Single Technology Appraisal

Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [ID6302]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [ID6302]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Taiho:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. AMMF – The Cholangiocarcinoma Charity - *endorsed by patient expert Helen Morement*
   b. Cholangiocarcinoma UK – *endorsed by clinical expert Professor John Bridgewater*
   c. Royal College of Pathologists

4. **Expert statements**
   a. Andrew Clay, patient expert, nominated by AMMF - The Cholangiocarcinoma Charity

5. **External Assessment Report** prepared by KSR

6. **External Assessment Report – factual accuracy check**

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

Futibatinib for Previously Treated Advanced Cholangiocarcinoma with FGFR2 Fusion or Rearrangement [ID6302]

Document B

Company evidence submission

February 2024

File name	Version	Contains confidential information	Date
ID6302_Futibatinib_CCA_Document B [CON]	V.1.1	Yes	23 February 2024

Contents

List of tables

List of figures

Abbreviations

CCA	Cholangiocarcinoma
5-FU	Fluorouracil
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
ALT	Alanine transaminase
ASC	Active symptom control
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BNF	British National Formulary
BOR	Best overall response
BSC	Best supportive care
BSG	British Society of Gastroenterology
CAD$	Canadian dollar
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CRF	Case report form
CSR	Clinical Study Report
CT	Computer tomography
dCCA	Distal cholangiocarcinoma
DCO	Data cut-off
DCR	Disease control rate
DOR	Duration of response
DSA	Deterministic sensitivity analyses
eCCA	Extrahepatic cholangiocarcinoma
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ VAS	EuroQol visual analogue scale
EQ-5D-3L	Euro-QoL-5 dimensions-3 levels
ESMO	European Society of Medical Oncology
ESS	Effective sample size
FGF	Fibroblast growth factor
FGFR2	Fusion growth factor receptor 2
FMI	Foundation Medicine, Inc.

GEM + CIS	Gemcitabine and cisplatin
GnRH	Gonadotropin-releasing hormone
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
INHB	Incremental net health benefit
IPD	Individual patient data
IRC	Independent review committee
ITC	Indirect treatment comparison
KM	Kaplan-Meier
LH-RH	Luteinising hormone-releasing hormone
LY	Life year
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MDT	Multidisciplinary team
mFOLFOX	Modified folinic acid, fluorouracil and oxaliplatin
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed model for repeated measures
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NT$	New Taiwan dollar
OCT	Optical coherence tomography
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
pCCA	Perihilar cholangiocarcinoma
PD	Progressive disease
PFS	Progression-free survival
PH	Proportional hazards
PPE	Palmar–plantar erythrodysesthesia
PR	Partial response
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analyses
PSM	Partitioned survival model

PSS	Personal Social Services
PSW	Propensity score weighting
QALY	Quality-adjusted life year
QD	Once daily
QOD	Every other day
QoL	Quality of life
QTcF	Fridericia's corrected QT interval
RCT	Randomised controlled trial
RDI	Recommended dosing intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RMST	Restricted mean survival time
SD	Stable disease
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
STC	Simulated treatment comparison
STM	State transition model
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
ToT	Time on treatment
TRAE	Treatment-related adverse event
UK	United Kingdom
US	United States
WHO	World Health Organisation
WTP	Willingness to pay

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.

Futibatinib is licenced by the Medicines and Healthcare products Regulatory Agency (MHRA) for treatment of adult patients with locally advanced or metastatic cholangiocarcinoma (CCA) with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy.[1]

The decision problem for this submission (Table 1) is for futibatinib for the treatment of adult patients with locally advanced or metastatic CCA with FGFR2 fusion or rearrangement that have progressed after at least one line of systemic therapy. This is consistent with the NICE final scope for this appraisal and any differences between the decision problem addressed within this submission and the NICE final scope are outlined in Table 1.

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	Adults with locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or rearrangement that has progressed after at least one prior systemic therapy	Adult patients with locally advanced or metastatic CCA with FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy	N/A
Intervention	Futibatinib	Futibatinib	N/A
Comparator(s)	• Pemigatinib • Modified FOLFOX regimen (folinic acid, fluorouracil and oxaliplatin) • Best supportive care (BSC)	Pemigatinib	Pemigatinib is the only targeted treatment recommended by NICE for the target population in the UK. UK clinical experts highlighted that patients known to have an FGFR2 fusion or rearrangement would receive pemigatinib in clinical practice, given the magnitude of the survival benefit for pemigatinib versus chemotherapy.[2] As such, chemotherapy or BSC are not considered to be relevant comparators to futibatinib in this appraisal
Outcomes	The outcome measures to be considered include: • Overall survival (OS) • Progression-free survival (PFS) • Response rates • Adverse effects of treatment • Health-related quality of life (HRQoL)	• Efficacy data ○ Objective response rate (ORR) ○ Duration of response (DOR) ○ PFS ○ OS ○ Disease control rate (DCR) • HRQoL data ○ European Organisation for Research and Treatment of	N/A

		Cancer Quality of Life Questionnaire (EORTC QLQ-C30) ○ Euro-QoL-5 dimensions-3 levels (EQ-5D-3L) ○ EuroQol visual analogue scale (EQ VAS) • Adverse event data	
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 (QALY). If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. 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 a National Health Service (NHS) and Personal Social Services (PSS) perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account. The availability and cost of biosimilar and generic products should be taken into account	As per the NICE reference case, cost-effectiveness is expressed in terms of incremental cost per QALY, and costs considered from the perspective of the NHS and PSS, with a lifetime horizon	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

Abbreviations: CCA: cholangiocarcinoma; DCR: disease control rate; DOR: duration of response; EORTC QLQ C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L: Euro-QoL-5 dimensions-3 levels; EQ VAS: EuroQol visual analogue scale; FGFR2: fibroblast growth factor receptor 2; HRQoL: health-related quality of life; N/A: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PFS: progression-free survival; ORR: objective response rate

B.1.2 *Description of the technology being evaluated*

A description of futibatinib is provided in Table 2 below.

Table 2: Technology being appraised

UK approved name and brand name	Futibatinib (Lytgobi®)
Mechanism of action	Futibatinib is a highly selective and covalently/irreversibly binding small-molecule inhibitor of FGFR1–4.[3, 4] FGFR aberrations have been shown to have oncogenic potential, and FGFR inhibition is therefore an important therapeutic target in CCA with a suitable genetic profile.[5] Futibatinib uses this therapeutic opportunity by blocking the adenosine triphosphate (ATP) binding pocket of FGFR1-4 irreversibly, which in turn results in the inhibition of FGFR-mediated signal transduction pathways, reduced tumour cell proliferation and increased cell death in tumours with FGFR1-4 genetic aberrations[3, 4, 6, 7]
Marketing authorisation/CE mark status	• A positive opinion from the Committee for Medicinal Products for Human Use (CHMP) was received on 26th April 2023[8] • Marketing authorisation approval from EMA was received in July 2023[8] • MHRA marketing authorisation was granted in August 2023[1]
Indications and any restriction(s) as described in the SmPC	• The EU and UK marketing authorisation wording for futibatinib in the indication of interest to this submission is: ○ *"Adult patients with locally advanced or metastatic CCA with FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy"* • Contraindications: hypersensitivity to the active substance or to any of the excipients[9]
Method of administration and dosage	• The dose for futibatinib in this indication is 20 mg of futibatinib to be taken orally once daily as a continuous therapy[9] • If a dose of futibatinib is missed by more than 12 hours or vomiting occurs after taking a dose, an additional dose should not be taken and treatment should be resumed with the next scheduled dose[9] • Treatment should be continued until disease progression or unacceptable toxicity[9] • In all patients, dietary restrictions that limit phosphate intake is recommended as part of hyperphosphatemia management. A phosphate-lowering therapy should be initiated when serum phosphate level is ≥5.5 mg/dL. If the serum phosphate level is >7 mg/dL, phosphate-lowering therapy should be initiated or intensified, and the dose of futibatinib should be modified based on the duration and severity of hyperphosphatemia[9] • Dose modifications or interruption of dosing should be considered for the management of toxicities. First recommended dose reduction: 16 mg futibatinib taken orally once daily; second reduction: 12 mg taken orally once daily. Treatment should be permanently discontinued if patient is unable to tolerate 12 mg futibatinib once daily[9]
Additional tests or investigations	Presence of FGFR2 gene fusion or rearrangement should be confirmed by an appropriate diagnostic test prior to initiation of futibatinib. This testing represents routine clinical practice in the UK – the National Genomic Test Directory lists FGFR2 testing for patients with CCA.[10] In addition, feedback received from UK clinical experts in CCA confirmed that

	genetic testing for FGFR2 aberrations is part of standard of care for CCA in the UK. Consequently, no additional tests or investigations are required to determine eligibility for futibatinib beyond those routinely conducted in NHS clinical practice
List price and average cost of a course of treatment	• List price of futibatinib: [redacted] per pack [redacted] • For a patient receiving treatment with futibatinib for 1 year with no dose pauses or interruptions, futibatinib would cost approximately [redacted]
Patient access scheme (if applicable)	A simple discount patient access scheme (PAS) is in place for futibatinib. The proposed futibatinib with-PAS price is [redacted] per pack, equivalent to a discount of [redacted]

Abbreviations: CCA: cholangiocarcinoma; CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; FGFR: fibroblast growth factor receptor; NHS: National Healthcare Service; MHRA: Medicines and Healthcare products Regulatory Agency; SmPC: summary of product characteristics

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

CCA

- Cholangiocarcinoma (CCA), also known as bile tract cancer, is a rare and aggressive cancer that develops from the biliary tree, with an estimated incidence rate of 4.3 per 100,000 cases in England in 2017.[11, 12]
- Based on the location of the primary tumour, CCA is classified as intrahepatic (iCCA) or extrahepatic (eCCA).[13, 14] CCA is also classified by the presence of fusion growth factor receptor 2 (FGFR2) gene fusions or rearrangements, which may drive tumorigenesis and represent a therapeutic target.[5] FGFR2 aberrations occur in 9–15% of iCCAs, but are very rare in eCCA.[15-19]
- Due to the silent nature of CCA, and the absence of specific symptoms at the earlier stages of the disease, approximately 74% of patients with iCCA will be diagnosed with locally advanced or metastatic disease.[20] At this point, patients face a poor prognosis, with very limited treatment options.[13]

Current clinical management

- CCA treatment guidelines include the British Society of Gastroenterology (BSG) 2023 guidelines, European Society of Medical Oncology (ESMO) 2022 guidelines and the National Comprehensive Cancer Network (NCCN) 2023 guidelines; other UK-specific guidelines on CCA were published prior to the recommendation of FGFR2-specific targeted therapies for CCA and therefore are not relevant for this submission.[21, 22] The UK treatment pathway for CCA presented in this submission was based on the above guidelines and validated with UK clinical experts in CCA consulted during this appraisal.[2]
- Surgical resection is the only potentially curative option for patients with CCA.[21, 22] However, only a limited number of patients diagnosed with CCA are eligible for resection, and relapses following surgery are common.[23, 24]
- First-line treatment for locally advanced or metastatic CCA not eligible for resection typically consists of systemic therapy with gemcitabine and cisplatin (GEM + CIS) with or without durvalumab.[21, 22, 25, 26]
- For patients who experience disease progression on first-line therapy, current treatment options in the UK are dependent on the patients' genetic profiles, including FGFR mutation status.[21, 22] Historically, second-line treatment has consisted of modified folinic acid, fluorouracil and oxaliplatin (mFOLFOX) in combination with active symptom control (ASC). However, since TA722, UK clinical experts confirmed almost all patients with an FGFR2 fusion or rearrangement would receive targeted treatment with pemigatinib.[27] The use of FGFR2-targeted treatments in eligible populations is supported by the ESMO 2022 and BSG 2023 guidelines.[22, 25]

Futibatinib

- Futibatinib is an oral, highly selective and covalently/irreversibly binding small-molecule inhibitor of FGFR1–4, which is positioned as a treatment option for adult patients with previously treated locally advanced or metastatic CCA harbouring FGFR2 fusions/rearrangements.[4]
- UK clinical experts in CCA confirmed that pemigatinib represents the only relevant comparator to futibatinib in this indication.
- The introduction of futibatinib will offer an alternative treatment option to pemigatinib in this patient population which may confer reduced resistance to FGFR inhibition, compared to pemigatinib.[3, 7, 28]

B.1.3.1 Cholangiocarcinoma with FGFR2 fusion or rearrangement

Disease overview and epidemiology

Cholangiocarcinoma (CCA), also known as bile tract cancer, is a rare and aggressive cancer that develops from the epithelial lining of the biliary tree.[11]

CCA is classified based on the location of the primary tumour (Figure 1).[13, 14] Intrahepatic CCA (iCCA) originates in the biliary tract, from the bile ducts proximal to the second-order ducts in the liver. The other cases are classified as extrahepatic CCA (eCCA), which in turn includes perihilar (pCCA) and distal CCA (dCCA).[13, 14] iCCA comprises ~20% of CCA cases; pCCA and dCCA comprise ~50% and ~30% of cases respectively.[13, 14] These CCA subtypes have different risk factors and epidemiology, as well as clinical presentation, therapeutic options and prognosis.[13, 29, 30] CCA is typically diagnosed at a late age, due to a combination of factors, including lack of specific symptoms at earlier stages of the disease, with a median age at diagnosis of 75 years in England.[31]

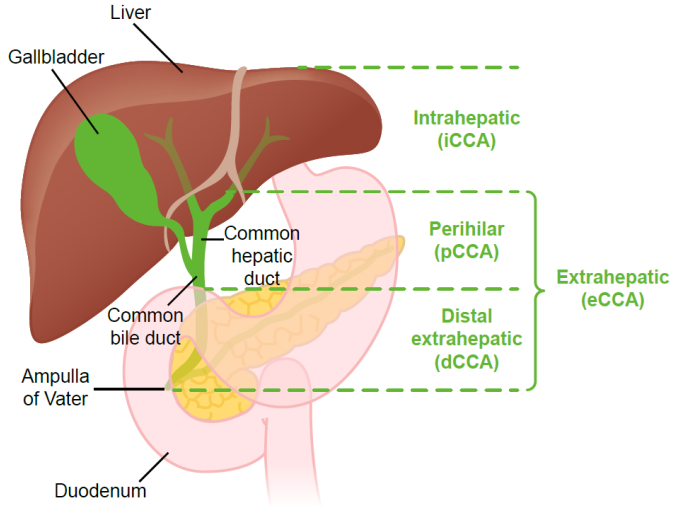
Globally, CCA accounts for ~15% of all primary liver cancers and ~3% of gastrointestinal malignancies.[13] Epidemiological data on CCA in the United Kingdom (UK) are scarce, however a study published in 2019 reported the age-standardised incidence rate of CCA in England in 2017 as 4.3 per 100,000.[12, 31] UK clinical experts confirmed that these data are currently the most robust epidemiological data available for the UK.

Genus *et al.* (2019) reported a slightly higher incidence rate for males compared to females of 4.6 versus 4.0 per 100,000.[12] The incidence rates for CCA were reported to rise steadily between 2001–2017.[12] A study published in 2021 reported an age-standardised incidence rate of iCCA in the UK as 2.7 per 100,000 in 1997–2017; age-adjusted iCCA incidence rates were slightly higher for men than for women across the reported time period in the UK overall and in England.[32] UK clinical experts noted that CCA may be underdiagnosed in the literature – the experts explained that, out of all patients who are diagnosed with cancer with liver lesions where the location of the primary tumour is unknown, approximately 1 in 9 will have iCCA, which is not accounted for in the literature.

Overall, UK clinical experts indicated that they expect approximately 2,500–3,000 prevalent patients to be living with CCA in the UK each year.

Both studies reported that the incidence rate of iCCA was growing in England across the respective study periods.[12, 32] Rising iCCA rates have been seen across a number of other geographies.[13, 33] This may be due to an increase in risk factors contributing to the development of CCA and to changing diagnostic methods and disease classifications.[13, 33, 34] Incidence rate dynamics of eCCA are less certain, with differing trends reported across studies.[14, 33, 34]

Figure 1. Classification of CCA by anatomical location



Abbreviations: CCA: cholangiocarcinoma; dCCA: distal cholangiocarcinoma; eCCA: extrahepatic cholangiocarcinoma; iCCA: intrahepatic cholangiocarcinoma; pCCA: perihilar cholangiocarcinoma
Source: Adapted from Valle *et al.* (2021).[14]

CCA pathogenesis

Most patients with CCA have no identifiable risk factors associated with the development of their disease.[13, 34] Although the specific causes of CCA are not fully understood, some risk factors for developing CCA are known. Some of these factors are specific to certain geographies, which, together with genetic variations, are believed to drive substantial differences in CCA epidemiology between areas. For example, in Western populations, iCCA has been shown to be more strongly associated with hepatitis C than hepatitis B infection, while in Asian populations this trend was reversed.[13, 22, 34] Known risk factors include both congenital and environmental factors, such as bile duct cysts, Caroli's disease (condition characterised by an abnormal widening of the intrahepatic bile ducts), hepatolithiasis (presence of gallstones in the biliary ducts) and cirrhosis, as well as parasitic infections and exposure to certain chemical substances.[34]

A shared feature of many of the known risk factors is chronic inflammation.[13] It has been suggested that chronic inflammation may play a part in oncogenesis by providing a high rate of cell turnover and an environment in which cytokines and growth factors allow for the accumulation of mutations and the proliferation of mutated cells.[35] A systematic review and meta-analysis conducted by Clements *et al.* (2020) identified cysts, gallstones and cirrhosis were reported to be the strongest risk factors for both iCCA and eCCA.[36]

However, the development and progression of CCA can be influenced by a variety of cell processes and signalling pathways; the overactivation of some of these pathways can result from genetic aberrations.[13, 37, 38]

Genetics of cholangiocarcinoma

CCA is a genetically diverse cancer; up to 88% of all biliary tract cancers harbour pathological molecular aberrations/alterations.[39] Different sub-types of CCA have notably different genetic profiles; the most frequent mutations in iCCA include IDH1/2, BRAF, BAP1, ARID1A and

FGFR2.[13, 14] Importantly, a number of mutations have been recognised as therapeutic targets in CCA treatment, including IDH1, BRAF and FGFR.[14]

FGFR2 is a receptor from the FGFR family.[30, 40] These receptors have intracellular domains that exhibit tyrosine kinase activity and play an important role in a variety of cellular processes, including developmental and physiological processes, through regulation of cell survival and proliferation.[30, 40] In normal cells, the binding of fibroblast growth factor ligands to their receptors FGFR1–4 leads to receptor dimerization, which in turn regulates a variety of downstream cellular processes.[41] In cancer, this activity can be disrupted in a number of ways.[5, 19, 22, 40]

FGFR2 aberrations include FGFR2 fusions, including rearrangements, and other aberrations; while the role of non-fusion aberrations in potential CCA therapies is still under investigation, the importance of FGFR2 fusions/rearrangements as a driver in CCA oncogenesis and a potential therapeutic target has been recognised.[5] Additionally, UK clinical experts confirmed that in reality, all FGFR2 rearrangements will be FGFR2 fusions; however, in some cases, genetic testing is not able to identify the fusion partner to FGFR2 – in these cases, FGFR2 fusions may be classified as rearrangements.

