatinib vs standard of care (SOC), defined as systemic chemotherapy or BSC, in the specified population.	The FIGHT-202 trial is a single arm phase II trial and therefore lacks a direct comparison with the current standard of care ASC or mFolfox. The data from FIGHT-202 are impressive. However, two issues need to be considered: -FIGHT-202 trial includes mainly intrahepatic cholangiocarcinoma, which are known to have a better prognosis than other subtypes (while the ABC-06 trial included all the subtypes). -FIGHT-202 trial considers FGFR2-fused cholangiocarcinoma that may have a better prognosis. I have drawn Figure 1 to summarize all the data we know so far that can help to put data from FIGHT-202 in context. ABC-06 is a phase III randomized trial that showed efficacy of mFolfox vs ASC in second line setting. From starting of second line, median overall survival is 6.2 months (mFolfox), and 5.3 months (in ASC). However, ABC-06 does not include only intrahepatic CCA which may have a better prognosis, while 98% of patients in the FIGHT-202 have intrahepatic cholangiocarcinoma. The cohorts of the FIGHT-202 without FGFR-2 fusions (but mainly intrahepatic cholangiocarcinoma) show a median overall survival ranging between 4.7 and 6.0 months. The ClarIDHy trial included only intrahepatic CCA (IDH1 mutated), but the median OS from starting second line treatment confirmed 6.0 months for patients treated with ASC. If we wanted to extend these data to all intrahepatic CCA we can consider the data from the pooled analyses of the phase

III prospective ABC trials (Lamarca JNCI 2019). A sub-analysis per subtype has shown that patients with intrahepatic cholangiocarcinoma live longer than other subtypes, but overall survival from starting first line treatment is 16.7 months (Lamarca et al, JNCI 2019). Considering that median time to progression to first line is 8.7 months, assuming there were no delays between end of first line and starting of second line, we can speculate patients lived about 8 months from the starting of second line treatment.

It is also suggested that patients with FGFR-2 fused cholangiocarcinoma have a better prognosis than other cholangiocarcinoma. These data come from a retrospective study (Jian et al, JCO Prec Onc 2018) where median overall survival of patients with advanced FGFR2-fused cholangiocarcinoma was 24 months (from diagnosis) vs 17 months in case of absence of FGFR2-fusion. However, these patients received a mixture of standard of care and FGFR2-inhibitors (drugs from the same class of Pemigatinib) which may provide a significant benefit in FGFR2-fused tumours. A sub-analysis in patients with FGFR2-fused tumours receiving FGFR2-inhibitors (similar to Pemigatinib) vs non FGFR2-targeted therapies (similar to standard of care) had a significant difference in median overall survival: 44 months vs 24 months, confirming a benefit of treating FGFR2-fused tumours with FGFR2-inhibitors. However, we cannot compare this value in survival with the one from FIGHT-202 as these 44 months were calculated from diagnosis, and 40% of patients received surgery, knowing that time to recurrence (and diagnosis of advanced cholangiocarcinoma) is between 17 and 24 months (from the Bilcap trial-Primrose, Lancet Oncology 2018). In addition, these patients underwent first line chemotherapy before being considered for FGFR2-targeted therapies, letting us speculate that survival of chemorefractory FGFR2-fused cholangiocarcinoma is around 10 months if treated with standard of care.

Figure 1. Schematic representation of survival data from different studies in cholangiocarcinoma. Red: FIGHT-202. Dark yellow: prospective studies. Light yellow: retrospective data (small numbers). CCA: cholangiocarcinoma. iCCA: intrahepatic CCA.



Key issue 2: The evidence about the efficacy of pemigatinib is for a subset of the specified population.	The efficacy of Pemigatinib is for FGFR2-fused cholangiocarcinoma. It implies that cholangiocarcinoma patients will need to be tested to understand which ones are suitable to this new drug. Test would be indicated in all cholangiocarcinoma patients to select those which are candidates, as FGFR2 fusion could be identified also in non-intrahepatic cholangiocarcinoma (2%). I would personally advise to extend the genomic testing to all biliary cancers as at the advanced stage is often difficult to identify the subtype of cholangiocarcinoma, as well as differentiate an intrahepatic cholangiocarcinoma from a gallbladder cancer. It is frequent that the epicentre of the mass is not localized and thus difficult to establish if it developed as intrahepatic cholangiocarcinoma and invaded gallbladder or arose from gallbladder and invaded the liver.
Key issue 3: There is a lack of any kind of evidence about the efficacy and safety of the comparator (systemic chemotherapy or BSC), in the specified population: a) The proportion of patients in, the main comparator study, with FGFR2 fusions/rearrangements	FIGHT-202 study is a single arm, phase II trial and lacks direct comparison. Please see reply to key issue 1 to put data from FIGHT-202 into contest. With regards to safety, toxicity profile of Pemigatinib was more manageable in a cross-study comparison. Personal experience with the use of mFolfox confirms that toxicity comes mainly from neutropenia and complications of central venous access, which are not present in Pemigatinib (please see PART 1 for details). Data on survival of intrahepatic cholangiocarcinoma and how they compare to FIGHT-202 trial data are presented in Figure 1.

was not reported, but estimated to be low. b) There were relatively few patients in the comparator studies who had intrahepatic cholangiocarcinoma (iCCA), compared to the pemigatinib study (FIGHT-202) where 98% of patients had iCCA.	
Key issue 4: The indirect evidence about the comparative efficacy of pemigatinib vs SOC is weak; the estimate of relative treatment effect in the model was based on an unanchored	Please see figure 1 for indirect comparison..

matched adjusted indirect comparison (MAIC) analysis between these two mismatched trials.	
Key issue 5: There is a lack of evidence about the comparative safety of pemigatinib vs SOC.	Direct comparison lacks because FIGHT-202 is not a randomized prospective trial. However, Pemigatinib was well tolerated with a manageable toxicity profile. Reported side effects included only one case of grade 4 toxicity. Most frequent toxicity included: -hypophosphatemia occurred in 33% of cases (grade 3 only in 7%). However, it was mild in the majority requiring only oral supplement. No grade 4 hypophosphatemia (with need for prompt intravenous therapy) were recorded. -stomatitis (grade 3 in only 5% of patients). Main side effects of standard of care mFolfox include neutropenia (reduction of neutrophils with increased risk of infection), which caused hospital admission in 12% of patients in the ABC06 trial; infection with admission in 19% of cases and fatigue in 19% of cases.
Key issue 6: It is not clear that pemigatinib meets the NICE end-of-life criteria	Yes, chemorefractory cholangiocarcinoma patients in absence of FGFR2-targeted therapy (such as Pemigatinib) have a life expectancy ranging between 4.7 to 10 months.
Key issue 7: It is not clear that all relevant	The relevant comparators as currently recommended in routine clinical practice include: mFolfox and Active Symptomatic Control (as detailed in PART 1). No other treatments have proven efficacy in this setting nor are used as standard of care in this setting.

comparators have been included in the cost effectiveness model.	
Key issue 8: The selection of the parametric curve for overall survival (OS) for pemigatinib.	I have no expertise to comment on this.
Key issue 9: The method used to extrapolate time on treatment (ToT).	I have no expertise to comment on this.
Key issue 10: There was no attempt by the company to conduct a MAIC analysis for adverse events (AEs). Therefore, the rates of AEs across the studies	I have no expertise to comment on this.

and their relevant populations remain unadjusted.	
Key issue 11: Health-related quality of life (HRQoL) was not measured using the EQ-5D in FIGHT-202 and had to be mapped from EORTC-QLQ-C30 data to EQ-5D-3L utilities using a published mapping algorithm.	Impact on quality of life can be related to: -better symptomatic control (due to higher partial responses with Pemigatinbn and thus activity on mass-induced symptoms) -longer life expectancy -less toxicities with reduced hospitalization from chemotherapy-induced neutropenia -absence of intravenous administration for Pemigatinib that is given as an oral treatment at home. Please see PART 1 for detailed comments on quality of life.
Key issue 12: The company base case model did not include wastage costs or the costs of genetic testing.	I have no expertise to comment on this.

Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Pemigatinib has been associated to a response rate of 36% and a median overall survival of 21.1 months since starting of the first dose.
- It is expected that overall survival ranges between 6 and 10 months for advanced chemo-refractory cholangiocarcinoma patients (without or with FGFR2 fusion) with the current standard of care.
- Tolerability favours Pemigatinib over current standard of care
- Analysis of cost/efficacy needs to include need of genomic testing, absence of intravenous administration, and impact on quality of life.
- As today, I believe it is unethical to run a phase III prospective trial for chemorefractory advanced FGFR2-fused cholangiocarcinoma patients offering ASC or mFoflox to these patients.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

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

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Tuesday 8 December 2020**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations and current treatment options	
About you	
1. Your name	**Maria Hawkins**
2. Name of organisation	**University College London**
3. Job title or position	**Professor in Radiation Oncology UCL, honorary Consultant Clinical Oncology, UCLH**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No disclosures to make**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The setting is second line treatment in locally advanced cholangiocarcinoma. In the 1st line setting the survival projections made at the time are about 11 mo, and as these patients have advanced cancer diagnosis, the prognosis is even poorer. The main aim of the treatment is to achievel progression free survival and maintain liver function and QoL by stopping disease progression
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	In this setting achieving stable disease or response (using RECIST criteria) are of clinical significance, as these maintain liver function

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	As the survival is so poor there is a high unmet clinical need for effective treatments of advanced/metastatic biliary tract cancers, especially after progression on first-line chemotherapy.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	The current NHS treatment options are as follows: For patients unfit for systemic treatment: active symptom control (including biliary drainage, antibiotics, analgesia, steroids, and antiemetics) For patients with good performance status and able to receive systemic treatment : with FOLFOX and active symptom control clinical trial entry if fit and trials available
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes : NCCN guidelines, ESMO guidelines, Italian practice guidelines for cholangiocarcinoma
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathways is well defined (as described above) and there is high concordance in clinical care that the treatment options outlined above are what are followed

• What impact would the technology have on the current pathway of care?	The technology would offer a clinically meaningful option for better disease free survival to a subgroup of patients that have disease harbouring the molecular characteristics
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, I believe the technology pemigatinib will be used in patient with tumour with FGFR alterations
• How does healthcare resource use differ between the technology and current care?	In addition to current standard there is a requirement for molecular profiling of the tumour to confirm the presence of the FGFR alterations.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This technology will be used in specialist oncology clinics, usually in cancer centres
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There is the need for molecular profiling for all tumours
13. Do you expect the technology to provide clinically meaningful	Yes, form the data presented there is a clinically meaningful progression free survival – the progression free survival to unselected systemic FOLFOX was 3 mo (ABC06 study) whilst with pemigatinib the median PFS was about 6 mo

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes it is likely that survival could be increased
• Do you expect the technology to increase health-related quality of life more than current care?	Yes it is likely that qoL will be improved
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	FGFR alterations are required for the technology to be effective.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	The administration and fitness to receive treatment are same level as other systemic treatments, so same to use

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes additional thest required: molecular characterization of tumour. This might involve another tumour biopsy if historical samples are inadequate for molecular analysis.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Not sure
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes, the technology appears to have significant effects in length of disease control (~double compared to other interventions) and possible survival.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, in the patients with FGFR molecular alterations will change outcomes
• Does the use of the technology address any particular unmet need of the patient population?	Yes , the technology offers the opportunity for personalised , precision medicine
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Approximately 64% of patients had grade 3 or worse adverse events. The most frequent grade 3 or worse adverse events (irrespective of cause) were hypophosphataemia (18 [12%]), arthralgia (nine [6%]), stomatitis (eight [5%]), hyponatraemia (eight [5%]), abdominal pain (seven [5%]), and fatigue (seven [5%]), a large number of patinets had nail changes. All these might affect qoL
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes , patients screened and then treated are representative of the current clinical practice

• If not, how could the results be extrapolated to the UK setting?	n/a
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS- (yes), OS (yes) toxicities (yes) qoL(no)
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not used
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The technology is too recent to comment
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
22. Are you aware of any new evidence for the comparator treatment(s)?	no

23. How do data on real-world experience compare with the trial data?	The trial data is representative of the real world population
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	The need for molecular testing being available to cholangiocarcinoma population
24b. Consider whether these issues are different from issues with current care and why.	Currently molecular testing not available as standard of care
Topic-specific questions	
25. NICE scope defined the population as 'advanced cholangiocarcinoma with FGFR2 fusion or rearrangement'. In FIGHT-202, majority of the patients (98%) had intrahepatic cholangiocarcinoma. Is the	Agree with definition. FIGHT-202 population is representative.

population in FIGHT-202 representative of the population defined in NICE scope?	
26. In your opinion: a. Are the comparators included sufficient and appropriate for this appraisal? i.e: • Active symptom control (ASC) • 5-fluorouracil + oxaliplatin + folic acid (mFOLFOX) + ASC b. Are there any other comparators that you consider relevant for this appraisal?	a. Yes , comparators are appropriate and sufficient as these are the current standard on the best randomised evidence available in this condition b. No, not to my knowledge

27. Is FGFR genetic testing part of routine clinical practice? If so, how often is FGFR genetic testing carried out in routine clinical practice. What are the cost implications of FGFR genetic testing?	No, currently not available, will have to be costed and implemented. Cost of the genetic testing depends on the technology used and the potential additional need to have another tissue biopsy.
28a. What is the life expectancy of people with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations in current clinical practice without pemigatinib? 28b. By how long, if any, do you expect pemigatinib to extend life at the end of life compared with current clinical practice without pemigatinib?	a. Expected survival is about 6 months b. Looking at the FIGHT-202 the median survival is 21 mo, therefore it appears thatsurvival could be increased by 1 year.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: There is a lack of direct evidence about the comparative efficacy and safety of pemigatinib vs standard of care (SOC), defined as systemic chemotherapy or BSC, in the specified population.	Agree , the FIGHT 202 trial was not randomised or blinded to the intervention, however it targeted the selected population with the FGFR alterations that Pemigatinib targets
Key issue 2: The evidence about the efficacy of	Yes, this is an example of correct application of personalised medicine, treating selected population where the correct molecular alteration is present.