Different studies focus on different types of FGFR2 aberrations, which is reflected in variable terminology throughout this section when reporting on the available literature.

Incidence rates of FGFR2 fusions are markedly different between CCA sub-types. UK clinical experts highlighted that FGFR2 fusions are very rare in eCCA and almost exclusive to iCCA, where they occur at ~9–15% prevalence.[15-19] There is a paucity of data in England and Wales regarding the incidence and prevalence of patients with CCA with FGFR aberrations, however feedback received from UK clinical experts in CCA indicated that they would expect approximately 8-10% of all patients with iCCA to be FGFR2 fusion positive.

CCA patients with FGFR fusions/rearrangements are typically associated with earlier diagnosis than the overall population of patients with CCA (median age at diagnosis ~57 years versus ~75 years). Reports also suggest that patients presenting with CCA with FGFR aberrations/alterations are more often women compared with patients without FGFR aberrations/alterations (56–61% versus 47–53% female with versus without FGFR2 aberrations/alterations).[6, 20, 31, 42-47] Whilst some observational studies have suggested that FGFR2 aberrations/alterations may be associated with a favourable prognosis in patients with CCA (excluding the potential benefits of targeted treatment with FGFR2 inhibitors), other studies have not found a significant association.[45, 48-54]

However, CCAs with FGFR2 aberrations, including fusions/rearrangements, have been found to be highly sensitive to FGFR inhibitors and therefore are suitable for targeted therapy.[5] The benefit of FGFR-specific therapies for the target patient population of this submission has been established; patients with an FGFR genetic aberrations treated with FGFR-targeted therapy have been shown to have improved survival compared to patients not receiving targeted treatment (overall survival: 44.8 versus 24.3 months, respectively; p=0.01).[45]

Impact of cholangiocarcinoma on patients and carers

Due to the lack of or non-specific nature of symptoms associated with the early stages of disease, CCA is usually diagnosed at the advanced stage of disease. This contributes to limited treatment options and poor prognosis for many patients.[13, 14] iCCA is typically classified into four

stages (I-IV) based on the depth of invasion into the gallbladder wall and the extent of spread to surrounding organs and lymph nodes; based on this classification, studies have reported that ~53% to 63% of patients with iCCA are diagnosed with stage III−IV disease.[21, 55-59] In a recent multicentre European study, 50.3% of patients with iCCA had disease with regional lymph node invasion at diagnosis, and 23.9% of patients with iCCA had distant metastases when diagnosed.[20]

As CCA is typically advanced at diagnosis, only around 50% of patients diagnosed with CCA undergo surgery, and the prognosis of the disease is extremely poor, with worse expected survival for patients with locally advanced or metastatic disease compared to those eligible for surgical resection.[13, 20] Prior to the introduction of pemigatinib, patients with CCA receiving best supportive care (BSC) had a median overall survival (OS) of 4.0 months, and for patients receiving active palliative therapies, such as chemotherapy, median OS was reported as 10.6 months.[20]

CCA represents ~2% of all cancer-related deaths worldwide yearly.[13] Mortality rates for CCA are rising; in England, annual mortality from CCA increased from approx. 3 per 100,000 in 2001 to approx. 5 per 100,000 in 2017.[13, 31, 60]

Symptoms of CCA arise due to direct compression from the tumour (such as biliary obstruction), constitutional factors or underlying pathology.[13, 14] The clinical presentation of CCA varies between subtypes; biliary obstruction and jaundice are common symptoms in patients with eCCA, whereas patients with iCCA are often asymptomatic prior to the appearance of late, nonspecific symptoms such as weight loss, nausea, fatigue, and abdominal pain, which contributes to late diagnosis.[13]

Information relating to the impact of CCA on the quality of life of patients with CCA in the UK is scarce.[61-63] Available data indicate that the burden of CCA symptoms on emotional health, cognitive function and physical wellbeing is considerable.[64-67] A survey of patients with CCA in the United States (US) conducted in 2019 (n=707 patients completed the survey) highlighted a number of issues faced by this patient population, including the negative quality of life impact from anxiety, depression, tiredness and treatment.[64]

Furthermore, an international study (conducted in a number of geographies including the UK) using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-BIL21 Questionnaire in patients with CCA (n = 172) and gall bladder cancer (n = 91) reported scores for eating, jaundice, tiredness, pain, anxiety, treatment side effects, drains, and weight loss for each disease subtype at baseline.[65] Overall, the highest scores were reported for tiredness and anxiety, indicating the greatest burden in those areas. Patients with iCCA scored significantly higher than patients with eCCA on the drain and weight-loss scales; none of the other scales were significantly different between CCA subtypes at baseline.[65]

Information on the impact of CCA on the caregivers in the UK is similarly limited. Recent studies conducted in Thailand, where CCA incidence is one of the highest in the world due to geographical risk factors such as parasitic infections, highlighted the need to assess the caregivers' quality of life (QoL) and found that symptoms and support care need were significant predictors of family caregivers' QoL.[68, 69] As both symptoms and care needs increase substantially at the later stages of the disease, the burden on caregivers can be expected to increase correspondingly as the disease progresses.

Economic burden of cholangiocarcinoma

A number of studies have found CCA presents a substantial economic burden, in particular in the advanced stages of disease.[70-72]

The economic burden differs between CCA subtypes. A US-based study published in 2023 found that patients with iCCA, which is the subtype of CCA most prevalent amongst patients with FGFR2 fusions/rearrangements, were associated with higher healthcare-related costs than patients with eCCA, in particular due to outpatient services costs.[71]

The indirect economic burden of CCA is also notable. A US-based study noted high levels of absenteeism among patients with CCA, with the number of mean all-cause days absent from work due to illness per patient per month between 2011–2019 reported as 6.0 and 4.3 for patients with iCCA and eCCA, respectively.[71]

Importantly, studies have found that the economic burden of CCA, and in particular iCCA, is increasing. An almost 2-fold increase in hospital admissions for iCCA and for related hospital charges was found in a US nationwide database study between 2005 and 2014.[73] A trend in increasing healthcare costs associated with hospitalisations among iCCA patients was observed in a Spanish study conducted between 2000 and 2018, which found that costs increased significantly between 2000 and 2008, stabilising after 2009; however, total costs were expected to increase further if iCCA incidence continues to increase in line with the current trends.[72] As increasing CCA and iCCA incidence rates have been seen in the UK as well, the economic burden of CCA in the UK can also be expected to increase further.[31, 33]

B.1.3.2 Futibatinib

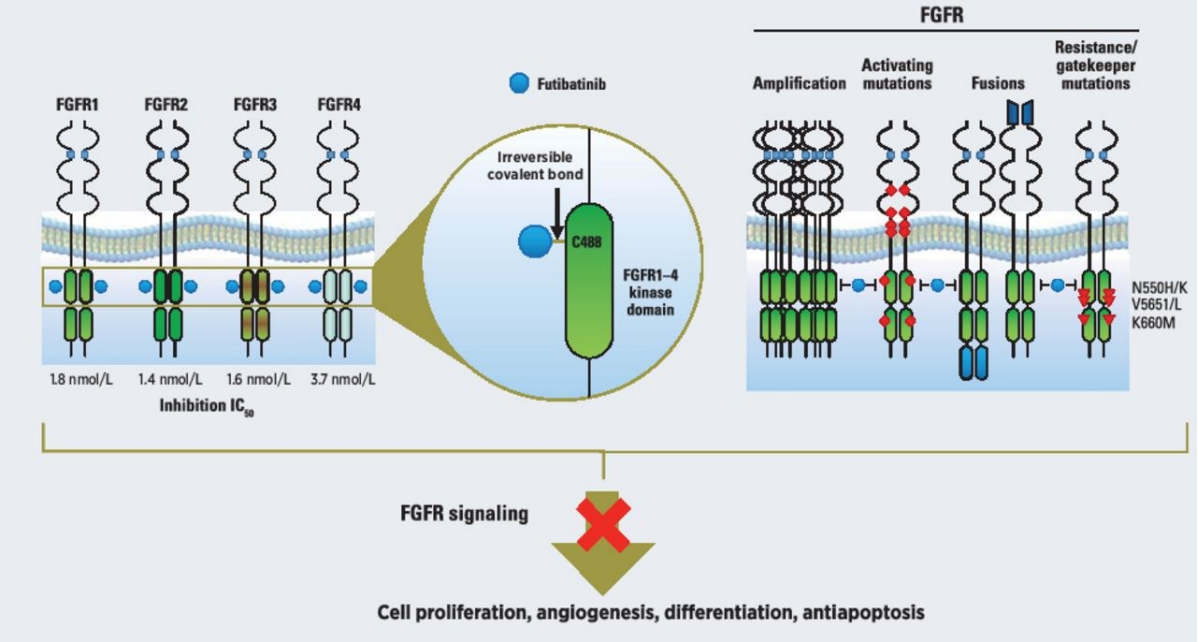
Description of futibatinib

Futibatinib is an oral, highly selective and covalently/irreversibly binding small-molecule inhibitor of FGFR1–4.[4]

The receptors from the FGFR family exhibit tyrosine kinase activity and play an important role in a variety of cellular processes, including regulation of cell survival and proliferation.[30, 40] In cancer, this activity can be disrupted in a number of ways, which can lead to abnormal cell proliferation and oncogenesis; blocking the abnormal receptors' activity is therefore a potential therapeutic target for stopping harmful proliferation processes in tumours.[5, 19, 22, 40]

In *vitro* studies have shown futibatinib to covalently and irreversibly bind to the ATP binding pocket of the FGFR kinase domain, inhibiting FGFR phosphorylation and, in turn, downstream signalling in FGFR-deregulated tumour cell lines; this contrasts to other available FGFR inhibitors that bind reversibly (Figure 2 shows a schematic of FGFR inhibition and its downstream effects).[3, 4, 28] Futibatinib exhibited potent, selective growth inhibition of several tumour cell lines harbouring various FGFR genomic aberrations, as well as significant dose-dependent tumour reduction and FGFR inhibition in various FGFR-driven human tumour xenograft models.[4]

Figure 2. Mechanism of action of futibatinib



Abbreviations: FGFR: fibroblast growth factor receptor
Source: Adapted from Sootome *et al.* (2020).[4]

Importantly, as highlighted in more detail in Section B.2.12, based on the *in vitro* studies, treatment with futibatinib may be expected to result in fewer resistant mutations compared with older FGFR2 inhibitors, such as pemigatinib.[3, 4] The BSG 2023 guidelines note the emergence of treatment resistance as an issue in treating CCA.[25] Based on these *in vitro* studies, futibatinib may therefore play a part in reducing the potential for treatment resistance to existing reversibly-binding FGFR-specific therapies, potentially improving response rates and durability of response in advanced CCA treatment.[3, 7, 28]

Futibatinib is currently being investigated in both a Phase I and Phase II clinical trial in the indication of relevance to this submission, which are discussed below in Section B.2.3.

B.1.3.3 Current treatment pathway and proposed positioning of futibatinib

CCA with FGFR2 fusion/rearrangement: current treatment pathway

A number of potentially relevant guidelines for the treatment of CCA in UK clinical practice are available, including the recently published British Society of Gastroenterology (BSG) 2023 guidelines.[25] As such, the treatment pathway presented below is informed by the BSG 2023 guidelines, as well as the recently published European Society of Medical Oncology (ESMO) guidelines (2022) and the National Comprehensive Cancer Network (NCCN) guidelines, and has been validated by UK clinical experts experienced in the treatment of CCA.[21, 22] Other guidelines of potential relevance to UK clinical practice, such as the International Liver Cancer Association guidelines on CCA, were published prior to the recommendation of an FGFR2 targeted therapy by NICE in 2021, and therefore do not reflect current standard of care for the patient population of relevant to this submission.[74]

The primary goal of treatment of CCA is to improve patient prognosis, optimise survival, and maintain and/or improve patient HRQoL.[21, 22, 75] Curative treatment is possible; however, the only potentially curative treatment option is surgical resection.[21, 22, 25] Liver transplantation has

recently been introduced as a possible treatment option for a subset of iCCA patients, however the evidence for this is limited and iCCA remains a contraindication for liver transplantation in most geographies.[25]

In UK clinical practice, patients with early resectable CCA are treated with surgery with or without adjuvant chemotherapy.[22] Whilst some guidelines cite a lack of evidence supporting the use of adjuvant treatments, the 2023 BSG guidelines recommend the use of 24 weeks of adjuvant chemotherapy (currently capecitabine) for patients who have undergone surgical resection for CCA.[21, 25]

Surgical resection is the only potentially curative option for patients with CCA.[21, 22] However, only ~50% of patients diagnosed with CCA undergo resection.[20] Relapse rates after surgery are high, with approximately 60% of patients experiencing relapse following null margin resection. Moreover, only around 36% of patients who undergo surgery achieve negative-resection margin; among those with microscopic residual disease after surgery, relapse rates rise to 77.4%.[20]

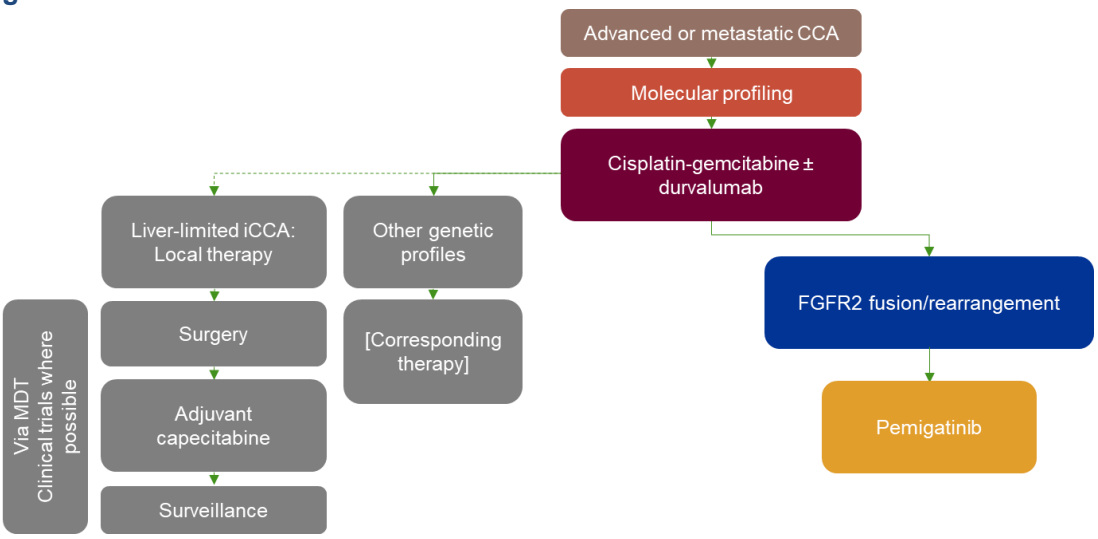
For patients that are not eligible for resection, treatment options include systemic therapy, enrolment in a clinical trial and best supportive care (BSC).[21, 22, 25] For locally advanced or metastatic CCA, first-line treatment will typically consist of systemic therapy with gemcitabine and cisplatin (GEM+CIS) with or without durvalumab.[25] Durvalumab has recently been recommended by NICE in combination with GEM+CIS for treating unresectable or advanced biliary tract cancer [TA944].[26]

Historically, second-line treatment has consisted of modified folinic acid, fluorouracil and oxaliplatin (mFOLFOX) in combination with active symptom control (ASC). ASC alone was offered if further chemotherapy was not suitable.[61] However, now for patients who experience disease progression on first list therapy the current treatment options in the UK are dependent on FGFR mutation status. While mFOLFOX and ASC remains the standard of care for patients without an FGFR fusion or rearrangement, recent guidelines recommend the use of FGFR inhibitors for patients with FGFR2 fusions.[22] The BSG 2023 guidelines recommend that CCA should be subjected to molecular profiling as soon as possible, and treatment options for targetable alterations such as FGFR2 fusions or rearrangements should be considered; this is in line with the ESMO 2022 guidelines and feedback from UK clinical experts.[25]

In the UK, the FGFR inhibitor pemigatinib is recommended by NICE for the treatment of patients with locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement that has progressed after prior systemic therapy (TA722).[3, 7, 27] As such, pemigatinib represents the main treatment option in the target patient population of this submission – this was confirmed by UK clinical experts, who highlighted that the survival gains observed for pemigatinib versus chemotherapy means that almost all patients with FGFR2 fusions or rearrangements will be treated with pemigatinib, if eligible.[2]

The current treatment pathway for CCA in the UK, based on the BSG 2023 and ESMO 2022 guidelines and feedback received from UK clinical experts, is summarised in Figure 3.

Figure 3. Current treatment pathway for CCA in the UK, adapted from the ESMO 2022 guidelines



Abbreviations: CCA: cholangiocarcinoma; ESMO: European Society of Medical Oncology; *FGFR2*, fibroblast growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; MDT: multidisciplinary team
Source: Adapted from Vogel *et al.* (2022).[22]

Positioning of futibatinib relative to the current treatment pathway and relevant comparators and unmet need

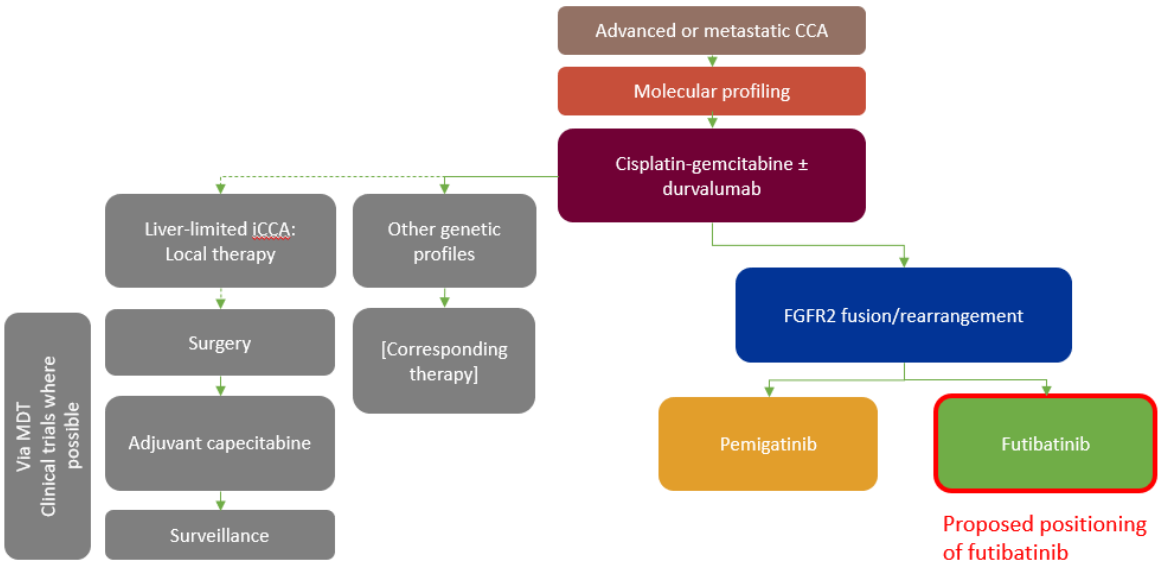
In UK clinical practice, futibatinib will be used in adult patients with locally advanced or metastatic CCA with FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy; this is in line with the population wording in the NICE final scope.

As pemigatinib is the only targeted treatment recommended by NICE in this indication, it is anticipated that futibatinib will be positioned alongside pemigatinib in UK clinical practice – pemigatinib represents the only relevant comparator to futibatinib in this indication. UK clinical experts highlighted that patients known to have an FGFR2 fusion or rearrangement would receive pemigatinib in clinical practice, given the magnitude of the survival benefit for pemigatinib versus chemotherapy.[2] As such, chemotherapy regimens (such as mFOLFOX) or BSC are not considered to be relevant comparators to futibatinib in this appraisal.

The proposed positioning and comparator selection for futibatinib in UK clinical practice was validated by UK clinical experts in CCA consulted as part of the appraisal process. The experts highlighted the unmet need for the introduction of treatment options, such as futibatinib, which, based on *in vitro* studies, have the potential to reduce the emergence of secondary resistance mutations in the FGFR2 kinase domain (further detailed in Section B.2.12).[3, 7, 42, 43] The experts highlighted that given this, they would preferentially treat patients with futibatinib, rather than pemigatinib.

The proposed positioning of futibatinib in the treatment pathway is shown in Figure 4 below.

Figure 4. Current treatment pathway for CCA in the UK, adapted from the ESMO 2022 guidelines, including the proposed positioning of futibatinib



Abbreviations: CCA: cholangiocarcinoma; ESMO: European Society of Medical Oncology; *FGFR2*, fibroblast growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; MDT: multidisciplinary team
Source: Adapted from Vogel *et al.* (2022).[22]

Summary

Despite recent progress in recognising the potential of genetic aberration-specific therapies for CCA, the unmet need in this patient population remains substantial, with poor prognosis and limited treatment options, in particular for patients with advanced or metastatic disease.[13, 22] In addition, treatment resistance and relapse rates are highlighted as potential issues with pemigatinib, the current standard of care for previously treated CCA patients with FGFR fusions or other rearrangements.[5]

Futibatinib, an orally administered selective small molecule which covalently/irreversibly binds to and inhibits FGFR2, has the potential to address this unmet need by reducing the emergence of treatment resistant mutations in CCA (see Section B.2.12) and therefore reducing relapse rates in patients with advanced disease.

B.1.4 *Equality considerations*

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

B.2 Clinical effectiveness

Study identification

- A SLR was conducted in September–October 2023 to identify relevant clinical evidence on the efficacy and safety of futibatinib and pemigatinib for the treatment of adult patients with previously treated locally advanced or metastatic CCA with fibroblast growth factor receptor 2 (FGFR2) gene rearrangements, including gene fusions
- The key trials presenting evidence on futibatinib and pemigatinib were the single-arm FOENIX-CCA2 and FIGHT-202 trials, respectively

Efficacy

- At the time of the final DCO of FOENIX-CCA2, with a median follow-up of 25.0 months, ORR following treatment with futibatinib was 41.7%. The number of responders with a DOR of ≥6 months was 32 (74.4%), and 8 (18.6%) patients had a DOR of at least 12 months. At the final DCO, the DCR per central radiological assessment by independent review committee (IRC) was 82.5%
- The median PFS for futibatinib at the final DCO was 8.9 months. At 6 and 12 months, the proportions of patients who were progression free were 65.0% and 35.4%, respectively. This translated to a median OS of 20.0 months for futibatinib, with OS rates at 6 and 12 months of 88.1% and 73.1%, respectively
- Patients' HRQoL was maintained throughout treatment: EQ VAS scores were maintained from baseline to treatment cycle 13 (mean change -1.8 to +4.8 across cycles)
- FOENIX-CCA2 indicates that treatment with futibatinib resulted in a substantial and sustained clinical response, while maintaining patients' HRQoL. UK clinical experts in CCA confirmed that this efficacy profile aligns with expectation for an FGFR2 inhibitor[2]

Indirect treatment comparisons (ITCs)

- Since FOENIX-CCA2 and FIGHT-202 were single-arm trials, an unanchored ITC had to be conducted in order to compare the efficacy of futibatinib and pemigatinib
- A MAIC analysis was conducted, comparing PFS and OS outcomes of FOENIX-CCA2 and FIGHT-202. The MAIC was conducted in line with NICE DSU TSD18, and its methods were verified by UK health economic experts[2]
- The MAIC indicates that futibatinib and pemigatinib have comparable efficacy with respect to PFS and OS, with no statistically significant differences observed between the two treatments
- The results of the MAIC aligned with the feedback from UK clinical experts in CCA who had experience of treating patients with both futibatinib and pemigatinib[2]
- UK clinical experts highlighted that while the two treatments are similar, they would preferentially treat patients with futibatinib rather than pemigatinib, given the reduced potential for treatment-emergent resistant mutations associated with futibatinib[2]

Safety

- The safety profile of futibatinib aligned with the expectations of clinical experts for an FGFR inhibitor, and adverse events were generally manageable.[2, 76] Safety profiles of futibatinib and pemigatinib were found to be similar, which was confirmed by clinical experts[2, 76]

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted in September–October 2023 to identify relevant clinical evidence on the efficacy and safety of futibatinib and pemigatinib for the treatment of adult patients with locally advanced or metastatic CCA with FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy. The SLR identified 16 relevant publications, reporting on five unique studies. In line with NICE recommendations, the quality of all included RCTs, non-randomised comparative trials and single-arm trials was assessed using the quality assessment tool developed by the York University CRD.[77]

Full details of the SLR, including search strategy, study selection process and detailed results are presented in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

The clinical evidence base for futibatinib as a treatment for CCA with FGFR2 fusion or rearrangement is based on Study TAS-120-101, a multinational, open-label, non-randomised, Phase I/II clinical trial composed of three parts:

- Phase I, Dose Escalation [FOENIX-101]: Evaluating futibatinib monotherapy at escalating doses of 8–200 mg every other day (QOD) and 4–24 mg once daily (QD) in the treatment of advanced solid tumours
- Phase I, Dose Expansion [FOENIX-101]: Evaluating the safety and efficacy of futibatinib in iCCA and other tumour types harbouring specific FGF/FGFR aberrations at the dose of 16 or 20 mg QD
- Phase II [FOENIX-CCA2]: Evaluating the efficacy of futibatinib 20 mg QD in patients with iCCA harbouring FGFR2 gene rearrangements, including fusions

The Phase II portion of the study (FOENIX-CCA2) forms the principal evidence base for futibatinib in this indication. Therefore, only the methodology and results of the Phase II study have been provided in this section.

The first patient was enrolled in FOENIX-CCA2 on 16th April 2018, and the final data cut-off (DCO) took place on 29th May 2021.

The information presented in this submission has been derived from the TAS-120-101 Clinical Study Report (CSR) and the Goyal *et al.* (2023) publication.[6, 76] Goyal *et al.* (2023), published in the *New England Journal of Medicine*, provides an overview of the trial design, eligibility criteria and baseline patient characteristics of the FOENIX-CCA2 trial, and presents the key efficacy and safety results from the preliminary DCO of the FOENIX-CCA2 trial (1st October 2020). The CSR provides the results of the final DCO of the FOENIX-CCA2 trial (29th May 2021). An overview of FOENIX-CCA2 is provided in Table 3.

Table 3: Clinical effectiveness evidence

Study	FOENIX-CCA2
Study design	Multinational, open-label, non-randomised Phase II study

Study	FOENIX-CCA2
Population	Adults with unresectable or metastatic iCCA harbouring FGFR2 fusion or other rearrangement (N=103 patients enrolled)
Intervention(s)	Futibatinib 20 mg, received orally once daily. Patients receiving futibatinib daily (with two permitted dose reductions) in continuous 21-day cycles until disease progression, drug intolerance, withdrawal of consent, or death
Comparator(s)	N/A – FOENIX-CCA2 is a single arm study
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	Efficacy data • Objective response rate (ORR) • **Progression-free survival (PFS)** • **Overall survival (OS)** Health-related quality of life (HRQoL) data • European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) • **Euro-QoL-5 dimensions-3 levels (EQ-5D-3L)** • EuroQol visual analogue scale (EQ VAS) **Adverse event data**
All other reported outcomes	• Duration of response (DOR) • Disease control rate (DCR)

Notes: Outcomes used in the economic model are highlighted in bold
Abbreviations: DCR: disease control rate; DOR: duration of response; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L: Euro-QoL-5 dimensions-3 levels; EQ VAS: EuroQol visual analogue scale; FGFR2: fibroblast growth factor receptor 2; HRQoL: health-related quality of life; iCCA: intrahepatic cholangiocarcinoma; N/A: not applicable; ORR: objective response rate; OS: overall survival
Source: Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 29 May 2021[76]; Goyal *et al.* (2023)[6]

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

As the pivotal trial supporting futibatinib in this indication, the methodology of FOENIX-CCA2 study is presented within this section.

B.2.3.1 Trial design

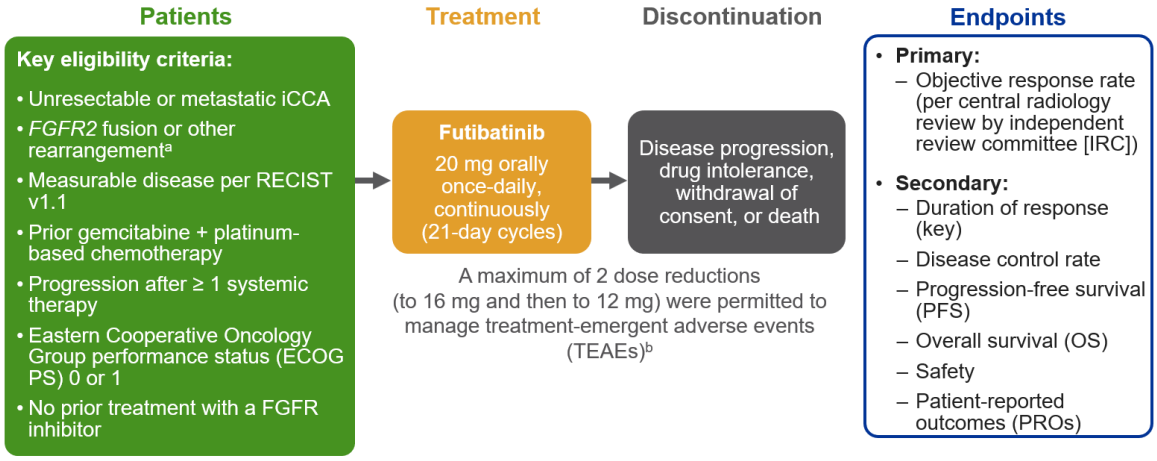
FOENIX-CCA2 was a Phase II multinational, open-label, non-randomised clinical trial, which studied the efficacy and safety of futibatinib in patients with iCCA with FGFR2 gene fusions or

other FGFR2 rearrangements.[78] Eligible patients were adults (≥18 years) with locally advanced, metastatic, unresectable iCCA harbouring FGFR2 gene fusions or other FGFR2 rearrangements and measurable disease as defined by Response Evaluation Criteria in Solid Tumours (RECIST) guidelines (version 1.1, 2009) for advanced solid tumours.[79] Key eligibility criteria for FOENIX-CCA2 are presented below in Table 5.

An overview of the FOENIX-CCA2 study design is presented in Figure 5 and a summary of the methodology is described in Table 4. Patients were screened between 16th April 2018 and 29th November 2019; the primary DCO occurred on 1st October 2020, and the final DCO occurred on 29th May 2021, after a median follow-up of 25.0 months.

Following study completion, any patients who were on study treatment and were deriving benefit from study therapy (in the opinion of the Investigator and Sponsor) could be permitted to continue treatment with futibatinib in a Study Extension phase. During Study Extension, patients could receive treatment until withdrawal criteria are met. The FOENIX-CCA2 study was considered complete when all patients had been followed for survival for up to 18 months after the last patient enrolled.[80]

Figure 5: Summary of the study design of FOENIX-CCA2



Footnotes: [a]Identified centrally in tumour tissue by Foundation Medicine (FMI) or by local laboratory testing of tumour tissue or circulating tumour DNA; [b]Treatment was discontinued if treatment-emergent AEs did not resolve after 2 dose modifications or if the next cycle of treatment was delayed >21 days
Abbreviations: AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group performance status; FGFR: fibroblast growth factor receptor; iCCA: intrahepatic cholangiocarcinoma; IRC: independent review committee; OS: overall survival; PFS: progression-free survival; PRO: patient-reported outcome; RECIST v1.1: Response Evaluation Criteria for Solid Tumours version 1.1; TEAE: treatment-emergent adverse events
Source: Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 29 May 2021[76]; Goyal *et al.* (2023)[6]

Table 4: Summary of FOENIX-CCA2 trial methodology

Methodology	Summary
Location	Multinational study, conducted in 47 sites across UK, USA, France, Spain, Australia, Canada, Italy, Germany, Netherlands, Portugal, Republic of Korea, Taiwan R.O.C., Hong Kong and Japan
Trial design	Open-label, single-arm, Phase II study in patients with iCCA with FGFR2 gene fusions or other FGFR2 rearrangements

Duration of study	• The first patient was screened on 16th April 2018 • Patients received futibatinib in continuous 21-day cycles without treatment breaks between cycles. Treatment continued until disease progression, drug intolerance, withdrawal of consent, or death • At the point of the primary analysis (DCO: 1st October 2020) the median follow-up was 17.1 months; median duration of treatment was 9.1 months • At the point of the final analysis (DCO: 29th May 2021) the median follow-up was 25.0 months; median duration of treatment was 9.1 months • Safety follow-up was conducted at end of treatment (+0–7 days) and 30 days after last dose
Method of randomisation	N/A – FOENIX-CCA2 is a single arm study
Method of blinding	N/A – FOENIX-CCA2 is a single arm study
Trial drugs and method of administration	• Patients received futibatinib at a starting dose of 20 mg once daily (QD) via the oral route of administration • Futibatinib was administered continuously, in 21-day cycles • A maximum of 2 dose reductions (to 16 mg and then to 12 mg) were permitted to manage treatment-emergent adverse events (TEAEs) • Treatment was discontinued if TEAEs did not resolve after 2 dose modifications or if the next cycle of treatment was delayed >21 days

Permitted and disallowed concomitant medication	• Patients were not permitted to receive any other investigational or any other anticancer therapy, including chemotherapy, immunotherapy, biological response modifiers, or antineoplastic endocrine therapy during the study treatment period
	• The following therapies were permitted:
	  ○ Bisphosphonate
	  ○ Denosumab
	  ○ Concomitant treatment with gonadotropin-releasing hormone (GnRH) agonists or luteinising hormone-releasing hormone (LH-RH) agonists is permitted in prostate cancer patients
	  ○ Non enzyme-inducing anticonvulsants such as: gabapentin, lamotrigine and levetiracetam
	  ○ Steroids are allowed for patients with primary brain tumours and brain metastases. Steroid use in other patients with other tumour types should be discussed between the investigator and the Sponsor's Medical Monitor
	  ○ Local or regional palliative cryotherapy or radiation, e.g., for bone pain or palliative surgery (non-anti-neoplastic intent)
	• Guidelines for the use of radiation for brain metastasis, therapy for bone metastasis and locoregional therapy are described in the study protocol
	• The medications/therapies for the following causes could be given concomitantly under the guidelines set out in the study protocol:
	  ○ Hematologic Support
	  ○ Management of diarrhoea
	  ○ Management of nausea/vomiting
	  ○ Management of hyperphosphatemia
	• A complete list of the permitted, disallowed and concomitant medications can be found in the study protocol (Amendment 10,