pemigatinib is for a subset of the specified population.	
Key issue 3: There is a lack of any kind of evidence about the efficacy and safety of the comparator (systemic chemotherapy or BSC), in the specified population: a) The proportion of patients in, the main comparator study, with FGFR2 fusions/rearrangements was not reported, but estimated to be low. b) There were relatively few patients in the comparator studies who had intrahepatic cholangiocarcinoma (iCCA), compared to the pemigatinib	The target population is representative of the cholangiocarcinoma population that we are treating, the intrahepatic cholangiocarcinoma are a subgroup. This is a rare cancer, and it is difficult to undertake comparative studies in subpopulations unless a strong rationale to do so

study (FIGHT-202) where 98% of patients had iCCA.	
Key issue 4: The indirect evidence about the comparative efficacy of pemigatinib vs SOC is weak; the estimate of relative treatment effect in the model was based on an unanchored matched adjusted indirect comparison (MAIC) analysis between these two mismatched trials.	I am unable to
Key issue 5: There is a lack of evidence about the comparative safety of pemigatinib vs SOC.	

Key issue 6: It is not clear that pemigatinib meets the NICE end-of-life criteria	Agree, uncertain to conclude
Key issue 7: It is not clear that all relevant comparators have been included in the cost effectiveness model.	I think all appropriate comparators have been included.
Key issue 8: The selection of the parametric curve for overall survival (OS) for pemigatinib.	? overestimate overall survival
Key issue 9: The method used to extrapolate time on treatment (ToT).	
Key issue 10: There was no attempt by the company to conduct a MAIC analysis for adverse events (AEs). Therefore, the rates of AEs	Agree this should be considered

across the studies and their relevant populations remain unadjusted.	
Key issue 11: Health-related quality of life (HRQoL) was not measured using the EQ-5D in FIGHT-202 and had to be mapped from EORTC-QLQ-C30 data to EQ-5D-3L utilities using a published mapping algorithm.	Agree, weakness of the FIGHT 202 study, and the mapping algorithm might be misrepresenting
Key issue 12: The company base case model did not include wastage costs or the costs of genetic testing.	Agree, the whole population that needs to be tested should be included
Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Pemigatinib should be considered as a treatment option in previously treated patients with cholangiocarcinoma who have FGFR2 fusions or rearrangements.
    - Molecular testing is key to identify the patients who have the molecular alteration that would benefit of treatment with pemigatinib
    - Finding effective treatments is an area of unmet need in cholangiocarcinoma
    -
    -

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

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

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Tuesday 8 December 2020**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations and current treatment options	
About you	
1.Your name	**Helen Morement**
2. Are you (please tick all that apply):	☐ a patient with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations? √ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	AMMF – The Cholangiocarcinoma Charity
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) √ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement √ Yes, I authored / was a contributor to my nominating organisations submission √ I agree with it and **do not wish to** complete this statement

	☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations? If you are a carer (for someone with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations) please share your experience of caring for them.	

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of **current NHS treatments** for relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations (for example how pemigatinib is given or taken, side effects of treatment etc) please describe these	
Advantages of this treatment	
9a. If there are advantages of pemigatinib over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your	

ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does pemigatinib help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	
Disadvantages of this treatment	
10. If there are disadvantages of pemigatinib over current treatments on the NHS please describe these? For example, are there any risks with pemigatinib? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	

Patient population	
11. Are there any groups of patients who might benefit more from pemigatinib or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
Equality	
12. Are there any potential equality issues that should be taken into account when considering relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations and pemigatinib? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race,	

religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14a. Are the comparators (the current treatment available in the NHS) in the company submission used in the NHS for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations? 14b. Is the assessment tool used in the clinical trial appropriate for assessing the severity of this condition? 14c. What are the main benefits of this treatment for patients? If there are several	

benefits please list them in order of importance. Are there any benefits of this treatment that have not been captured? d. What are the benefits of this treatment for carers?	
Key issue 1: There is a lack of direct evidence about the comparative efficacy and safety of pemigatinib vs standard of care (SOC), defined as systemic chemotherapy or BSC, in the specified population.	
Key issue 2: The evidence about the efficacy of pemigatinib is for a subset of the specified population.	

Key issue 3: There is a lack of any kind of evidence about the efficacy and safety of the comparator (systemic chemotherapy or BSC), in the specified population: a) The proportion of patients in, the main comparator study, with FGFR2 fusions/rearrangements was not reported, but estimated to be low. b) There were relatively few patients in the comparator studies who had intrahepatic cholangiocarcinoma (iCCA), compared to the pemigatinib study (FIGHT-202) where 98% of patients had iCCA.	
Key issue 4: The indirect evidence about the comparative efficacy of pemigatinib vs SOC is weak;	

the estimate of relative treatment effect in the model was based on an unanchored matched adjusted indirect comparison (MAIC) analysis between these two mismatched trials.	
Key issue 5: There is a lack of evidence about the comparative safety of pemigatinib vs SOC.	
Key issue 6: It is not clear that pemigatinib meets the NICE end-of-life criteria	
Key issue 7: It is not clear that all relevant comparators have been included in the cost effectiveness model.	

Key issue 8: The selection of the parametric curve for overall survival (OS) for pemigatinib.	
Key issue 9: The method used to extrapolate time on treatment (ToT).	
Key issue 10: There was no attempt by the company to conduct a MAIC analysis for adverse events (AEs). Therefore, the rates of AEs across the studies and their relevant populations remain unadjusted.	
Key issue 11: Health-related quality of life (HRQoL) was not measured using the EQ-5D in FIGHT-202 and had to be mapped from EORTC-QLQ-	

C30 data to EQ-5D-3L utilities using a published mapping algorithm.	
Key issue 12: The company base case model did not include wastage costs or the costs of genetic testing.	
15. Are there any important issues that have been missed in ERG report?	
PART 3 -Key messages	
16. In up to 5 sentences, please summarise the key messages of your statement: • • • • •	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

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

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Tuesday 8 December 2020**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations and current treatment options	
About you	
1.Your name	**Andrea Sheardown**
2. Are you (please tick all that apply):	☐ a patient with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations? ☐ a patient organisation employee or volunteer? ☒ other (please specify): I am a Cholangiocarcinoma patient that had a successful Liver Resection in November 2015, followed by 6 months of Chemotherapy.
3. Name of your nominating organisation.	AMMF – The Cholangiocarcinoma Charity
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission

	☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations? If you are a carer (for someone with relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations) please share your experience of caring for them.	I have no direct experience with the FGFR2 alteration, because at the time of my own diagnosis of Intrahepatic Cholangiocarcinoma (CCA) in October 2015 there was limited information available. It was a very traumatic experience to even get to the stage of diagnosis with the lack of expertise in this field at a local hospital. The symptoms I had been displaying were misread as indigestion or muscle strain, even my blood tests were all normal. I was only 44 when diagnosed with CCA, I had been living a healthy lifestyle and always been physically active, so when I was initially given the devastating news that I had just weeks to live it was a huge shock to us all. Thankfully, I managed to push for a 2nd opinion from the team of Liver Specialists at The Queen Elizabeth Hospital in Birmingham and successfully managed to undergo a resection in November 2015 to remove the large tumour from my liver.