	Section 7.7–7.8)[80]
Primary endpoints (including scoring methods and timings of assessments)	Objective response rate according to RECIST 1.1 guidelines[79] defined as the proportion of patients who had best overall response (BOR) of complete response (CR) or partial response (PR) based on central radiological assessment by an independent review committee (IRC)
Secondary endpoints (including scoring methods and timings of assessments)	• Duration of response: defined as the time from the first documented response (CR or PR) to the first documented objective progressive disease (PD) or death due to any cause • DCR: the proportion of patients with objective evidence of CR, PR, or stable disease (SD), except that there is no requirement for a confirmation of an SD response • PFS: the time from the first dosing date to the date of the first documented progression or death due to any cause, whichever occurs first • OS: the time between the first dosing date and the date of death. ORR, DOR, DCR and PFS endpoints will be calculated based on IRC and based on investigator assessment • Safety and tolerability: analysed through the incidence of death, adverse event, concomitant medications, physical examination, vital sign measurements, clinical laboratory results, ECG results, ECOG performance status, and other safety observations • Patient-reported outcomes (PROs): EQ-5D, EQ-VAS and EORTC QLQ-C30 ○ Patient's overall health state on a visual analogue scale (EQ-VAS) at each assessment time point was summarised using descriptive statistics. Proportion of patient's reporting problems for the 5 EQ-5D dimensions at each assessment time point was summarised by level of problem. Percentages were based on number patients assessed at each assessment time point ○ A by-patient listing of EQ-5D with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number) and EQ-VAS was provided ○ For EORTC QLQ-C30, all scales and single items were scored on a categorical scale and linearly transformed to 0-to-100 scales with higher scores for a functional scale representing higher levels of functioning, higher scores for the global health status/quality of life representing higher levels of global health status/quality of life, and higher scores for a symptom scale representing higher level of symptoms ○ Baseline and change from baseline in EORTC QLQ-C30 global health status/quality of life (QoL) composite scale data and the remaining EORTC QLQ-C30 scale data were summarised by time point using descriptive statistics for each cohort. In addition, the percentage of patients demonstrating a clinically meaningful deterioration (defined as a 10-point change from baseline) was presented for each scale at each assessment time point. Percentages were based on number patients assessed at each assessment time point ○ PROs were evaluated at screening and as close as possible to the tumour assessment schedule: at the end of every 2 cycles (up

	to +2 weeks) through Cycle 4 and every 3 cycles (±7 days) thereafter until disease progression or initiation of new anticancer therapy (whichever is first)
Exploratory objective	To investigate the pharmacokinetics and to explore the relationship between pharmacokinetics and efficacy or toxicity of futibatinib
Pre-specified subgroup analyses	To assess consistency of treatment effect, the primary endpoint was analyses by several demographic and disease variables for iCCA patients enrolled in the trial: • Age (<65 versus ≥65 years) • Gender (male versus female) • Race (Caucasian/white, Black, Asian, other) • Baseline ECOG score (0 versus 1) • Prior systemic therapy 1 line, 2 lines, and 3 or more lines for advanced/metastatic disease • North America, Europe, Asia Pacific (excluding Japan), Japan • Prior surgical resection of primary tumour (Yes versus No) • Prior (neo) adjuvant treatment (Yes versus No) • Baseline FGFR rearrangements status by local lab (commercial test provided to clinician as standard of care based on tumour tissue) and/or central lab (clinical trial assay performed on tumour tissue) • Patients with solid tissue sample and report

Abbreviations: CR: complete response; DCO: data cut-off; DCR: disease control rate; DOR: duration of response; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L: Euro-QoL-5 dimensions-3 levels; EQ VAS: EuroQol visual analogue scale; FGFR2: fibroblast growth factor receptor 2; HRQoL: health-related quality of life; iCCA: intrahepatic cholangiocarcinoma; LH-RH: luteinizing hormone-releasing hormone; N/A: not applicable; PD: progressive disease; ORR: objective response rate; OS: overall survival; PR: partial response; R.O.C.: Republic of China; SD: stable disease; TEAE: treatment-emergent adverse events; QD: once daily; UK: United Kingdom; USA: United States of America
Source: Taiho Oncology. Data on File. FOENIX-CCA2 Clinical Study Protocol Amendment 10;[80] Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 29 May 2021;[76] Goyal *et al.* (2023)[6]

Eligibility criteria

Key inclusion and exclusion criteria for FOENIX-CCA2 are presented in Table 5. The complete set of exclusion/inclusion criteria is provided in the trial protocol.[80]

Table 5: Eligibility criteria for FOENIX-CCA2

Key inclusion criteria	Key exclusion criteria

• Provided written informed consent
• Age ≥18 years (or according to the country's regulatory definition for legal adult age)
• Histologically or cytologically confirmed, locally advanced, metastatic cancer meeting the following criteria:
  ○ Histologically or cytologically confirmed, locally advanced, metastatic, unresectable iCCA harbouring FGFR2 gene fusions or other FGFR2 rearrangements
  ○ Patient has been treated with at least one prior systemic gemcitabine and platinum-based chemotherapy
	• History and/or current evidence of clinically significant non-tumour related alteration of calcium-phosphorus homeostasis
	• History and/or current evidence of clinically significant ectopic mineralization/calcification
	• History and/or current evidence of clinically significant retinal disorder confirmed by retinal examination
	• History or current evidence of serious uncontrolled ventricular arrhythmias
	• Fridericia's corrected QT interval (QTcF) > 470 ms on electrocardiogram (ECG) conducted during screening
	• Treatment with any of the following within

○ Documentation of radiographic disease progression on the most recent prior therapy • Patient has measurable disease as defined by RECIST guidelines (version 1.1, 2009)[79] for advanced solid tumours • Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 on Day 1 of Cycle 1 • Able to take medications orally (e.g., no feeding tube) • Adequate organ function • Creatinine clearance (calculated [using the Cockcroft-Gault formula] or measured value): ≥ 40 mL/min • Women of child-bearing potential must have a negative pregnancy test (urine or serum) within 7 days prior to administration of the first dose of futibatinib. Both males and females of reproductive potential must agree to use effective birth control during the study prior to the first dose and for 6 months after the last dose • Willing and able to comply with scheduled visits and study procedures	the specified time frame prior to the first dose of futibatinib: ○ Major surgery within the previous 4 weeks ○ Radiotherapy for extended field within 4 weeks or limited field radiotherapy within 2 weeks ○ Locoregional therapy within 4 weeks ○ Any non-investigational anticancer therapy within 3 weeks or have not recovered from side effects of such therapy prior to futibatinib administration (mitomycin within prior 5 weeks). Targeted therapy or immunotherapy within 3 weeks or within 5 half-lives (whichever is shorter) ○ Any investigational agent received within 5 half-lives of the drug or 4 weeks, whichever is shorter. Concurrent participation in an observational study may be allowed after review by the Sponsor's Medical Monitor ○ Patients with prior FGFR-directed therapy • A serious illness or medical condition(s) including, but not limited to, the following: ○ Known brain metastasis (not including primary brain tumours) unless patient is clinically stable for ≥ 1 month ○ Known acute systemic infection ○ Myocardial infarction, severe/unstable angina, symptomatic congestive heart failure within the previous 2 months ○ Chronic nausea, vomiting, or diarrhoea considered to be clinically significant in the opinion of the investigator ○ Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death ○ Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that in the judgment of the investigator would make the patient inappropriate for entry into this study • Patients with a history of another primary malignancy that is currently clinically significant, and has potential for metastases or currently requires active intervention (except for GnRH or LH-RH agonists in

	prostate cancer or adjuvant hormonal therapy in breast cancer) • Pregnant or lactating female

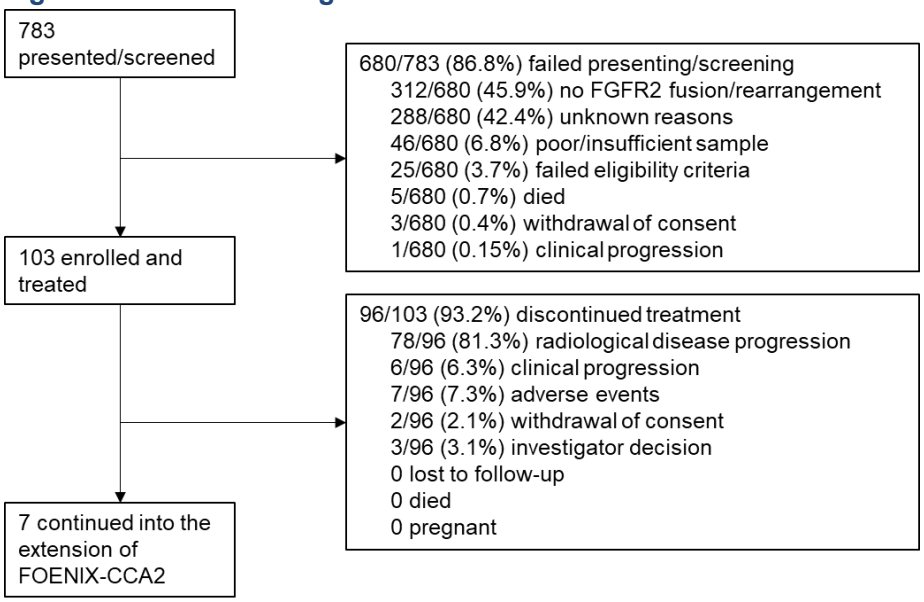
Note: Full inclusion and exclusion criteria can be found in FOENIX-CCA2 Clinical Study Protocol Amendment 10, Section 7.3[80]
Abbreviations: ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; FGFR2: fibroblast growth factor receptor 2; GnRH: gonadotropin-releasing hormone; iCCA: intrahepatic cholangiocarcinoma; LH-RH: luteinizing hormone-releasing hormone; QTcF: Fridericia's corrected QT interval
Source: Taiho Oncology. Data on File. FOENIX-CCA2 Clinical Study Protocol Amendment 10. Section 7.3;[80] Goyal *et al.* (2023)[6]

B.2.3.2 Participant flow

A CONSORT diagram showing patient flow through FOENIX-CCA2 is shown in Figure 6.

103 patients were enrolled into the FOENIX-CCA2 trial. The median follow-up time was 25.0 months at the time of the final DCO. A total of 96 (93.2%) patients discontinued treatment by the time of the final DCO. The primary reason for discontinuation from study treatment was either due to radiographic or clinical disease progression (81.5%). Only 7/96 (7.3%) of patients discontinued treatment due to adverse events. No patients discontinued study treatment due to death, loss to follow-up, or pregnancy. Seven (6.8%) patients continued into the extension portion of this study.

Figure 6: CONSORT diagram for FOENIX-CCA2



Abbreviations: FGFR2: fibroblast growth factor receptor 2
Source: Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 29 May 2021. Table 14B.1.2.1[76]; Goyal *et al.* (2023)[6]

B.2.3.3 Baseline characteristics

Baseline demographic characteristics

Demographic characteristics of the 103 patients enrolled in the FOENIX-CCA2 trial are summarised in Table 6. The median age of all patients was 58.0 years (range: 22 to 79 years) and 56.3% were female. Approximately half of the patients were White/Caucasian (49.5%). UK

clinical experts in CCA noted that the baseline patient demographics in FOENIX-CCA2 broadly aligned with UK clinical practice.[2]

Table 6: Summary of demographics and patient characteristics (safety population)

	All treated patients (N=103)
Age (years)	
N	103
Mean (SD)	55.7 (12.23)
Median (min, max)	58.0 (22, 79)
Age groups	
< 65 years	80 (77.7)
≥ 65 years	23 (22.3)
Sex, n (%)	
Male	45 (43.7)
Female	58 (56.3)
Race, n (%)	
Caucasian/White	51 (49.5)
Black or African American	8 (7.8)
Asian/Oriental	30 (29.1)
Native Hawaiian or Other Pacific Islander	1 (1.0)
Unknown	13 (12.6)
Region, n (%)	
North America	47 (45.6)
Europe	28 (27.2)
Asia Pacific (excluding Japan)	14 (13.6)
Japan	14 (13.6)
Ethnicity, n (%)	
Hispanic or Latino	2 (1.9)
Not Hispanic or Latino	89 (86.4)
Unknown	12 (11.7)

Abbreviations: SD: standard deviation
Source: Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 1 October 2020. Table 14B.1.5.1;[81] Goyal *et al.* (2023)[6]

Baseline disease characteristics

A summary of baseline disease characteristics for the 103 patients in the Safety Population is provided in Table 7. The median age at iCCA diagnosis was 57.5 years (range: 21 to 78 years) with a median time since initial diagnosis of 12.7 months (range: 2.0 to 61.4 months). ECOG PS was 0 for 46.6% and 1 for 53.4% of patients. UK clinical experts in CCA confirmed that the baseline characteristics of the FOENIX-CCA2 trial were broadly generalisable to UK clinical practice.[2]

In line with the trial inclusion criteria, all 103 patients had iCCA. This is aligned with FGFR2 fusions and rearrangements being most common in this population, and being rarely observed in

eCCA. UK clinical experts noted that if a patient is diagnosed with eCCA but receives a positive FGFR2 fusion/rearrangement genetic test, the initial diagnosis of eCCA is considered to be erroneous, and the patient would be re-classified as having iCCA.[2]

Eighty (77.7%) patients had FGFR2 fusions with detectable partner genes, and the remaining 23 (22.3%) patients had FGFR2 rearrangements other than fusions. UK clinical experts in CCA clarified that in reality, all FGFR rearrangements are gene fusions. Rearrangements are the result of tests where the fusion partner for FGFR2 is not detected. UK clinical experts indicated there is no meaningful clinical difference between patients classified with an FGFR2 fusion versus rearrangement.[2]

Table 7: Summary of baseline disease characteristics (safety population)

	All treated patients (N=103)
Time since initial diagnosis (months)	
n	103
Mean (SD)	17.46 (13.116)
Median (min, max)	12.70 (2.0, 61.4)
Age at initial diagnosis (years)	
n	90
Mean (SD)	55.2 (11.81)
Median (min, max)	57.5 (21, 78)
Time since most recent progression (months) to first dose date	
n	100
Mean (SD)	2.81 (4.427)
Median (min, max)	1.50 (0.2, 28.3)
Age at most recent progression (years)	
n	87
Mean (SD)	56.5 (11.6)
Median (min, max)	60.0 (22, 78)
ECOG PS, n (%)	
0	48 (46.6)
1	55 (53.4)
Summary of FGFR2 status	
Patients with sample for FGFR2 status	103 (100.0)
FGFR2 Status	
FGFR2 fusion	80 (77.7)
FGFR2 rearrangement	23 (22.3)

Notes: One patient had both liquid sample and tissue sample from the primary tumour site. FGFR2 final status was derived from the results by FMI central, results by FMI local, and results by local laboratory, in order of precedence
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; FGF: fibroblast growth factor; FGFR: fibroblast growth factor receptor; FMI: Foundation Medicine, Inc.; SD: standard deviation
Source: Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 1 October 2020. Table 14B.1.6.1, Table 14B.1.7.1 and Table 14B.1.5.1;[81] Goyal *et al.* (2023)[6]

Concomitant medications

The most frequently reported (reported for ≥ 50% of patients) concomitant medications at the time of study entry are listed in Table 8. All 103 (100%) patients reported the use of concomitant medications which were generally consistent with medications administered to patients with CCA. The use of phosphate binders (e.g., sevelamer) administered for the treatment of hyperphosphatemia was also expected for FGFR2 therapy, as confirmed by UK clinical experts.[2]

Table 8: Concomitant medications and therapies at the time of study entry reported for > 50% of the safety population

Anatomical therapeutic chemical class WHO drug name (preferred term)	All treated patients (N=103) n (%)
Patients who took at least 1 concomitant medication	103 (100.0)
All other therapeutic products	**96 (93.2)**
Sevelamer	66 (64.1)
Lanthanum carbonate	27 (26.2)
Analgesics	**76 (73.8)**
Paracetamol	56 (54.4)
Oxycodone	18 (17.5)
Drugs for acid related disorders	**64 (62.1)**
Omeprazole	20 (19.4)
Drugs for constipation	**55 (53.4)**
Sennoside A+B	16 (15.5)

Notes: Patients with 2 or more medications within a class level and drug name are counted only once within that class level and drug name. Concomitant medications include medications that either (1) started before first dose of study drug and were continuing at the time of first dose of study drug, or (2) started on or after first dose of study drug. Medications terms were coded using WHO Drug Dictionary version 2016 or current
Abbreviations: WHO: World Health Organisation
Source: Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 1 October 2020. Section 10.4.4.2;[81] Goyal *et al.* (2023)[6]

Prior cancer therapy

All patients reported receiving at least one prior systemic anticancer therapy. Patients received one (46.6%), two (30.1%), or ≥ three prior lines of therapy (23.3%). This was generally in line with the expectations of UK clinical experts in CCA, who stated that they would expect to most commonly use an FGFR2-inhibitor as a second-line treatment for eligible patients.[2] The experts noted that patients in FOENIX-CCA2 may be slightly more heavily pre-treated compared to clinical practice; it was however highlighted that the efficacy of futibatinib is not expected to vary by treatment line.[2]

The median time from last dose of prior anticancer therapy to the first dose of futibatinib was 1.51 months (range: 0.1 to 22.5 months).

Prior systemic anticancer therapy for advanced/metastatic disease was reported for 101 (98.1%) patients. All patients received a combination treatment with gemcitabine and platinum-based therapy, including 94 (91.3%) patients who received the combination of gemcitabine plus cisplatin.[81] UK clinical experts confirmed is this aligned with current UK practice.[2] Two patients

enrolled received chemotherapy with gemcitabine/cisplatin in the adjuvant setting and experienced disease recurrence within the last 6 months of the last dose of the regimen.

A total of 27.2% of patients received prior radiotherapy, and all 103 patients in the Safety Population had at least 1 prior surgery, including 39.8% with primary, metastatic tumour surgery, or any other anti-cancer surgery.

A summary of prior treatments received by the patients in the safety population of FOENIX-CCA2 is provided in Table 9.

Table 9: Prior treatments (safety population)

	All treated patients (N=103) n (%)
Patients having at least 1 prior anticancer therapy	103 (100.0)
Treatment type	
Neoadjuvant	4 (3.9)
Adjuvant	14 (13.6)
Advanced	101 (98.1)
Maintenance therapy	3 (2.9)
Number of regimens	
1	48 (46.6)
2	31 (30.1)
≥3	24 (23.3)
Best response to prior anticancer therapy	
Complete response	[redacted]
Partial response	[redacted]
Stable disease	[redacted]
Progressive disease	[redacted]
Not evaluable	[redacted]
Unknown	[redacted]
Time from the last prior anticancer therapy to the first dose date of futibatinib (months)	
n	103
Mean (SD)	[redacted]
Median (min, max)	1.51 (0.1, 22.5)
Patients who had at least 1 prior radiation therapy for primary disease	**28 (27.2)**
Patients who had at least 1 prior anti-cancer surgery	**41 (39.8)**

Abbreviations: SD: standard deviation
Source: Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 1 October 2020. Section 10.4.4.3;[81] Goyal *et al.* (2023)[6]

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

An overview of the analysis sets in the FOENIX-CCA2 trial is provided in Table 10.

Table 10: FOENIX-CCA2 analysis set definitions

Analysis set	Description	Number of patients
Safety set	All patients who received at least 1 dose of futibatinib	N = 103
Efficacy set	All patients with iCCA with FGFR2 gene fusions or other rearrangements who received at least 1 dose of futibatinib	N = 103
PRO set	All patients who received futibatinib treatment and had EQ-5D or EORTC QLQ-C30 assessment at baseline and at least one subsequent post-baseline assessment	N = 92
Per-protocol set	All treated patients who had no relevant protocol deviations. For patients who had a relevant deviation during the study, data collected before the point of deviation could be included in the analysis preformed on this population	N = 100

Abbreviations: EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L: Euro-QoL-5 dimensions-3 levels; FGFR2: fibroblast growth factor receptor 2; iCCA: intrahepatic carcinoma
Source: Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 1 October 2020. Appendix 16.1.9;[81] Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 29 May 2021. Addendum Section 14[76]

Primary efficacy endpoints

The primary efficacy endpoint of FOENIX-CCA2 was the objective response rate (ORR) (per IRC). The statistical methods for the primary analysis of the primary endpoint in FOENIX-CCA2 are presented in Table 11.

Table 11: Statistical methods for the primary analysis of FOENIX-CCA2

	FOENIX-CCA2 primary analysis
Hypothesis	The null hypothesis for the primary endpoint of the FOENIX-CCA trial was that the true ORR would be ≤10%
Statistical analysis	**Primary efficacy analyses** • The primary endpoint, ORR, was defined as the proportion of patients who achieved best overall response of PR or CR per RECIST 1.1 based on Independent Review Committee (IRC) in the Efficacy Population, was summarised by a binomial response rate • ORR was calculated from the best of overall response recorded from the start of treatment until progression disease or start of subsequent

	new anticancer treatment • The best overall response, CR and PR, was confirmed with at least 4 weeks intervals of two consecutive time points. A minimum of 6-week interval between initial of treatment (first dose date) and tumour measurement was required for SD • 95% confidence interval (binomial proportion confidence interval [CI]) for ORR was constructed with Clopper-Pearson 95% CI. The null hypothesis would be rejected if the 2-sided 95% CI lower bound was greater than 10%. This translates in observing at least 17 responders out of 100 in the efficacy set • ORR would be assessed by both IRC and investigator review **Secondary efficacy analyses** • DOR was defined as the time between the date of first response and the subsequent date of objectively documented progression of disease or death • The CR or PR would be derived based on investigators or independent radiologist assessment • OS was defined as the time between the first dosing date and the date of death. PFS was defined as the time from the first dosing date to the date of the first documented progression or death due to any cause, whichever occurs first • DOR, PFS, and OS would be analysed using Kaplan–Meier product-limit estimates. Median PFS and OS would be presented with 2-sided 95% CI if estimable. The cumulative PFS and OS would be plotted over time • DCR was defined as the proportion of patient with objective evidence of CR, PR, or SD, except that there is no requirement for a confirmation of an SD response. DCR would be calculated and a 2-sided Clopper–Pearson 95% CI will be constructed • All the analyses of efficacy, safety, and pharmacodynamics data for this study were performed using SAS® statistical software package, Version 9.3 or a later version
Sample size, power calculation	• Sample size considerations were based on differentiating a historical control ORR of 10% or less with a target ORR of 20%, based on the patient cohort that was being evaluated in the Phase 1 FOENIX-101 study • Assuming the true ORR is 20%, 100 patients would be required to provide 81% power to reject the null hypothesis that the true ORR is ≤10%, using a 2-sided Fishers exact test (alpha=0.05) • As such, approximately 100 iCCA patients with FGFR2 gene fusions or other rearrangements were planned to be enrolled in the FOENIX-CCA2 trial
Data management, patient withdrawals	• Missing data were not imputed in the patient level listings. The listings only presented the data recorded on the original CRF. If an AE had a completely missing onset date, then the AE was considered a TEAE. A medication with a completely missing start date was considered a prior medication. A medication with a completely missing stop date was considered a concomitant medication • Data handling rules for partially missing dates are described in the CSR Appendix 16.1.9

Abbreviations: AE: adverse event; CI: confidence interval; CRF: case report form; CSR: clinical study report; IRC: independent review committee; ORR: objective response rate
Source: Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 1 October 2020. Appendix 16.1.9[81]

B.2.5 *Critical appraisal of the relevant clinical effectiveness evidence*

The FOENIX-CCA2 trial was assessed for risk of bias and generalisability using the quality assessment tool developed by the York University CRD in line with NICE requirements.[77] Overall, the results of the FOENIX-CCA2 trial may be considered at low risk of bias, as summarised in Table 12.

Whilst FOENIX-CCA2 was single arm in nature, the trial had a clearly formulated goal the exposure and the outcomes were both accurately measured to minimise bias and the results were considered precise, believable and generalisable to the UK population. The appropriateness of FOENIX-CCA2 trial design was confirmed by UK clinical experts in CCA.[2]

Table 12: Overview of quality assessment for FOENIX-CCA2

	FOENIX-CCA2 (NCT02052778)[76]	Rationale
Was the cohort recruited in an acceptable way?	Yes	The trial included a number of patient recruitment locations, and the trial protocol had clear pre-specified inclusion and exclusion criteria that matched the aim of the study. However, the open-label single-arm design could introduce selection bias
Was the exposure accurately measured to minimise bias?	Yes	The futibatinib dosage allowed dose reductions and reasons for discontinuation were pre-specified in the study protocol. All dose reductions and discontinuations within the study were recorded
Was the outcome accurately measured to minimise bias?	Yes	Outcome measures were prespecified in the study protocol, including the specific criteria to be used to measure tumour response. Validated tumour response measurements (RECIST version 1.1) and standard safety monitoring and grading using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) were used. The primary endpoint included response assessment by an IRC; researcher assessment outcomes were compared to the IRC outcomes as part of the trial sensitivity analyses. However, neither patients nor assessors were blinded to study treatment
Have the authors identified all important confounding factors?	Unclear	All confounding factors relevant to the disease area of interest were not explicitly specified
Have the authors taken account of the confounding factors in the	Yes	The study contained pre-specified subgroup and sensitivity analyses, which explored a range of potentially relevant confounding factors

design and/or analysis?		
Was the follow-up of patients complete?	Yes	Follow-up of all patients was completed in line with the trial protocol as of the final DCO (29th May 2021)
How precise (for example, in terms of confidence interval and p values) are the results?	Trial results were precise	The primary endpoint was met with a high level of certainty relative to the pre-specified null hypothesis (null hypothesis: ORR ≤10%; ORR per IRC at final DCO: 41.7% [95% CI: 32.1, 51.9])

Abbreviations: CI: confidence interval; CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; DCO: data cut-off; ORR: objective response ratio.

B.2.6 *Clinical effectiveness results of the relevant studies*

Summary of the clinical effectiveness evidence relevant to the decision problem

- At the time of the final DCO in the FOENIX-CCA2 trial, with a median follow-up of 25.0 months, ORR following treatment with futibatinib was 41.7% (95% confidence interval [CI]: 32.1, 51.9), including 42 (40.8%) patients with a best response of PR and 1 (1.0%) patient with a best response of CR
- The number of responders with DOR of ≥6 months was 32 (74.4%), and 8 (18.6%) patients had responses of at least 12 months. At the final DCO, the DCR per central radiological assessment by independent review committee (IRC) was 82.5% (95% CI: 73.8, 89.3)
- [redacted] ([redacted]) patients had experienced a PFS event (i.e., disease progression or death) and 25 (24.3%) were censored at the final DCO. The median PFS was 8.9 months. At 6 and 12 months, the proportions of patients who were progression free were 65.0% and 35.4%, respectively
- At the time of the final DCO, a total of [redacted] OS events were observed. The median OS was 20.0 months. The OS rates at 6 and 12 months were 88.1% and 73.1%, respectively
- Patients' HRQoL was maintained throughout treatment: EQ VAS scores were maintained from baseline to treatment cycle 13 (mean change -1.8 to +4.8 across cycles)
- Taken together the clinical results indicate that futibatinib resulted in a substantial and sustained clinical response, while maintaining patients' HRQoL. UK clinical experts in CCA confirmed that this efficacy profile aligns with expectation for an FGFR2 inhibitor[2]

B.2.6.1 Data cuts

Data for the FOENIX-CCA trial are available from two DCOs: preliminary DCO (1st October 2020, median follow-up 17.1 months) and final DCO (29th May 2021, median follow-up 25.0 months). The following section only presents the results of the latest DCO; as the data with the longest follow-up, these data are the most relevant to the submission and are the data used in the economic model (as detailed in Section B.3.3).

B.2.6.2 Primary endpoint: ORR per IRC

The primary endpoint of the study was ORR, defined as the proportion of patients with objective evidence of confirmed complete response (CR) or partial response (PR) according to RECIST v1.1 per IRC.

The ORR results from the final DCO (29th May 2021) of FOENIX-CCA2 are summarised in Table 13 and depicted in Figure 7. Per IRC, for the 103 patients in the efficacy population, the confirmed ORR was 41.7% (95% confidence interval [CI]: 32.1%, 51.9%), including 42 (40.8%) patients with a best response of PR and 1 (1.0%) patient with a best response of CR.

DCR, defined as the proportion of patients with objective evidence of CR, PR, or SD, was a secondary endpoint in FOENIX-CCA2. At the final DCO, the DCR per IRC was 82.5% (95% CI: 73.8%, 89.3%).[76]

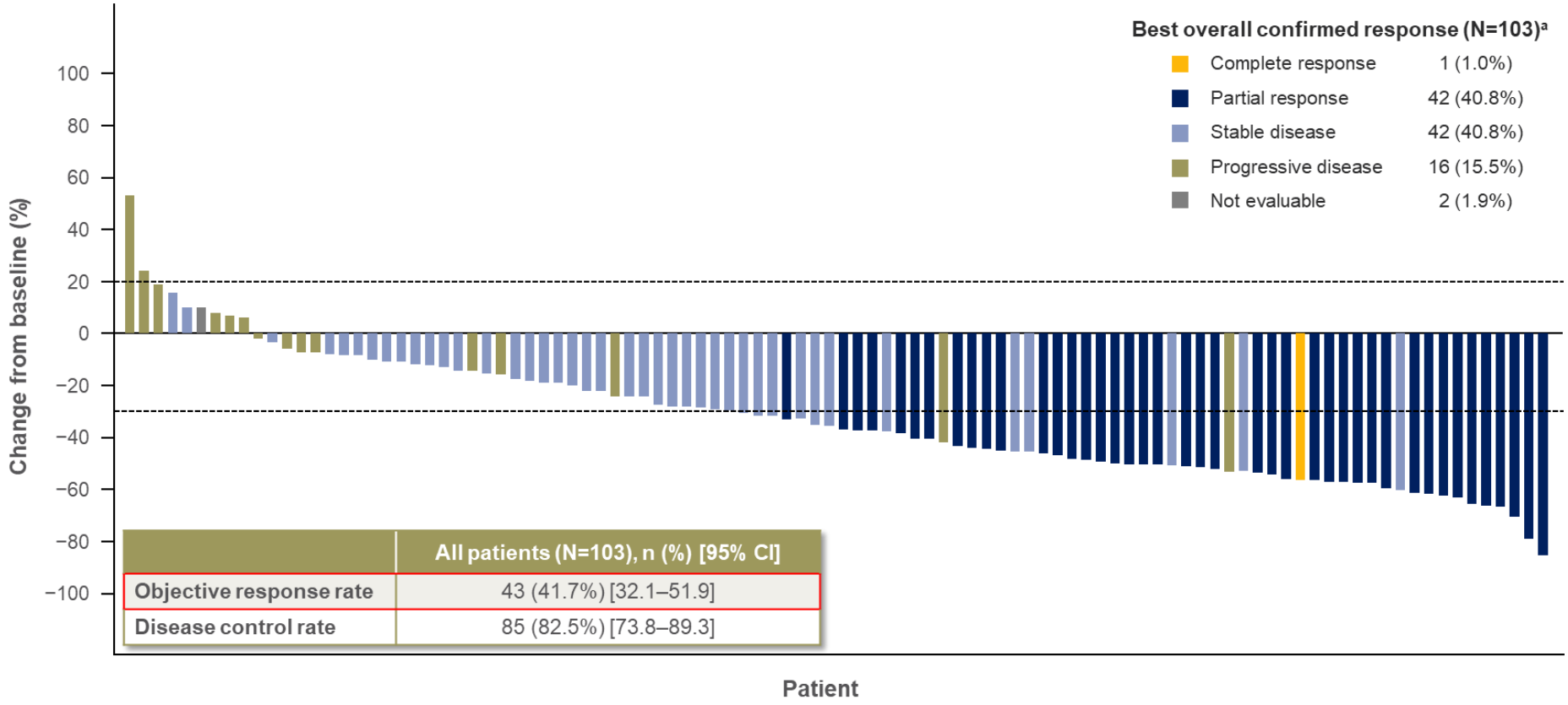
Each individual patient's response to futibatinib treatment in terms of percentage decrease in tumour size from baseline, as per RECIST v1.1, are illustrated in Figure 7, demonstrating that at the final DCO, tumour diameter had decreased in 91.3% (94/103) patients.

Table 13: Tumour response rate by IRC (efficacy population): final DCO

	All treated patients (N=103) n (%)
Best overall response	
Complete response (CR)	1 (1.0)
Partial response (PR)	42 (40.8)
Stable disease (SD)	42 (40.8)
Progressive disease (PD)	16 (15.5)
Not evaluable	2 (1.9)
Unconfirmed CR or PR	6 (5.8)
Objective response rate (ORR)	43 (41.7)
95% CI	32.1, 51.9
Disease control rate (DCR), n (%)	85 (82.5)
95% CI	73.8, 89.3

Notes: Objective response rate is based on confirmed PR/CR. Disease control rate is based on confirmed PR/CR/SD
Abbreviations: CI: confidence interval; CR: complete response; DCO: data cut-off; PR: partial response; SD: stable disease
Source: Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 29 May 2021. Table 14B.2.1.1[76]

Figure 7: Waterfall plot of patients target lesion sum of diameters percent change from baseline and best of response (efficacy population): final DCO



Notes: [a]Assessed by independent central review. One patient was not displayed because of no post-baseline assessments. Two patients were not displayed in Independent Review plot because there was no accepted Sum of Diameter information for these 2 patients
Abbreviations: CR: complete response; DCO: data cut-off; NE: not estimable; PD: progressive disease; PR: partial response; SD: stable disease
Source: Goyal *et al.* (ASCO 2022)[82]

B.2.6.3 Secondary endpoint: DOR

DOR was defined as the time from the first documented response (CR or PR) to the first documented objective progressive disease (PD) or death due to any cause. The median DOR by Kaplan-Meier analysis of the 43 responders was 9.46 months (95% CI: 7.62, 10.35; Figure 8).