	With no clear treatment pathways available following my surgery, we were left with no other viable option than to seek a private consultation with a CCA specialist. Through this private referral I was then able to go on to have a 6-month course of Capecitabine chemotherapy. I was hospitalised 3 times over the 6 months due to some of the adverse side effects from this treatment. If at this stage, I had been able to have had the Molecular Profiling to determine the molecular mutations of my tumour, my treatment could have been quite different. There is a high probability of my cancer returning, so new targeted therapy treatments like pemigatinib are critical to CCA patients like me going forward.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	7a. Currently CCA patients here in the UK are left with limited options if they are unable to have a resection. With the lack of current treatment pathways, patients find it exceedingly difficult to get referred to a CCA specialist soon enough for any effect treatment. Within the NHS many CCA patients like me are forced to seek private alternatives. If surgery is not an option, patients are instead offered a chemotherapy combination, which has not changed in a number of years and has had extremely limited success. This treatment which may or may not extend life, often leaves patients with a diminished quality of life, and has a huge impact on both the patient and their families/carers. Without Molecular profiling and more targeted treatment therapies like those available in other countries, CCA patients here in the UK will always face an uncertain future. 7b. I am not alone with my frustrations on these limited treatment options available to CCA patients here in the UK. I participate regularly on the online forum 'Cholangiocarcinoma Support (UK & Europe)' and these same views and concerns

	are echoed across this forum too. CCA is still referred to as a cancer affecting the over 65's. However recent evidence has confirmed that CCA is increasing across all age groups and especially those classed in there 'prime of life'. This point is also echoed on the forums too.
8. If there are disadvantages for patients of **current NHS treatments** for relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations (for example how pemigatinib is given or taken, side effects of treatment etc) please describe these	I have not had direct experience of using pemigatinib as part of my own treatment plan. The main disadvantage to CCA patients here in the UK is the lack of Molecular Profiling at diagnosis. To identify someone displaying this FGFR2 alteration you need a tumour sample. This can only be obtained from either a resection or biopsy, which for many patients ends up not being possible due to the late stage in their diagnosis. With limited treatments options available for CCA, those patients unable to have a resection must put themselves through gruelling chemotherapy with no guarantees of extending their life and this can have a huge impact on the quality of life to both the patient and family.
Advantages of this treatment	
9a. If there are advantages of pemigatinib over current treatments on the NHS, please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others?	9a. Advantages of this treatment to patients displaying this FGFR2 alteration could be life changing. If molecular profiling identifies the FGFR2 fusion, then the targeted therapy pemigatinib could offer a lifeline to these patients in comparison to the huge side effects from the alternative chemotherapy treatments. Their treatment could mean less time in the hospital and allow patients to be with their families at the same time as receiving treatment, reducing the burden on the

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does pemigatinib help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	NHS. It would allow their quality of life to be improved from being able to spend time with their families and possibly even continue with their daily activities. 9b. Molecular Profiling is needed for all CCA patients at the time of diagnosis to enable the use of more targeted therapies like pemigatinib in a timely manner, resulting in potentially more lives being saved. 9c. Pemigatinib would give CCA patients with the FGFR2 fusion the chance of a targeted treatment plan and pave the way for other similar targeted therapies for those diagnosed with CCA.
Disadvantages of this treatment	
10. If there are disadvantages of pemigatinib over current treatments on the NHS please describe these? For example, are there any risks with pemigatinib? If you are concerned about any potential side affects you have heard about, please describe them, and explain why.	I have not had direct experience of pemigatinib, the main issue is the time factor in diagnosing someone with CCA early enough for them to be considered for this treatment.
Patient population	
11. Are there any groups of patients who might benefit more from pemigatinib or any who may benefit less? If so, please describe them and explain why.	All patients that are diagnosed early enough with CCA and able to have a biopsy to confirm their molecular mutations could benefit from this targeted treatment if presenting the FGFR2 alterations.

Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
Equality	
12. Are there any potential equality issues that should be taken into account when considering relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations and pemigatinib? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	

More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	In order for any CCA patient to know if this treatment or that of any other potential targeted therapy could be applicable to them, molecular profiling would need to be available for all CCA patients at diagnosis.

PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.

14a. Are the comparators (the current treatment available in the NHS) in the company submission used in the NHS for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations? 14b. Is the assessment tool used in the clinical trial appropriate for assessing the severity of this condition? 14c. What are the main benefits of this treatment for patients? If there are several benefits please list them in order of importance. Are there any benefits of this treatment that have not been captured?	

d. What are the benefits of this treatment for carers?	
Key issue 1: There is a lack of direct evidence about the comparative efficacy and safety of pemigatinib vs standard of care (SOC), defined as systemic chemotherapy or BSC, in the specified population.	
Key issue 2: The evidence about the efficacy of pemigatinib is for a subset of the specified population.	
Key issue 3: There is a lack of any kind of evidence about the efficacy and safety of the comparator (systemic chemotherapy or BSC), in the specified population:	

a) The proportion of patients in, the main comparator study, with FGFR2 fusions/rearrangements was not reported, but estimated to be low. b) There were relatively few patients in the comparator studies who had intrahepatic cholangiocarcinoma (iCCA), compared to the pemigatinib study (FIGHT-202) where 98% of patients had iCCA.	
Key issue 4: The indirect evidence about the comparative efficacy of pemigatinib vs SOC is weak; the estimate of relative treatment effect in the model was based on an unanchored matched adjusted indirect comparison (MAIC) analysis	

between these two mismatched trials.	
Key issue 5: There is a lack of evidence about the comparative safety of pemigatinib vs SOC.	
Key issue 6: It is not clear that pemigatinib meets the NICE end-of-life criteria	
Key issue 7: It is not clear that all relevant comparators have been included in the cost effectiveness model.	
Key issue 8: The selection of the parametric curve for overall survival (OS) for pemigatinib.	

Key issue 9: The method used to extrapolate time on treatment (ToT).	
Key issue 10: There was no attempt by the company to conduct a MAIC analysis for adverse events (AEs). Therefore, the rates of AEs across the studies and their relevant populations remain unadjusted.	
Key issue 11: Health-related quality of life (HRQoL) was not measured using the EQ-5D in FIGHT-202 and had to be mapped from EORTC-QLQ-C30 data to EQ-5D-3L utilities using a published mapping algorithm.	