The median duration of follow-up for responses was [redacted] months, and the median duration of follow-up from the onset of responses was [redacted] months.[76] The number of responders with DOR of ≥6 months was 32 (74.4%), and 8 (18.6%) patients had responses of at least 12 months[76]

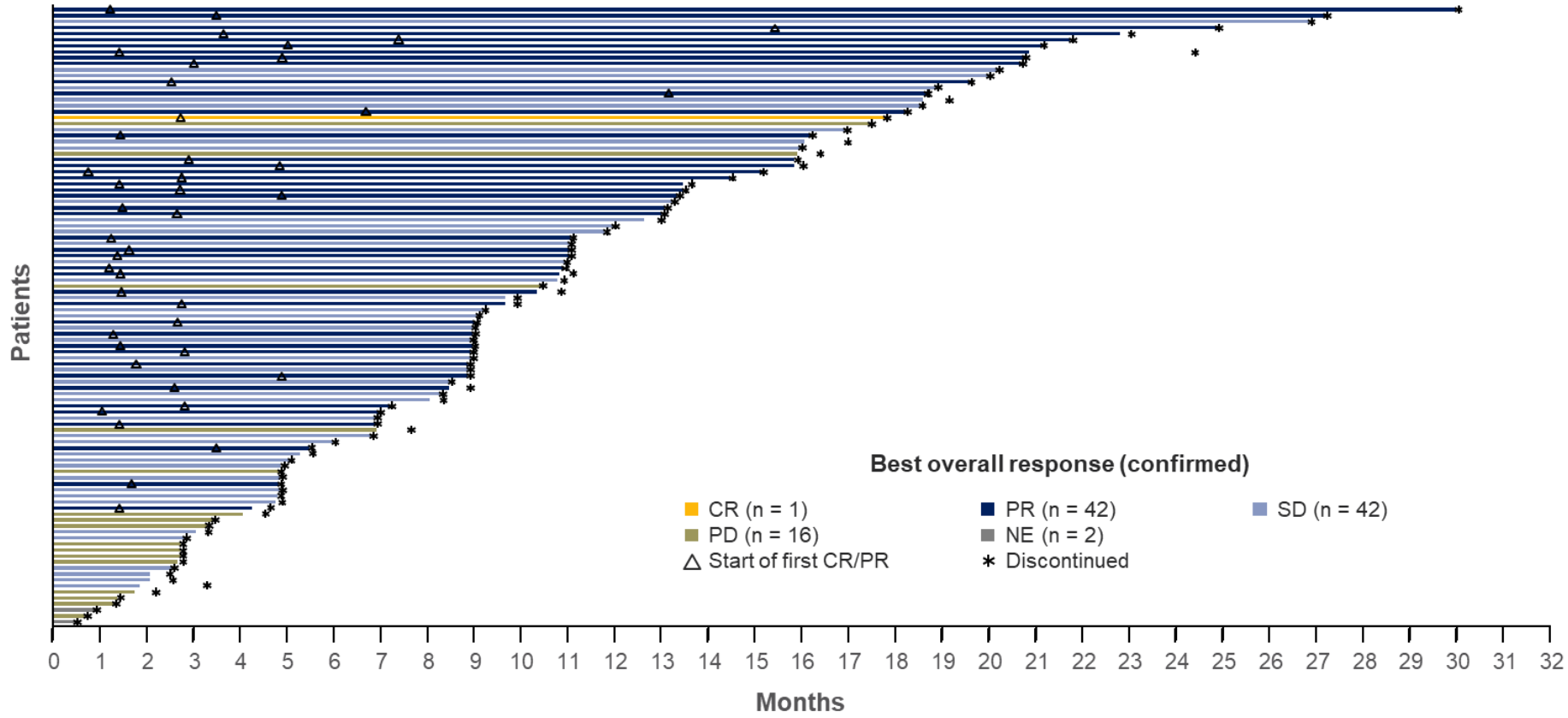
These results show a sustained treatment response, and a substantial proportion of patients who maintained response for over 1 year. The combination of high ORR and extended DOR provides prolonged treatment benefit to patients, translating to stable quality of life (Section B.2.6.6).

Table 14: Time to Response and Duration of Response (Responders)

	Responders as per IRC (N=43), n (%)
Duration of response (months)	
N	43
Median[a] (95% CI)	9.46 (7.62, 10.35)
Time to response (months)	
N	43
Median (min, max)	2.63 (0.7, 15.4)
Number of patients with duration of response of at least (%)	
3 months	[redacted]
6 months	32 (74.4)
12 months	8 (18.6)
Patients with ongoing response of duration ≥ 4 months[b]	[redacted]
Patients with ongoing response of duration ≥ 6 months[b]	[redacted]

Notes: Responders are patients with confirmed partial response or complete response; [a]Calculated using the Kaplan–Meier method; responses were based on independent central review per RECIST v1.1; [b]Patients with ongoing response consist of responders who had neither progressed nor initiated other anticancer therapy
Abbreviations: CI: confidence interval; IRC: independent review committee; SD: standard deviations
Source: Goyal *et al.* (ASCO 2022);[82] Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 29 May 2021. Table 14B.2.1.3[76]

Figure 8: Duration of response (based on IRC): final DCO



Notes: Responders: Patients with confirmed PR or CR
Abbreviations: CR: complete response; DCO: data cut-off; DOR: duration of response; IRC: independent review committee; NE: not evaluable; PD: progressive disease; PR: partial response; SD: stable disease
Source: Goyal *et al.* (ASCO 2022)[82]

B.2.6.4 Secondary endpoint: PFS

PFS was defined as the time from the date of first dose to the date of objective disease progression or death due to any cause (whichever occurred first).

As of the final DCO, [redacted] patients had experienced a PFS event (i.e., disease progression or death) and 25 (24.3%) were censored. As over [redacted] of patients had experienced a PFS event at the DCO, the PFS data are considered relatively mature. The median PFS was 8.9 months. At 6 and 12 months, the proportions of patients who were progression free were 65.0% and 35.4% (see Table 15, Figure 9).

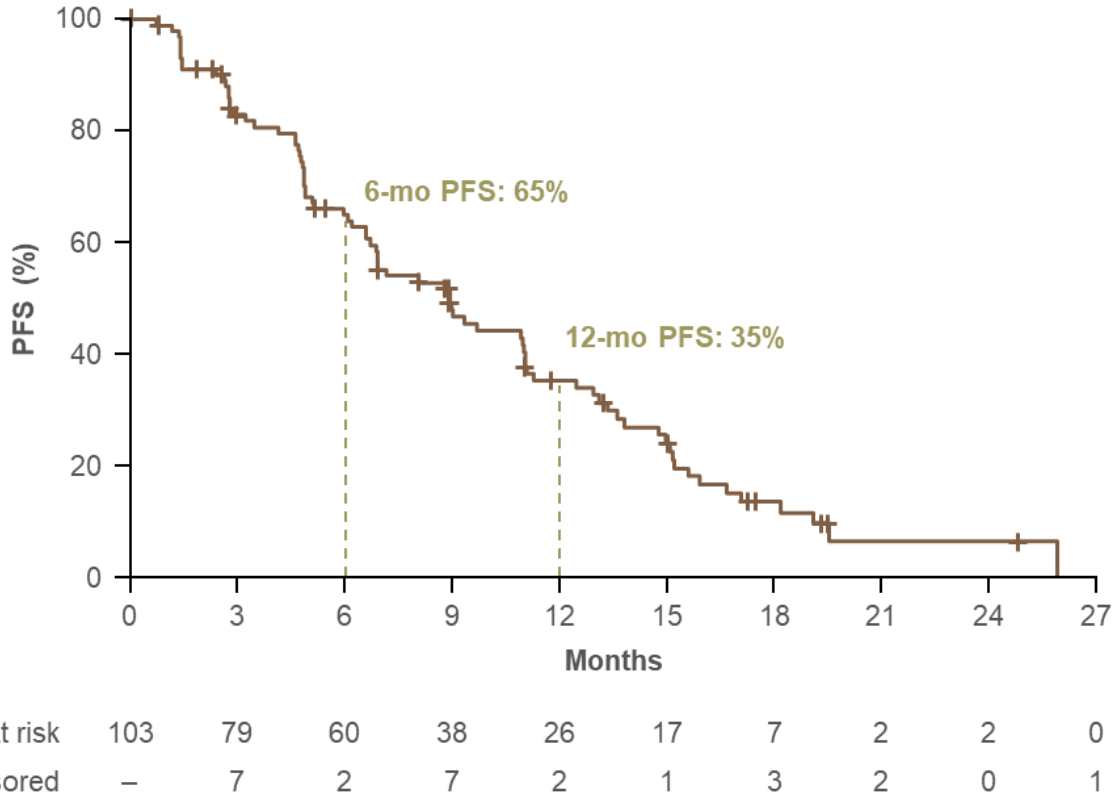
A naïve comparison shows that PFS outcomes at the final DCO were comparable between futibatinib in FOENIX-CCA2 and pemigatinib in the FIGHT-202 trial (median PFS 8.9 months versus 7.0 months for patients with FGFR2 fusions/rearrangements[83]) and notably better than the results expected for chemotherapy treatments, as confirmed by UK clinical experts.[2]

Table 15: Summary of progression-free survival by IRC (efficacy population): final DCO

	All treated patients (N=103)
Disease progression or deaths, n (%)	[redacted]
Censored patients, n (%)	25 (24.3)
No baseline assessment	[redacted]
No post-baseline assessment	[redacted]
New anticancer treatment	[redacted]
Two or more missed assessment	[redacted]
Treatment discontinued without PD/death	[redacted]
PD/Death greater than 21 days after the last dose	[redacted]
Patient still on treatment without PD	[redacted]
PFS (months)	
Median (95% CI)	8.9 (6.7, 11.0)
1st quartile (95% CI)	[redacted]
3rd quartile (95% CI)	[redacted]
PFS Rate (%) (95% CI)	
At 3 months	[redacted]
At 6 months	65.0 (54.6, 73.6)
At 9 months	[redacted]
At 12 months	35.4 (25.5, 45.4)

Notes: PFS is calculated from the date of the first dose of study drug to the date of 1st objective evidence of disease progression or date of death due to any cause, whichever occurs first. Point estimates of PFS rate are based on Kaplan-Meier method and 95% confidence intervals are based on the Greenwood Formula
Abbreviations: CI: confidence interval; DCO: data cut-off; PD: progressive disease; PFS: progression-free survival
Source: Goyal *et al.* (ASCO 2022);[82] Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 29 May 2021. Table 14B.2.1.2[76]

Figure 9: Kaplan-Meier curve for PFS: final DCO



Abbreviations: DCO: data cut-off; PFS: progression-free survival
Source: Goyal et al. (ASCO 2022)[82]

B.2.6.5 Secondary endpoint: OS

OS was defined as the time between the first dosing date and the date of death.

At the time of the final DCO, a total of [redacted] OS events were observed for this study. The median OS was 20.0 months. The OS rates at 6 and 12 months were 88.1% and 73.1%, respectively (see Table 16, Figure 10).

The OS outcomes for futibatinib at the final DCO were broadly aligned to those of pemigatinib in the FIGHT-202 clinical trial (median 20.0 months versus 17.5 months for patients receiving pemigatinib in FIGHT-202 with FGFR2 fusions or rearrangements[83]). UK clinical experts in CCA confirmed that the OS outcomes from futibatinib and pemigatinib were comparable, and represented a substantial improvement over the chemotherapy treatments previously available to this patient population.[2]

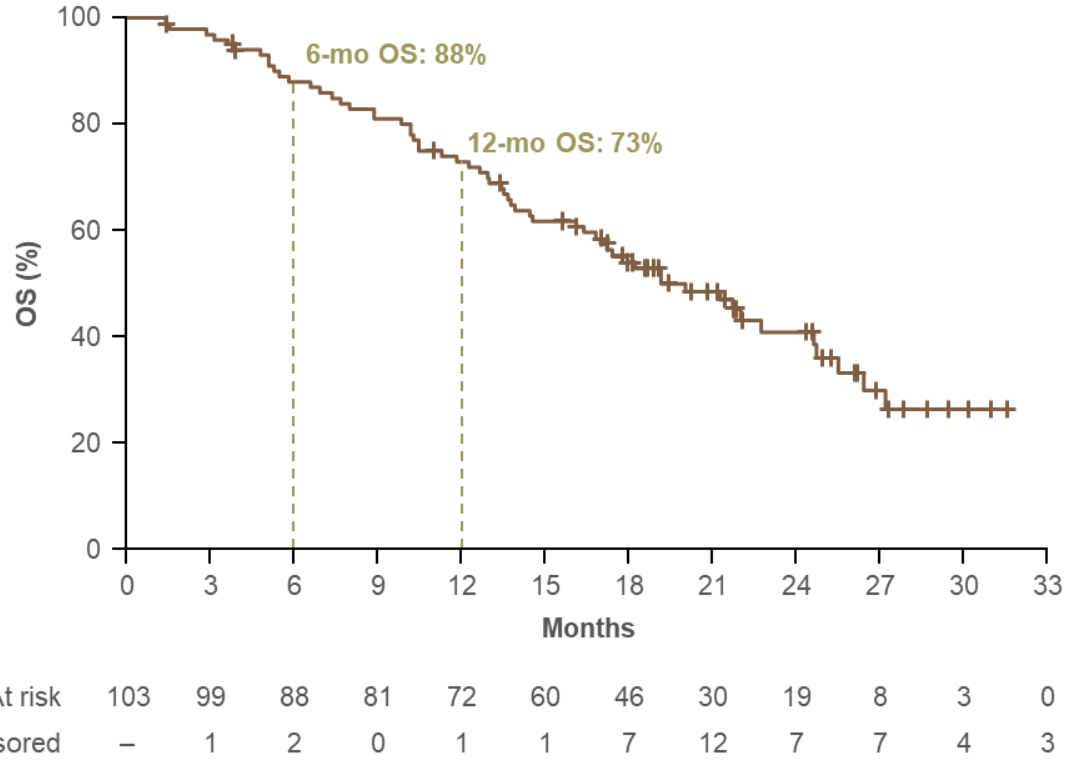
Table 16: Summary of overall survival (efficacy population): final DCO

	All treated patients (N=103)
Deaths, n (%)	[redacted]
Censored patients, n (%)	45 (43.7)
Patient discontinued treatment due to any reason before data cut-off	[redacted]
Overall survival (months)	

Median (95% CI)	20.0 (16.4, 24.6)
1st Quartile (95% CI)	[redacted]
3rd Quartile (95% CI)	[redacted]
Overall survival rate (%) (95% CI)	
At 3 months	[redacted]
At 6 months	88.1 (80.0, 93.1)
At 9 months	[redacted]
At 12 months	73.1 (63.2, 80.7)

Notes: Point estimates of overall survival rate are based on Kaplan-Meier method and 95% confidence intervals are based on the Greenwood Formula
Abbreviations: CI: confidence interval; DCO: data cut-off; NE: not estimable
Source: Goyal *et al.* (ASCO 2022);[82] Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 29 May 2021. Table 14B.2.1.4[76]

Figure 10: Kaplan-Meier curves for OS: final DCO



Abbreviations: DCO: data cut-off; OS: overall survival
Source: Goyal et al. (ASCO 2022)[82]

B.2.6.6 Secondary endpoint: PROs

Patient-reported outcome (PRO) measures included the EORTC QLQ-C30 (5 functional and 9 physical measures) and the EQ-5D-3L (utility index and 5 dimensions: anxiety/depression, mobility, pain/discomfort, self-care, and usual activity). Patient-reported outcomes were collected at Screening, Cycles 2 and 4, every 3 cycles after Cycle 4, and at the end of treatment. Change in mean score from baseline was assessed using predefined clinically meaningful thresholds for each time point with at least 19 observations (through Cycle 13).

Ninety-two of 103 (89.3%) enrolled patients had PRO data at baseline and at least 1 follow-up assessment; 45/103 (43.7%) patients had PRO data at Cycle 13. In the subsequent visits, less than 50% of patient population provided PRO data, therefore assessments of PRO outcomes presented below were conducted up to Cycle 13. The PRO assessments for the final DCO (21 May 2021) were consistent with those from the preliminary DCO (1 October 2020).

EQ-VAS

Mean EQ VAS scores were sustained from baseline to Cycle 13 (mean change -1.8 to +4.8 across cycles) (Table 17, Figure 11).

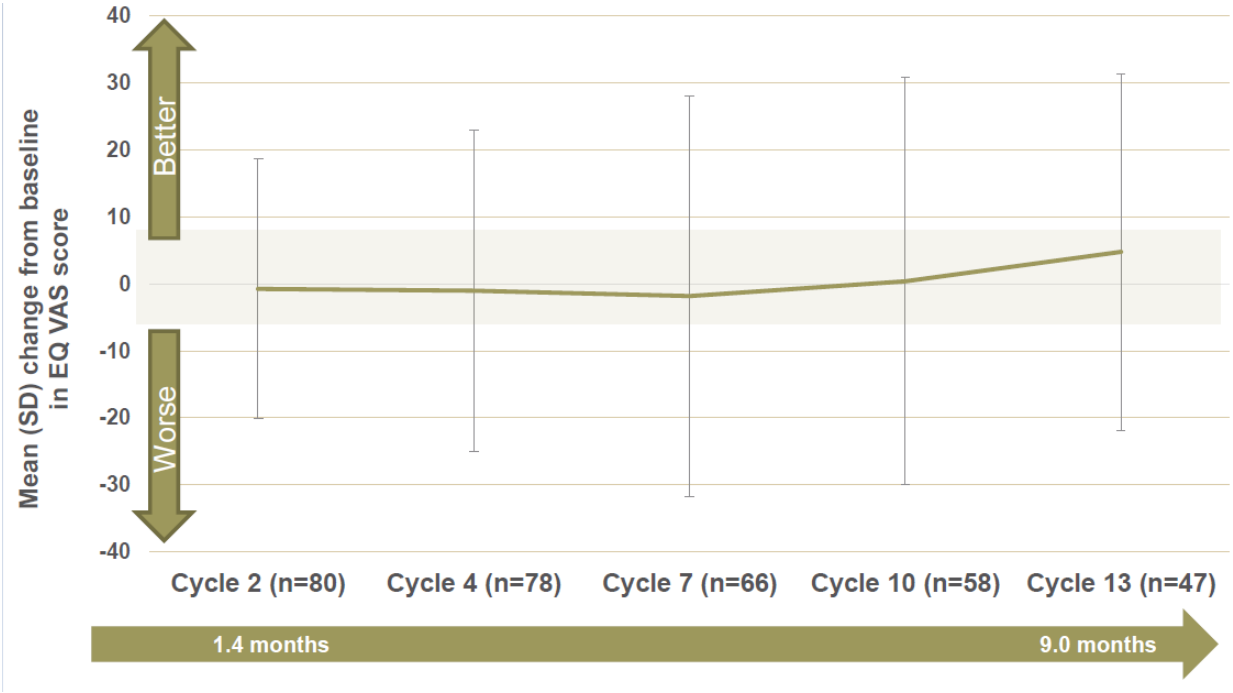
The UK clinical experts confirmed that the HRQoL data were in line with clinical expectations for a FGFR inhibitor in UK clinical practice.[2] These results indicate that the quality of life of patients was maintained throughout treatment with futibatinib.