Key issue 12: The company base case model did not include wastage costs or the costs of genetic testing.	
15. Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Incidence of CCA is increasing across all age groups, especially those groups deemed in their 'Prime of life'.
- It is exceedingly difficult to diagnose CCA accurately and in a timely manner for treatment, with those treatment options currently being extremely limited.
- There is a lack of centres of expertise for CCA patients, resulting in many patients losing their lives before undergoing any form of treatment plan.
- Molecular Profiling is critical to the future of CCA patients and needs to be offered at the time of diagnosis or 1st line treatments.
- For CCA patients that are found to have an FGFR fusion, pemigatinib offers a realistic treatment, extending survival with good quality life.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

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Technical engagement response form

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

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **by 5pm on Tuesday 8 December 2020**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement 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.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	**Does this response contain new evidence, data or analyses?**	Response
Key issue 1: There is a lack of direct evidence about the comparative efficacy and safety of pemigatinib vs standard of care (SOC), defined as systemic chemotherapy or BSC, in the specified population.	Yes	Although it is accepted there are no direct comparisons with standard of care, the data presented are consistent with those for similar drugs currently undergoing evaluation in clinical studies, namely futibatinib, [1] infigratinib[2] and derazantinib[3]. The data are all demonstrate a remarkably consistent progression free survival of approximately 7 months independent of the line of therapy.
Key issue 2: The evidence about the efficacy of pemigatinib is for a subset of the specified population.	No	
Key issue 3: There is a lack of any kind of evidence about the efficacy and safety of the comparator (systemic chemotherapy or BSC), in the specified population: a) The proportion of patients in, the main comparator study, with FGFR2 fusions/rearrangements was not reported, but estimated to be low.	Yes	The ABC-06 study did not report efficacy or safety in an FGFR2 fusion population as these analyses have yet to be done however the genomic data do not suggest that FGFR2 fusion patients would behave any differently to non-FGFR2 fusion patients. This statement is complication by the potential genomic heterogeneity in the larger population. [4]

b) There were relatively few patients in the comparator studies who had intrahepatic cholangiocarcinoma (iCCA), compared to the pemigatinib study (FIGHT-202) where 98% of patients had iCCA.		
Key issue 4: The indirect evidence about the comparative efficacy of pemigatinib vs SOC is weak; the estimate of relative treatment effect in the model was based on an unanchored matched adjusted indirect comparison (MAIC) analysis between these two mismatched trials.	No	
Key issue 5: There is a lack of evidence about the comparative safety of pemigatinib vs SOC.	No	
Key issue 6: It is not clear that pemigatinib meets the NICE end-of-life criteria	Yes	The median overall survival from ABC-02 and FIGHT-202 are 11.7 months and 21.1 months. It is accepted that these data are difficult to interpret because they include patients at different stages of their disease process.
Key issue 7: It is not clear that all relevant comparators have been included in the cost effectiveness model.	No	
Key issue 8: The selection of the parametric curve for overall survival (OS) for pemigatinib.	No	

Key issue 9: The method used to extrapolate time on treatment (ToT).	No	
Key issue 10: There was no attempt by the company to conduct a MAIC analysis for adverse events (AEs). Therefore, the rates of AEs across the studies and their relevant populations remain unadjusted.	No	
Key issue 11: Health-related quality of life (HRQoL) was not measured using the EQ-5D in FIGHT-202 and had to be mapped from EORTC-QLQ-C30 data to EQ-5D-3L utilities using a published mapping algorithm.	No	
Key issue 12: The company base case model did not include wastage costs or the costs of genetic testing.	No	

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: **Genomic complexity**	B.3.2.1	Yes	Our experts believe the ERG have not given full consideration for the variability and complexity of the genomics. Full consideration needs to be taken of the complexity of the possible genomic outputs (fusion and rearrangements). All of these reflect the promiscuity of FGFR2 fusions and the need for expertise when interpreting profiling reports.
Additional issue 2: **Testing requirement**	B.3.2.1	Yes	RNA as well as DNA testing will be required by the GLH's to fully capture the responsive population. £550 is a bit on the low side for the pair.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

1. Goyal L, Meric-Bernstam F, Hollebecque A, et al. FOENIX-CCA2: A phase II, open-label, multicenter study of futibatinib in patients (pts) with intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 gene fusions or other rearrangements. Journal of Clinical Oncology 2020;38:108-.
2. Javle M, Lowery M, Shroff RT, et al. Phase II Study of BGJ398 in Patients With FGFR-Altered Advanced Cholangiocarcinoma. Journal of Clinical Oncology 2018;36:276-82.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **by 5pm on Tuesday 8 December 2020**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement 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.

About you

Your name	**Shevani Naidoo**
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.	**N/A**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG comment
Key issue 1: There is a lack of direct evidence about the comparative efficacy and safety of pemigatinib vs standard of care (SOC), defined as systemic chemotherapy or BSC, in the specified population.	**No**	The company acknowledges the concerns raised by the evidence review group regarding the comparative efficacy and safety of pemigatinib versus standard of care in the specified patient population. However, the available evidence base has been systematically reviewed and the evidence supporting this appraisal reflects the best available evidence at the time the company dossier was submitted. The company has strived to provide robust data for pemigatinib in the context of a clinical setting where current treatments provide limited benefit, for patients with a rare disease (cholangiocarcinoma) and an infrequent molecular alteration (FGFR2 fusions/rearrangements), and hence, only limited data are available for other treatment options. The uncertainty that results from the lack of direct	The ERG does not consider that this response addresses the concerns outlined in key issue 1. Furthermore, the ERG does not consider that the ongoing RCT referred to in the response: *'FIGHT-302, a phase III trial investigating pemigatinib versus chemotherapy in patients with unresectable or metastatic cholangiocarcinoma with FGFR2 rearrangement, is expected to provide evidence on the comparative efficacy and safety of pemigatinib versus standard of care in previously untreated patients'* will resolve the uncertainty with respect to the comparative efficacy of pemigatinib in previously treated patients. The ERG does not consider that evidence about the relative efficacy of pemigatininb in previously un-treated patients can be applied to questions about the relative efficacy of pemigatinib in previously treated patients with relapsed or refractory disease.

		evidence for comparative efficacy is directly linked to the rarity of the disease being considered. Current estimates suggest that approximately 25 patients will be eligible for treatment in 2020. Therefore, the level of uncertainty and challenges associated with evidence generation should be viewed within the context of the prevalence of the disease. If a confirmatory trial were to be conducted in the same setting, the study population of the confirmatory trial would have to be restricted to ≥ third-line due to these patients having access to pemigatinib as a commercially available treatment, and this would greatly impact accrual of the trial (Pemazyre™ received FDA approval in the same indication on 17 APR 2020). Fewer than 50% of patients get second-line therapy due to the dismal prognosis. In a first-line trial, 100% of patients will have the chance to be treated with a targeted drug. Of note, in ABC-06 only 14% of patients received ≥ third line of therapies, which only reinforces the difficulties in accrual that this study would face. [4] Furthermore, other FGFR inhibitors are conducting compassionate use programs in the same previously treated population and their confirmatory studies in the first-line setting (futibatinib [NCT04093362] and infigratinib	

		[NCT03773302]), which would also impact accrual of a confirmatory study in the second-line setting. FIGHT-302, a phase III trial investigating pemigatinib versus chemotherapy in patients with unresectable or metastatic cholangiocarcinoma with FGFR2 rearrangement, is expected to provide evidence on the comparative efficacy and safety of pemigatinib versus standard of care in previously untreated patients.[1] This will help support the evidence in previously treated patients, resolving this uncertainty, and is expected to read out in 2026.	
Key issue 2: The evidence about the efficacy of pemigatinib is for a subset of the specified population.	**No**	The company agrees that the evidence for efficacy of pemigatinib is for a subset of the specified population (those with FGFR2 fusions/rearrangements) as pemigatinib is a potent and selective FGFR1, 2 and 3 inhibitor. However, it should be considered that FGFR2 fusions and rearrangements are found almost exclusively in cholangiocarcinoma (CCA) with the intrahepatic anatomical subtype.[2] This was also acknowledged by the ERG. In FIGHT-202, patients with non-intrahepatic disease were not excluded and one patient in the FGFR2 positive cohort (cohort A; n=107) had extrahepatic disease. There is no biological rationale that pemigatinib would not provide benefit to non-	As noted in our report, the ERG acknowledges that FGFR2 fusions and rearrangements are rare in patients with extrahepatic disease and notes the company's assertion that: *'There is no biological rationale that pemigatinib would not provide benefit to non- intrahepatic CCA patients with FGFR 2 fusion/rearrangements.'* However, it remains the case that there is a lack of evidence about the efficacy of pemigatinib in these patients.

		intrahepatic CCA patients with FGFR 2 fusion/rearrangements. It is important from an equity perspective that patients with other anatomical classifications of CCA (i.e. perihilar or distal, both of which are classified as extrahepatic CCA) are not excluded from receiving pemigatinib if they have a FGFR2 fusion or rearrangement. When consulted on molecular profiling, stakeholders (including health care professionals and patient groups) recommend that all CCA patients be molecularly assessed and not just those patients with intrahepatic disease.[3] Thus, the suitability of treatment with pemigatinib should be decided based on FGFR2 status and not anatomical subtype. Any consideration to the contrary could disadvantage patients who already have very limited treatment options available to them.	
Key issue 3: There is a lack of any kind of evidence about the efficacy and safety of the comparator (systemic chemotherapy or BSC), in the specified population:	**No**	The company acknowledges the concerns raised by the evidence review group regarding the lack of evidence of efficacy and safety for the comparator in the specified patient population. The available evidence base has been systematically reviewed and the dossier supporting this appraisal reflects the best available evidence at this time.	The ERG does not consider that this response addresses the concerns outlined in key issue 3. Please also see comments on response to key issues 1, with respect to the ongoing trial FIGHT-302.

a) The proportion of patients in, the main comparator study, with FGFR2 fusions/rearrangements was not reported, but estimated to be low. b) There were relatively few patients in the comparator studies who had intrahepatic cholangiocarcinoma (iCCA), compared to the pemigatinib study (FIGHT-202) where 98% of patients had iCCA.		In this context, the phase 3, randomized, second-line study in biliary tract cancer showed a median OS of 6.2 months with mFOLFOX (oxaliplatin/5-FU chemotherapy) vs 5.3 months for active symptom control (ABC-06).[4] Following recent clinical consultation, this study was still assessed as an appropriate and robust representation of standard of care in the UK in the absence of formalised treatment guidelines.[5, 6] At the time of this appraisal, the proportion of patients in the ABC-06 study with FGFR2 fusions/arrangements was not reported but Incyte understands that translational research (including molecular profiling) was a secondary endpoint of this study and this data would be made available in the future. The evidence review group acknowledged that ABC-06 included 44% of participants with intrahepatic cholangiocarcinoma making this study a relevant source for comparator data. Additionally, sub-group analyses by primary tumour site (intrahepatic, extrahepatic, gallbladder and cyst duct, ampulla) showed no significant differences in the primary outcome of overall survival. Additional studies were assessed to inform comparative effectiveness during the clarification process. Following review the ERG agreed that all the identified studies had limitations in matching the FIGHT 202 population.	

		As highlighted in issue 1 there are significant hurdles in delivery a confirmatory trial in the same setting. Issue 2 also gives context for the high proportion of patients with intrahepatic cholangiocarcinoma included in the FIGHT-202 study in comparison to studies of non-molecularly selected patients. FIGHT-302, a phase III trial investigating pemigatinib versus chemotherapy in patients with unresectable or metastatic cholangiocarcinoma with FGFR2 rearrangement, is expected to provide evidence on the comparative efficacy and safety of pemigatinib versus standard of care in previously untreated patients.[1] This will help support the evidence in previously treated patients, resolving this uncertainty, and is expected to read out in 2026.	
Key issue 4: The indirect evidence about the comparative efficacy of pemigatinib vs SOC is weak; the estimate of relative treatment effect in the model was based on an unanchored matched adjusted indirect comparison (MAIC) analysis	**Yes**	The company acknowledges that there are limitations to the use of a MAIC. However, based on the current data available (FIGHT-202, a single arm trial for the intervention), the most appropriate method of indirect treatment comparison has been performed and has followed the guidance set out NICE TSD 18.[7] The MAICs using ABC-06 have also been updated to reflect the latest FIGHT-202 data [redacted], see company additional evidence appendix). We believe there are no alternative methods that could be applied without additional data (rationale	The ERG notes, and agrees with the company's statement that: *'As such, we agree that the uncertainty surrounding this method of comparison is unresolvable at this time.'* The ERG acknowledges the receipt of the updated data for FIGHT-202, but notes that these additional data do not affect the concerns raised in key issue 4. Please also see comments on response to key issues 1, with respect to the ongoing trial FIGHT-302.

between these two mismatched trials.		for the limited data is discussed in issue 1), and there were no suggestions of alternative methods given in the evidence review group report. As such, we agree that the uncertainty surrounding this method of comparison is unresolvable at this time. Regarding the choice of trials, although we acknowledge there are differences between FIGHT 202 and ABC-06, we believe this is the most appropriate study and treatment for comparison based on the current evidence base, for this decision problem. Alternative studies were considered in response to the evidence review group questions, but these are subject to the same unresolvable limitations and additional differences. However, when further comparative efficacy data for the selected population become available in the future (such as that from FIGHT-302), the uncertainty in the relative efficacy of pemigatinib versus chemotherapy in FGFR2-selected patients can be reduced.	
Key issue 5: There is a lack of evidence about the comparative safety of pemigatinib vs SOC.	**Yes**	The company acknowledges the uncertainty of current estimates of comparative safety between pemigatinib and standard of care. However, as mentioned in issue 1, this is due to a lack of available evidence.	The ERG acknowledges the receipt of the updated data for FIGHT-202, but notes that these additional data do not affect the concerns raised in key issue 5. The ERG agree that the model results are not sensitive to AEs and therefore this issue is of limited importance to cost-effectiveness.