Table 17: EQ VAS – mean and mean change from baseline by visit to the PRO primary assessment timepoint (PRO population)

	All treated patients (N=92)	
Screening	**Actual**	
n	88	
Mean	71.72	
SD	20.307	
Median	80.00	
Min, Max	6.5, 100.0	
Cycle 13	**Actual**	**Change from baseline**
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Notes: Only patients with data at both baseline and the relevant post-baseline visit are included in the change from baseline summary statistics
Abbreviations: DCO: data cut-off; SD: standard deviation
Source: Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 29 May 2021. Table 14B.4.1.3[76]

Figure 11: Mean change from baseline in EQ VAS scores over time



Notes: The shaded box indicates scores with no clinically meaningful change from baseline based on a change of +7 for improvement, and −7 for worsening. Error bars represent SD
Abbreviations: EQ VAS, EurQol visual analog scale; SD: standard deviation
Source: Goyal et al. (ASCO 2022)[82]

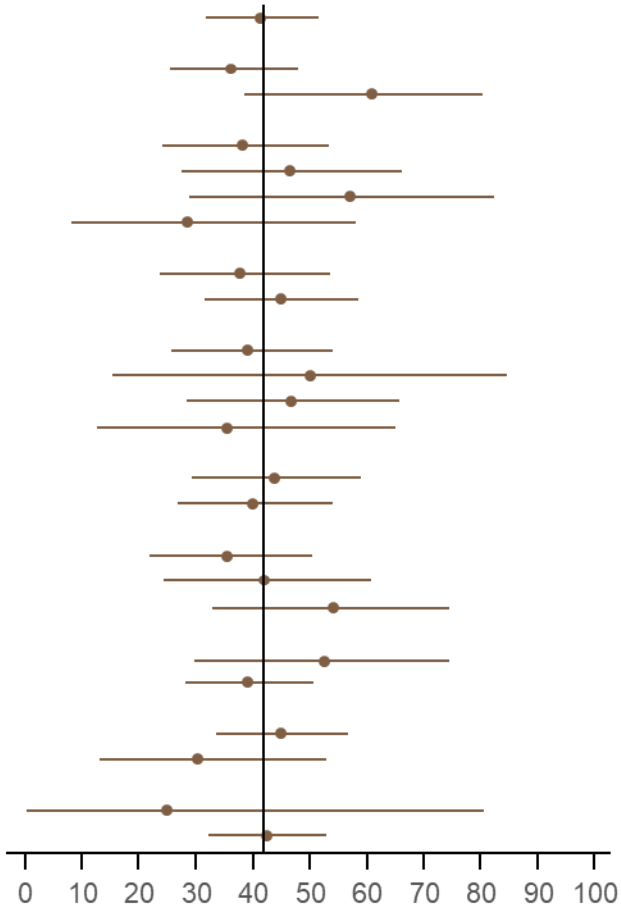
B.2.7 *Subgroup analysis*

B.2.7.1 Subgroup analysis for the primary endpoint

The results of a pre-specified subgroup analysis for ORR are provided in a forest plot in Figure 12. Overall the results of the subgroup analysis were consistent across subgroups and supported the conclusions of the primary analysis.

Figure 12: ORR subgroup analysis (based on IRC): efficacy population

Subgroup	Patients with response, n/N (%)	ORR (95% CI), %
All patients	43/103 (41.7)	41.7 (32.1–51.9)
Age		
<65 years	29/80 (36.3)	36.3 (25.8–47.8)
≥65 years	14/23 (60.9)	60.9 (38.5–80.3)
Region		
North America	18/47 (38.3)	38.3 (24.5–53.6)
Europe	13/28 (46.4)	46.4 (27.5–66.1)
Asia Pacific	8/14 (57.1)	57.1 (28.9–82.3)
Japan	4/14 (28.6)	28.6 (8.4–58.1)
Sex		
Male	17/45 (37.8)	37.8 (23.8–53.5)
Female	26/58 (44.8)	44.8 (31.7–58.5)
Race		
White	20/51 (39.2)	39.2 (25.8–53.9)
Black	4/8 (50.0)	50.0 (15.7–84.3)
Asian	14/30 (46.7)	46.7 (28.3–65.7)
Other	5/14 (35.7)	35.7 (12.8–64.9)
Baseline ECOG PS		
0	21/48 (43.8)	43.8 (29.5–58.8)
1	22/55 (40.0)	40.0 (27.0–54.1)
Prior systemic therapy		
1	17/48 (35.4)	35.4 (22.2–50.5)
2	13/31 (41.9)	41.9 (24.5–60.9)
≥3	13/24 (54.2)	54.2 (32.8–74.4)
Prior surgical resection of primary tumor		
Yes	11/21 (52.4)	52.4 (29.8–74.3)
No	32/82 (39.0)	39.0 (28.4–50.4)
***FGFR* status**		
FGFR2 fusion	36/80 (45.0)	45.0 (33.8–56.5)
FGFR2 rearrangement	7/23 (30.4)	30.4 (13.2–52.9)
Prior (neo)adjuvant treatment		
Yes	1/4 (25.0)	25.0 (0.6–80.6)
No	42/99 (42.4)	42.4 (32.5–52.8)



Abbreviations: ECOG: Eastern Cooperative Oncology Group; FGFR2: fibroblast growth factor receptor 2; IRC: independent review committee; ORR: overall response rate
Source: Goyal et al. (ASCO 2022)[82]

B.2.7.2 Post-hoc subgroup analysis of ORR and PFS by co-alteration

An exploratory analysis of data form FOENIX-CCA2 was carried out to assess the impact of co-alterations on futibatinib sensitivity (Table 18).[84] The results suggest that response rates to futibatinib are consistent across co-mutations. In particular, ORR and PFS were comparable for patients with or without TP53 co-alterations.

Table 18: Post-hoc subgroup analysis of ORR and PFS by co-alteration

Gene	Molecular status (n)	ORR (95% CI), %	Median PFS (95% CI), months
All patients (n = 93)	—	43.0 (32.8–53.7)	8.9 (6.6–13.1)
BAP1	Unaltered (53)	49.1 (35.1–63.2)	8.0 (4.9–13.8)
	Altered (40)	35.0 (20.6–51.7)	9.0 (5.1–13.3)
CDKN2A	Unaltered (73)	43.8 (32.2–55.9)	9.7 (6.9–13.8)
	Altered (20)	40.0 (19.1–63.9)	4.9 (3.4–13.3)
CDKN2B	Unaltered (77)	42.9 (31.6–54.6)	11.0 (7.2–15.1)
	Altered (16)	43.8 (19.8–70.1)	4.8 (3.4–4.9)
TP53	Unaltered (80)	43.8 (32.7–55.3)	9.0 (6.6–13.3)
	Altered (13)	38.5 (13.9–68.4)	7.0 (1.4–13.8)
ARID1A	Unaltered (81)	42.0 (31.1–53.5)	9.0 (6.2–13.1)
	Altered (12)	50.0 (21.1–78.9)	8.8 (4.9–18.2)

Notes: Analysis performed for the preliminary DCO (1 October 2020)
Abbreviations: ORR: objective response rate; PFS: progression-free survival
Source: Goyal L *et al.* Oral presentation at the AACR Annual Meeting 2021; April 10-15, 2021. Abstract CT010[84]

B.2.8 *Meta-analysis*

Given the lack of head-to-head randomised controlled trial (RCT) data for futibatinib versus the relevant comparators in UK clinical practice, a network meta-analysis was not performed.

B.2.9 *Indirect and mixed treatment comparisons*

Methodology

- In order to compare the efficacy of futibatinib and pemigatinib, it was necessary to conduct an indirect treatment comparison (ITC), comparing the results of the FOENIX-CCA2 and FIGHT-202 clinical trials. In line with the precedent from the pemigatinib NICE appraisal, a matching adjusted indirect comparison (MAIC) was conducted[61]
- The MAIC was carried out in line with best practice described by NICE and its methods were verified by UK experts.[2, 85] The outcome variables analysed were PFS and OS

Results

- The MAIC demonstrated that futibatinib and pemigatinib were associated with similar PFS and OS, with no statistically significant differences detected between the two treatments
- The PFS hazard ratio (HR) between futibatinib and pemigatinib was 1.07 (95% CI: 0.86–1.30) in the base case ITC; restricted mean survival time (RMST) analyses of PFS at 25.92 months found that futibatinib extended restricted mean PFS by 0.17 months (95% CI: -1.12, 1.56) when compared to pemigatinib
- The OS HR between futibatinib and pemigatinib was 0.95 (95% CI: 0.72–1.21). RMST analyses of OS at 27.24 months found that futibatinib extended restricted mean OS by 0.87 months (95% CI: -0.85, 2.52) versus pemigatinib
- The robustness of these results was confirmed by sensitivity analyses and by comparing the adjusted and naïve outcomes, all of which showed extremely similar results. No statistically significant differences between futibatinib and pemigatinib were detected in any of the analyses considered

As FOENIX-CCA2 is a single-arm trial, it does not compare futibatinib to the relevant comparator in UK clinical practice (pemigatinib), and therefore, in order to obtain relative efficacy estimates for futibatinib versus pemigatinib, it was necessary to conduct an ITC.

B.2.9.1 ITC methodology

The primary aim of the ITC was to compare the efficacy of futibatinib and pemigatinib, the only relevant comparator for futibatinib in UK clinical practice.

The outcome variables analysed were PFS and OS, as these were the endpoints used to inform the economic model. A safety ITC was also explored, but it was not considered feasible due to the differences in AE reporting definitions between FOENIX-CCA2 and FIGHT-202. In addition, UK clinical experts in CCA confirmed that the safety profiles of futibatinib and pemigatinib were very similar, and they did not expect there to be any meaningful difference in AE profiles, meaning that the absence of a safety ITC should not be considered to represent a major source of uncertainty.[2]

In order to identify the relevant clinical evidence for the efficacy and safety of futibatinib and pemigatinib in adults with unresectable or metastatic iCCA harbouring FGFR2 fusion or other rearrangement, an SLR was conducted, as reported in Section B.2.1 and Appendix D.

The SLR identified five clinical trials, which are described in Appendix D. As described in Appendix D.2.3, the FOENIX-CCA2 and FIGHT-202 clinical trials were considered the most relevant sources of evidence for futibatinib and pemigatinib, respectively. Of the remaining three trials for pemigatinib, two trials (FIGHT-101[86] and FIGHT-207[87]) were tumour-agnostic, and therefore only reported very limited results for the patient population of relevance to this submission. Whilst the remaining trial, NCT04256980 aligned with the patient population of interest,[88] it only enrolled N=31 patients exclusively in China, and therefore was considered less relevant than the FIGHT-202 trial, which is an international trial and was previously used to inform the prior NICE submission for pemigatinib (TA722).

The latest published DCO for FIGHT-202 was identified in a conference poster reporting final results from the trial (Vogel et al., 2022[83]).

Due to both FOENIX-CCA2 and FIGHT-202 being single-arm trials, an unanchored ITC method was necessary. Two established methods for conducting unanchored comparisons are described in NICE TSD18.[85] These are matching adjusted indirect comparison (MAIC) and simulated treatment comparison (STC).

Given the precedent for the use of a MAIC as part of the pemigatinib NICE appraisal,[61] as well as extensive precedent in NICE appraisals of oncology therapies, then a MAIC was also considered to represent the most appropriate ITC methodology for comparing futibatinib and pemigatinib in this appraisal. It should be noted that, for the primary DCO of FOENIX-CCA2, both a MAIC and an STC were conducted, and very similar results were observed from both analyses, providing confidence in the use of a MAIC. UK health economic experts confirmed the suitability of a MAIC to compare the efficacy of futibatinib and pemigatinib.[2]

A feasibility assessment was concluded to assess whether a MAIC was suitable for the data available. The assessment concluded that there was sufficient published evidence to enable an unanchored comparison using the MAIC method to estimate the relative treatment effect of futibatinib versus pemigatinib: the sample size of the FIGHT-202 subgroup of patients with FGFR2 fusions or rearrangements was sufficient for analysis (Cohort A; n=107) and comprehensive baseline data were available.

In a MAIC analysis, adjustments are made to the baseline characteristics of the study population of the intervention so they align more closely to the baseline characteristics of the study population of the comparator. This process of adjustment is referred to as propensity score weighting (PSW). In line with best practice (NICE TSD 18), the goal is to adjust for all potential prognostic factors and treatment effect variables that may confound the relationship between treatments and study outcomes, which is essential for a MAIC to be valid.[85]

The MAIC analysis comparing futibatinib and pemigatinib utilised the individual patient data (IPD) from the final DCO of the FOENIX-CCA2 trial, and the pseudo-IPD data generated from the published final data for the FIGHT-202 trial.[83] To account for potential differences between the studies, seven confounding factors were included in the base case Cox regression model (age, gender, ECOG status, prior lines, prior surgery, baseline hypoalbuminemia status, and TP53 alteration status). A sensitivity analysis was also performed additionally including the race covariate (White vs other). UK clinical experts in CCA indicated that all relevant treatment effect modifiers and prognostic variables had been adjusted for.[2]

Full methodology of the MAIC is provided in Appendix D.

B.2.9.2 MAIC results

Baseline characteristics

A comparison of key patient baseline characteristics for FIGHT-202 and FOENIX-CCA2 (unadjusted and population-adjusted) is presented below in Table 19.

The effective sample size (ESS) for the futibatinib group in the base case was 91.3, which was only a small reduction from the trial sample size and suggested good overlap in baseline characteristics between studies. No patient received a very large weighting, with the maximum rescaled weight being 1.78 (minimum 0.33). Further details on patient weighting are available in Appendix D.2.5.

Table 19: Baseline patient characteristics for FOENIX-CCA2 and FIGHT-202

Treatment (study)	Sample size or estimated sample size	Mean/ median age	% Male	% ECOG PS 0	% Albumin <35 g/L	% One prior therapy line	% Prior surgery	% TP53 alteration	% White[b]
Futibatinib unadjusted (FOENIX-CCA2)	N=103	55.7	43.7	46.6	19.4	46.6	39.8	12.6	49.5
Futibatinib population-adjusted (FOENIX-CCA2)	ESS=91.3	56.0	39.3	42.0a	19.6	60.7	35.5	8.4	73.8
Pemigatinib (FIGHT-202)[c]	N=108	56.0	39.3	42.0[a]	19.6	60.7	35.5	8.4	73.8

Footnotes: [a]Five patients (5%) had ECOG PS 2 in the pemigatinib group compared with no patients in the futibatinib group; [b]Race (% white versus other) was used in a sensitivity analysis; [c]Informed by the Cohort A (n=107, FGFR2 fusions or rearrangements) of the FIGHT-202 trial
Abbreviations: CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; ESS: estimated sample size; OS: overall survival; PFS: progression-free survival; TP53: tumour protein p53
Source: Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 1 October 2020;[81] Vogel et al. (2022)[89]

PFS

As previously detailed, the median PFS from FOENIX-CCA2 was 8.9 months (95% CI: 6.7–11.0); in comparison, median PFS from FIGHT-202 was lower at 7.0 months (95% CI: 6.1–10.5) (Table 20).

The unadjusted and weighted futibatinib PFS curves compared with the pemigatinib PFS curve are shown in Figure 13. The futibatinib and pemigatinib KM curves appear to track each other very closely until ~18 months, at which point very low numbers of patients are at risk in both treatment arms.

The Cox model was used to calculate HRs for the relative effect of futibatinib versus pemigatinib. Table 21 summarises the results from the unadjusted Cox model and covariate-adjusted MAIC analyses for PFS. This analysis resulted in an adjusted PFS HR of 1.07 (95% CI: 0.86, 1.30), with no statistically significant difference between the two treatment groups.

In addition to HRs, restricted mean survival time (RMST) analyses were conducted for the base case analysis, based on the length of PFS follow-up in the FOENIX-CCA2 trial ([redacted] months). The results of the RMST analyses similarly indicated no statistically significant difference in PFS survival for futibatinib and pemigatinib, with the futibatinib RMST PFS being slightly higher than that for pemigatinib (10.17 months versus 9.997 months).

A sensitivity analysis was also conducted, with the race covariate added to the base-case analysis covariates. The results of this analysis were similar to those in the base case (Table 21).