		In addition to the updated efficacy data from FIGHT 202 ([redacted]), safety data was also provided [redacted]. The safety profile of pemigatinib in FIGHT 202 continues to be consistent with that reported in the first analysis and maintains a positive benefit/risk ratio. In order to demonstrate that cost-effectiveness estimates are insensitive to comparative safety data, extreme value testing has been conducted, varying the modelled adverse events for the comparator to extreme lower and upper bounds. Using the updated company base case and increasing mFOLFOX+ASC (oxaliplatin/5-FU+active symptom control) and ASC adverse event rates by 100% resulted in a decrease to the incremental cost-effectiveness ratio of £352 and £482 for pemigatinib vs. mFOLFOX+ASC and ASC, respectively. By setting adverse event rates for mFOLFOX+ASC to 0 and keeping pemigatinib rates the same, a £353 and £482 increase in the incremental cost-effectiveness ratio was observed for pemigatinib vs. mFOLFOX+ASC and ASC, respectively (see Table 13 in the company additional evidence appendix).	

		This clearly demonstrates that while the comparative safety of treatments remains an important consideration, given that there are no other safety concerns associated with pemigatinib and that it does not influence the cost-effectiveness estimates, it should not be considered a key issue for decision making.	
Key issue 6: It is not clear that pemigatinib meets the NICE end-of-life criteria	**Yes**	There are no approved therapies for patients with advanced/metastatic cholangiocarcinoma who have progressed on at least 1 line of prior therapy. Chemotherapy, locoregional therapy, and targeted therapies have limited clinical activity in molecularly unselected populations. Overall survival estimates for comparators in the model are taken from molecularly unselected patients observed in the ABC-06 study. Since overall survival for the current standard of care in the target population is uncertain, it is argued that it is unclear whether pemigatinib meets the end-of-life criteria. An updated data cut from [redacted] for the FIGHT-202 study has been provided, which aims to reduce the uncertainty associated with long-term survival outcomes of patients treated with pemigatinib, but the uncertainty for comparator long-term survival remains. [redacted]	The ERG acknowledges the receipt of the updated data for FIGHT-202, but notes that these additional data do not fully address the concerns raised in key issue 6. Although the model results suggest that the criteria are met, the substantial unquantified uncertainties in the comparison of mismatched populations make it difficult to be certain that the end-of-life criteria have been met.

		[redacted] Although there is no conclusive answer regarding prognosis of FGFR2-rerranged cholangiocarcinoma, if there were any prognosis impact of this alteration, it is not expected that the overall response rate, duration of response, progression free survival, and median overall survival observed in this population with pemigatinib could be due to good prognosis of the disease alone. While further evidence generation is not possible to resolve this issue currently, the company has tested existing modelling assumptions using extreme values to help support decision makers in assessing whether pemigatinib meets the requisite end of life criteria. The economic model has a functionality to apply a hazard ratio to the comparator overall survival extrapolations, demonstrating the differences in any potential prognostic effects between FIGHT-202 and ABC-06, such as the prevalence of FGFR2 rearrangements. No adjustment was applied in the company base case, which is consistent with applying a hazard ratio of 1. A threshold analysis was conducted, with HR estimates (for wild-type	

		patients versus FGFR2 rearrangements) varied between 0.2 and 4 – considered to be far outside the plausible limits of any required adjustment (this was estimated as 1.54 and 1.77 from Jain et al.[8] data [inverse presented in Table 34, Section B.3.3.3 of the company submission]). At all levels, the mean total life years for comparators active symptom control (ASC) alone or oxaliplatin/5-FU (mFOLFOX) +ASC never rose above 24 months, rising to a maximum mean life expectancy of 21.61 months for mFOLFOX+ASC. In the same manner, mean incremental life year gains for pemigatinib versus mFOLFOX+ASC fell to a minimum value of 7.64 months at a hazard ratio of 4 (see Table 13 of the company additional evidence appendix). In addition, clinical opinion elicited at a recent clinical validation meeting was that pemigatinib in this indication clearly meets the NICE end-of-life criteria, despite uncertainty in comparative efficacy between pemigatinib and mFOLFOX+ASC.[5] By conducting the aforementioned analysis, it is clear that the end of life criteria for normal life expectancy less than 24 months and extension to life of greater than 3 months are consistently met, even when modelling assumptions and uncertainty are tested at their extreme limits.	

Key issue 7: It is not clear that all relevant comparators have been included in the cost effectiveness model.	**No**	The clinical experts consulted by the company stated that oxaliplatin/5-FU+active symptom control (mFOLFOX+ASC) is considered the standard of care for patients with previously treated cholangiocarcinoma, and in some circumstances clinicians may offer alternative regimens, which are better suited for patients who are not suitable for intravenous therapies. These alternative therapies are associated with worse outcomes, including additional safety concerns, with minimal cost savings due to the reduced need for IV administration. The clinical systematic literature review also failed to identify any published evidence for the alternative regimens suggested by clinicians (CAPOX –oxaliplatin/capecitabine) and therefore it was not feasible to include these regimens within the economic analysis. In response to evidence review group clarification questions, the evidence review group requested several additional MAIC analyses for comparators not considered to be standard of care by UK clinicians. These were completed and provided to the evidence review group at the clarification stage but have not been considered further. While clinical expert opinion sought by the company has stated that mFOLFOX+ASC is currently considered the UK standard of care for	The ERG note an additional technical response from a clinical expert, as well as the additional clinical validation performed by the company, which both state that mFOLFOX+ASC and ASC are the current standard practice for this population across the UK.[9, 10] Therefore, the ERG consider that these treatments do probably reflect standard practice, although it is not clear whether other treatments are sometimes provided. The ERG acknowledge that the company provided MAICs for other potential comparators in their response to clarification.[11] However, given that these analyses suffer from the same uncertainties as the existing comparisons in the model relating to performing MAIC analysis on populations which do not match the population who will receive pemigatinib in clinical practice, they were not thought to resolve any further uncertainty in the model.

		this indication[5, 6], the company would welcome further clinical input on this issue from any clinicians advising NICE.	
Key issue 8: The selection of the parametric curve for overall survival (OS) for pemigatinib.	**Yes**	Additional follow up for pemigatinib overall survival data is provided in response to technical engagement, consisting of an updated datacut from the FIGHT-202 study ([redacted]). Details of the data-cut and updated survival analysis are provided separately in the company additional evidence appendix. The additional follow up reduces uncertainty of long-term survival outcomes for patients treated with pemigatinib, and further clinical validation supports the use of the log-logistic distribution in the base case analysis since it predicts a decline in the predicted hazard over time that is consistent with the published literature.[5, 12] Based on the updated FIGHT-202 data survival analysis, the company consider the log-logistic extrapolation to be the most appropriate for overall survival, considering the visual and statistical fit and clinical plausibility of the shape and pattern of long-term hazards.	The ERG has considered the updated overall survival analyses in their addendum which accompanies this response.
Key issue 9: The method used to extrapolate time on treatment (ToT).	**Yes**	Similarly to issue 8, updated analysis of time on treatment extrapolations has been provided using the updated data cut from FIGHT-202, presented in the company additional evidence appendix.	The ERG has considered the updated time on treatment analyses in their addendum.

		Extrapolations are consistent with previously provided clinical expert opinion. Due to the similarity between extrapolations and their visual and statistical fit, the company base has been revised to use the distribution preferred by the evidence review group (Weibull), due to its proximity to estimates from clinical opinion.[5, 6]	
Key issue 10: There was no attempt by the company to conduct a MAIC analysis for adverse events (AEs). Therefore, the rates of AEs across the studies and their relevant populations remain unadjusted.	**No**	The company acknowledges that a MAIC analysis for AEs may have provided more accurate estimates of comparative safety between pemigatinib and standard of care. However, as discussed for efficacy, MAIC analyses are not without limitations. The company has presented a naïve comparison of treatment safety, using the publicly available data from ABC-06, and in response to issue 5, additional scenario analyses have been conducted to demonstrate the negligible impact of AE rates on the incremental cost-effectiveness ratios for pemigatinib versus standard of care.	The ERG does not consider that this response addresses the concerns outlined in key issue 10, but again note that AEs have very little impact on cost-effectiveness results.
Key issue 11: Health-related quality of life (HRQoL) was not measured using the EQ-5D in FIGHT-202 and had to be mapped from EORTC-QLQ-C30 data to EQ-5D-3L	**No**	In response to the approach used in the company's economic analysis, the evidence review group (ERG) responded with the following: *"However, given that EQ-5D data was unavailable, mapping is an appropriate alternative and the ERG agree with the company's selection of the Longworth et al. algorithm."* As such, it is the company's	The ERG can confirm that they agree with the company's mapping approach as the next best approach, given the lack of EQ-5D data. The ERG also welcomes the company's decision to use model 3 to estimate health state utility values (HSUVs) in their updated base-case, as it avoids the use of implausible HSUVs obtained from model 5 in the company's original base-case.

utilities using a published mapping algorithm.		understanding that the mapping methods used are not a key issue for this appraisal. Regarding the regression model used to inform health state utilities, in scenario analyses in the original submission, the impact of including a covariate for treatment state was tested and shown to have a limited impact on the ICER. In response to some of the ERGs comments, considering the implausible utility values and limited number of observations for the progression-free off-treatment health state, the company base case has been altered to reflect the ERG's preference for using "model 3", including covariates for baseline utility and progression status only. The company agree that having EQ-5D data would reduce uncertainty further and should this remain as an issue, EQ-5D data is being collected as part of the FIGHT-302 trial[1], reading out in 2026 albeit for previously untreated patients.	
Key issue 12: The company base case model did not include wastage costs or the costs of genetic testing.	**No**	The revised base presented in response to technical engagement includes wastage costs, as preferred by the evidence review group. The impact of the corresponding changes on the updated base case incremental cost-effectiveness ratio are described below.	For patients with cholangiocarcinoma, the 2020/2021 National Genomic Test Directory does not include testing for FGF/FGFR gene alterations.[15] Also, the website of the National Genomic Test Directory indicates that the genomic laboratory hubs are currently in a state of transition towards the full implementation of the

		The company considered the issue of testing and has worked to understand the current landscape in the NHS. The cost of genetic testing has not been included in the company base case because Incyte believes that testing is being integrated into routine care for specific cancers like cholangiocarcinoma (CCA). Molecular testing in cancer is becoming commonplace in the NHS and is currently carried out extensively in tumours such as non-small cell lung cancer and melanoma. The 2020/2021 National Genomic Test Directory specifies which genomic tests are commissioned by the NHS in England, the technology available to carry out the test, and the patients eligible to have access. CCA is already included in the Test Directory for the detection of a neurotrophic tyrosine receptor kinase (NTRK) rearrangement. This means treating oncologists can request this test if they wish to determine their patients' eligibility of an NTRK inhibitor. Indeed the guidance from NICE regarding entrectinib and larotrectinib state that they are recommended as an option for patients if 'they have no satisfactory treatment options'.[13, 14] There are no approved therapies for patients with advanced/metastatic CCA who have progressed on at least 1 line of prior therapy. Patients may receive chemotherapy or other regimens in second line, but these are not typically associated	National Genomic Test Directory and that some tests that are listed may not yet be available.[16] The lack of current genetic testing was confirmed by one of the clinical experts who provided a response to technical engagement stating that "no molecular profiling is currently recommended within the NHS for cholangiocarcinoma as chemotherapy activity is not dependent on the genomic characterization".[9] The ERG preferred base-case results are based on the assumption that no patients currently receive testing for FGF/FGFR gene alterations as part of routine clinical practice. A scenario was performed by the ERG that excludes the costs of genetic testing. The ERG considered their preferred assumptions to be in line with the final scope by NICE that indicates that the costs of testing for FGF/FGFR gene alterations should be included in the model for patients who would not otherwise have been tested and that a sensitivity analysis should be provided without these costs.

		with meaningful therapeutic outcomes and are generally regarded as having significant safety concerns. One would argue that these treatment options are less than 'satisfactory'. Therefore, given the recommendation for the NTRK inhibitors, metastatic CCA patients are likely to be eligible for the test to assess NTRK rearrangements. Genomic testing is not carried out in isolation for one target. Instead, a multi-gene panel is used to identify alterations across a range of genes of interest. Thus, when a biopsy sample is tested for the presence an NTRK rearrangement, the presence of alterations in other genes such as FGFR will automatically be identified. Incyte has not included the cost of genetic testing in the base case model because, as demonstrated above, genetic testing is not specific to the identification of FGFR2. Furthermore, it is already being carried out in the NHS for CCA patients to identify the presence of NTRK rearrangements and this process is likely to become routine clinical practice.	

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
No additional issues	N/A	N/A	N/A

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER vs.	
			mFOLFOX + ASC	ASC
Changes following ERG clarification	Following ERG clarification the company made two changes. Correction of the method used to calculate AE rates and application of age-adjustment for health state utilities.	NA	Company base case ICER before technical engagement: £57,467	Company base case ICER before technical engagement: £60,806
Key issue 11	The company base case previously used model 5 including covariates for baseline utility, progression status, treatment status and an interaction term progression status*treatment status.	In response to the ERGs suggestions, model 3 is now used which includes only covariates for baseline utility and progression status.	£57,685 + £218	£59,340 -£1,466
Key issue 12	The base case previously did not include the cost of wastage	The model now includes the cost of wastage consistent with patients receiving a pack of 14 tablets every 3 weeks.	£58,478 + £1,281	£62,067 +£1,261

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER vs.	
			mFOLFOX + ASC	ASC
Key issues 1, 8 and 9	The base case used FIGHT-202 data from the original (March-2019) data cut	Updated survival analysis for overall survival, progression-free survival and time on treatment have been conducted using an additional data cut with follow-up until [redacted]. In addition, MAIC analyses informing estimates of comparative efficacy have also been updated using the updated FIGHT-202 data. Parametric curves used in the updated based case remain consistent with the previous base case with the exception that the ERGs preference of the Weibull distribution for time on treatment is now used.	£55,852 -£1,615	£60,340 -£466
Company's preferred base case following technical engagement	The company's preferred base case includes the combined changes listed above.		**£56,386** **-£1,081**	**£58,963** **-£1,843**

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