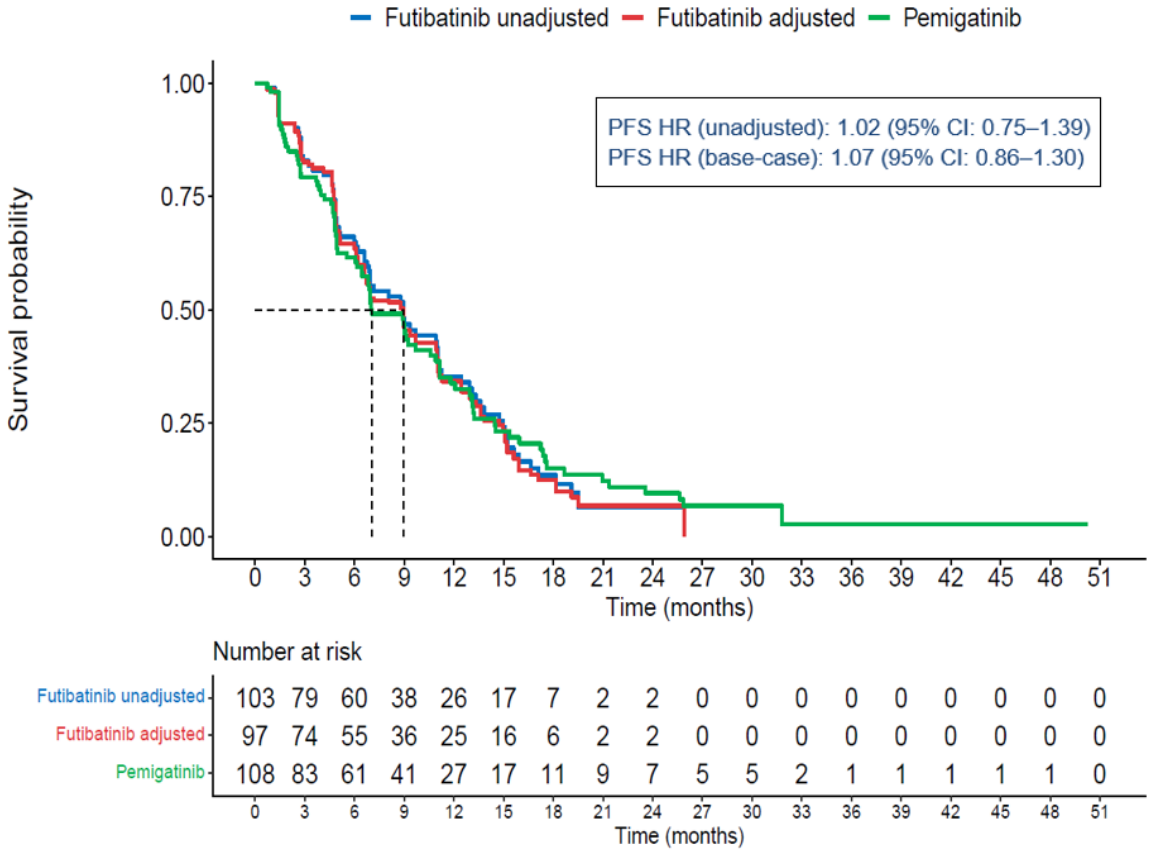
Overall, the results of the MAIC point towards futibatinib and pemigatinib having a very similar efficacy profile. This is supported by UK clinical expert opinion.[2]

Table 20: Unadjusted KM estimates of PFS for futibatinib and pemigatinib

Model	N	Events, n (%)	Median, months (95% CI)	Estimated PFS events from recreated KM, n (%)	Estimated median, months (95% CI) from recreated KM
FOENIX-CCA2	103	[redacted]	8.94 (6.74, 11.00)	N/A	N/A
FIGHT-202	108	85 (78.70)	7.0 (6.1, 10.5)	88.00 (81.48)	7.03 (6.14, 10.60)

Abbreviations: CI: confidence interval; KM: Kaplan–Meier; N/A: not applicable; PFS: progression-free survival

Figure 13: KM plot of unadjusted and MAIC-weighted PFS for futibatinib and pemigatinib



Abbreviations: IRC: Independent review committee; KM: Kaplan–Meier; MAIC: matching-adjusted indirect comparison; PFS: progression-free survival

Table 21: Unadjusted and adjusted PFS model results

Model	HR for PFS	95% CI; p value	RMST (months) for PFS at 25.92 months	RMST difference (months) for PFS (95% CI; p value)	Notes
Unadjusted analyses					
Cox-naïve/unadjusted	1.02	0.75–1.39; p=0.918	Futibatinib unadjusted: 10.01 Pemigatinib 9.997	0.02 (-2.07, 2.11); p=0.988	No covariate adjustment
Adjusted Cox MAIC model analyses					
Base-case	1.07	0.86–1.30; p=0.520	Futibatinib adjusted: 10.17	0.17 (-1.12, 1.56); p=0.804	Adjusted for age, gender, ECOG status, prior lines, prior surgery, baseline hypoalbuminemia status, TP53 alteration status

Sensitivity analysis	1.11	0.89–1.36; p=0.335	N/A	N/A	Base-case covariates + race

Abbreviations: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; PFS: progression-free survival; RMST: restricted mean survival time

OS

The observed data for futibatinib and pemigatinib are presented in Table 22, with a median OS of 20.0 months for futibatinib (95% CI: 16.4, 24.6), compared with a median OS for pemigatinib of 17.5 months (95% CI: 14.4–22.9; Table 22).

The unadjusted and weighted futibatinib OS curves compared with the recreated pemigatinib OS curve are shown in Figure 14. The unadjusted and adjusted futibatinib OS curves appear to show that futibatinib is associated with a slight OS benefit versus pemigatinib from Month ~6 to Month ~27; after this point, extremely low numbers of patients at risk remain in the futibatinib data due to the length of follow-up of the futibatinib trial.

Table 23 summarises the results from the unadjusted Cox model and covariate-adjusted MAIC analyses. The MAIC base-case HR estimate shows a comparable risk of death for futibatinib versus pemigatinib patients (HR: 0.95; 95% CI: 0.72–1.21), with no statistically significant differences between the two treatments. This effect remained statistically non-significant in the sensitivity analysis, which explored the addition of race to base-case covariates.

Additionally, results of the RMST analysis are presented in Table 23 based on the follow-up time for OS in the FOENIX-CCA2 trial ([redacted] months). Based on RMST calculation, futibatinib slightly extended restricted mean OS when compared to pemigatinib across all analyses considered, with an increase of 0.87 months (95% CI: -0.85, 2.52) in the base case ITC.

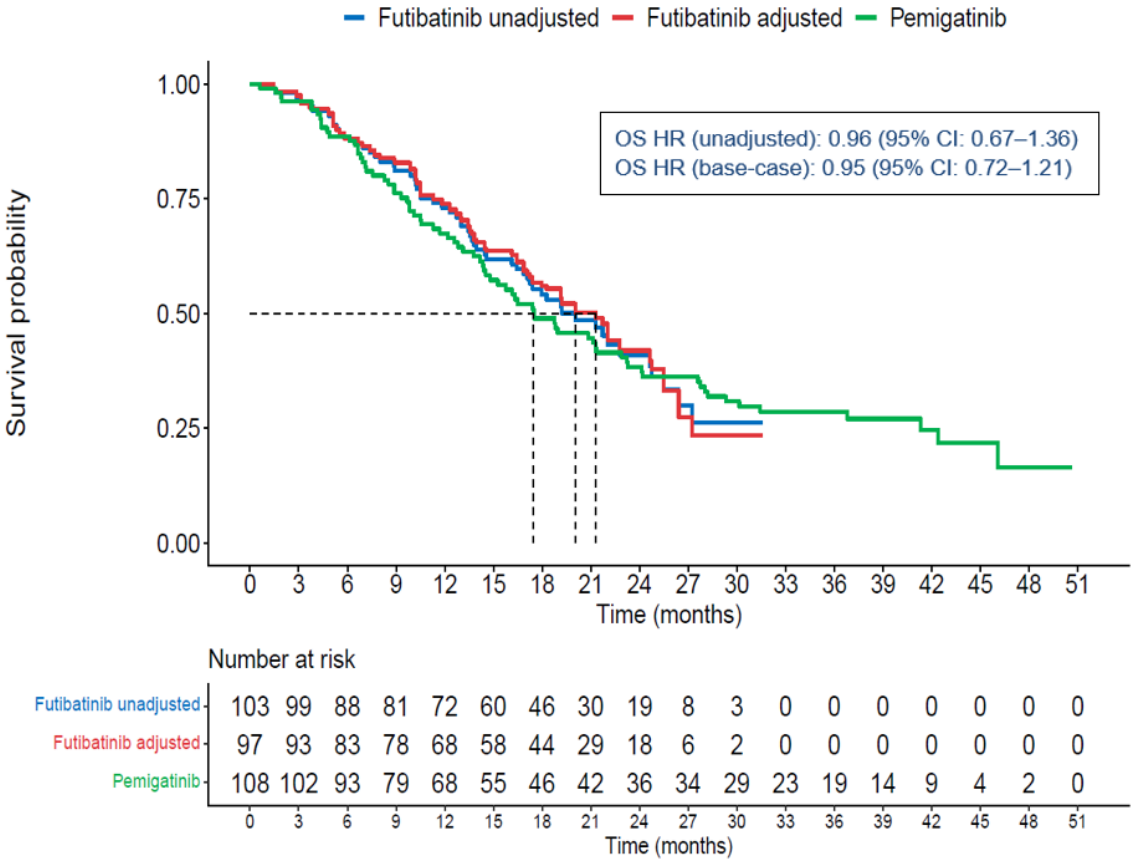
Overall, the results of the MAIC point towards futibatinib and pemigatinib having a very similar efficacy profile. This is supported by UK clinical expert opinion.[2]

Table 22: Unadjusted KM estimates of OS for futibatinib and pemigatinib

Model	N	Events, n (%)	Median, months (95% CI)	Estimated OS events from recreated KM, n (%)	Estimated median, months (95% CI) from recreated KM
FOENIX-CCA2	103	[redacted]	20.0 (16.4–24.6)	N/A	N/A
FIGHT-202	108	76 (70.37)	17.5 (14.4–22.9)	75.00 (69.44)	17.50 (14.40–22.90)

Abbreviations: CI: confidence interval; KM: Kaplan–Meier; N/A: not applicable; NR: not reported; OS: overall survival

Figure 14: KM plot of unadjusted and MAIC-weighted OS for futibatinib and pemigatinib



Abbreviations: KM: Kaplan–Meier; MAIC: matching-adjusted indirect comparison; OS: overall survival

Table 23: Unadjusted and adjusted OS model results

Model	HR for OS	95% CI; p value	RMST (months) for OS at 27.24 months	RMST difference (months) for OS (95% CI; p value)	Notes
Unadjusted analyses					
Cox-naïve/unadjusted	0.96	0.67–1.36; p=0.799	Futibatinib unadjusted: 18.41 Pemigatinib: 17.59	0.82 (-1.59, 3.22); p=0.505	No covariate adjustment
Adjusted Cox MAIC model analyses					
Base-case covariates	0.95	0.72–1.21; p=0.699	Futibatinib adjusted: 18.46	0.87 (-0.85, 2.52); p=0.312	Adjusted for age, gender, ECOG status, prior lines, prior surgery, baseline hypoalbuminemia status, TP53 alteration status
Sensitivity analysis includes	0.96	0.71–1.25; p=0.777	N/A	N/A	Base case covariates + race

race covariate (white vs other)					

Abbreviations: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; IPD: individual patient data; MAIC: matching-adjusted indirect comparison; OS: overall survival; RMST: restricted mean survival time

B.2.9.3 Uncertainties in the MAIC

The MAIC was conducted in line with best practice outlined in NICE TSD18.[85] Despite this, it had a number of inherent limitations, due to the single-arm nature of both the futibatinib and pemigatinib pivotal trials.

Most importantly, one of the assumptions for an unanchored ITC is that all prognostic factors and effect modifiers are known and adjusted for in the analyses. This is a strong assumption, as potential matching covariates are limited to those reported in the comparator trials and those collected in FOENIX-CCA2. However, clinical experts in CCA confirmed that the variables adjusted for in the PSW are sufficient, and health economic experts consulted during an advisory board agreed that the MAIC methodology represented the best approach available, given the limitations of the clinical evidence base.[2] The conclusions of the MAIC were additionally supported by conducting sensitivity analyses. All sensitivity analyses produced comparable outcomes to those obtained in the base case, supporting the robustness of these results.

In addition to MAIC, another unanchored ITC method recommended by NICE is an STC.[85] However, as previously detailed, given the extensive precedent for the use of MAICs in NICE oncology appraisals, including TA722 for pemigatinib, the MAIC approach was preferred for this analysis. It should be noted that for the primary DCO of FOENIX-CCA2, both a MAIC and an STC were conducted, which produced similar results.

B.2.9.4 MAIC conclusions

In order to compare the efficacy of futibatinib and pemigatinib, a MAIC was conducted, comparing PFS and OS outcomes of the FOENIX-CCA2 and FIGHT-202 trials. All clinically relevant covariates were adjusted for, and sensitivity analyses were performed in order to verify the results.

For all analysed outcomes, the MAIC showed similar results for futibatinib and pemigatinib, indicating that the efficacy of futibatinib is at least equal to the efficacy of pemigatinib, with no statistically significant differences detected between the two treatments in any of the analyses considered. This conclusion aligned with the clinical experience of the UK clinical experts in CCA, and the methods of MAIC were verified by both economic and clinical experts.[2]

B.2.10 *Adverse reactions*

Summary of futibatinib safety profile

- The frequency of serious treatment-related adverse events (TRAEs) observed in FOENIX-CCA2 was low: all TRAEs were grade ≤3 in severity, except for two grade 4 events (one grade 4 TRAE of increased alanine transaminase [ALT] and one grade 4 TRAE eye disorder)[82]
- The most common TRAEs included hyperphosphatemia (85.4%), alopecia (33.0%), dry mouth (30.1%), and diarrhoea (28.2%)[82]
- No treatment-related deaths occurred. Only four patients (4%) discontinued treatment due to TRAEs
- The side effects of futibatinib observed in the FOENIX-CCA2 trial were generally tolerable and aligned with clinical expectations for an FGFR2 inhibitor[2, 76]

A summary of the safety data from FOENIX-CCA2 is presented below. Further safety data can be found in Appendix F.

B.2.10.1 Safety summary

In the FOENIX-CCA2 trial, most patients experienced mild-to-moderate AEs which were manageable. The most common TRAE (85.4%), and the most common grade 3–4 TRAE (30.1%) was hyperphosphatemia, which aligns with expectation for an FGFR2 inhibitor. Other adverse events commonly reported in patients who receive FGFR inhibitors were generally mild, including nail toxic effects and retinal disorders.[6]

UK clinical experts in CCA confirmed that the safety profile of futibatinib aligned with expectation for an FGFR2 inhibitor, and that the safety profiles of futibatinib and pemigatinib were similar.[2]

B.2.10.2 Treatment duration and exposure

The median number of cycles of treatment received was 13.0 (range: [redacted]), with a median duration of treatment of 9.07 months (range: [redacted]). The median relative dose intensity was [redacted]. The median total dose received was [redacted] mg (range: [redacted]).[76]

B.2.10.3 Adverse events

The safety profile of futibatinib observed in FOENIX-CCA2 was generally manageable and in line with expectation for an FGFR2 inhibitor. No new safety signals were identified compared with the preliminary DCO, which provides evidence towards the long-term safety of futibatinib. A summary of TEAEs observed in the FOENIX-CCA2 trial is presented in Table 24.

Table 24: Summary of TEAEs

	Safety population (N=103), n (%)	
	Any grade	Grade ≥3
TEAEs (any cause)	[redacted]	[redacted]
Serious AEs	[redacted]	
Dose modification due to AE:		
Dose interruption	[redacted]	
Dose reduction	[redacted]	
Drug discontinuation	[redacted]	
TRAEs	[redacted]	[redacted]
Serious AEs	[redacted]	
Dose modification due to AE:		
Dose interruption	[redacted]	
Dose reduction	[redacted]	
Drug discontinuation	4 (3.9)	
AEs with outcome of death	0	

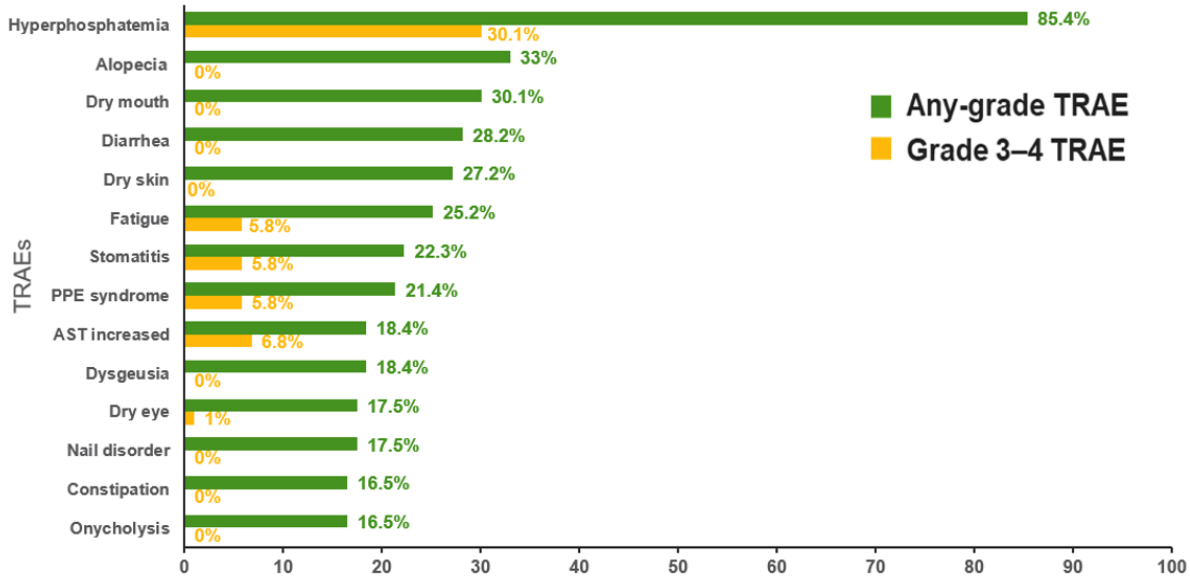
Abbreviations: AE: adverse event; TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event
Source: Goyal *et al.* (ASCO 2022);[82] Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 29 May 2021[76]

Summary of treatment-related adverse events (TRAEs)

All TRAEs were grade ≤3 in severity, except for two grade 4 events (increased ALT [n = 1] and eye disorder [n = 1]). The frequency of serious TRAEs was low, and no treatment-related deaths occurred. Only four patients discontinued treatment due to TRAEs.

The most common TRAEs included hyperphosphatemia, alopecia, dry mouth, and diarrhoea. A summary of most common (≥15%) TRAEs seen in FOENIX-CCA2 is shown in Figure 15.

Figure 15: Most common (≥15%) TRAEs



Notes: N=103 patients; Adverse events were graded using CTCAE Version 4.03 except for hyperphosphatemia and blood phosphorus increased; Incidence of cataracts was 4% (4; all grade), of which 3% (3) were ≥grade 3; Grade 3 hyperphosphataemia defined as serum phosphate level ≥7 mg/dL. Two grade 4 events were reported (increased ALT [n = 1] and eye disorder [n = 1]), and no grade 5 TRAEs occurred
Abbreviations: AE: adverse event; AST: aspartate aminotransferase; CTCAE: common terminology criteria for adverse events; PPE: palmar–plantar erythrodysesthesia; TRAE: treatment-related adverse event
Source: Goyal et al. (ASCO 2022)[82]

Deaths

A total of [redacted] patients died on study treatment or within 30 days of their last dose of futibatinib. No deaths were assessed to be treatment-related.[82]

Adverse events of special interest (AESIs)

The AESIs of hyperphosphatemia, retinal disorders, hepatotoxicity, nail disorders, palmar-plantar erythrodysesthesia (PPE) syndrome and rash were considered to be AESIs in the FOENIX-CCA2 trial.

An overview of AESIs observed during the FOENIX-CCA2 trial is presented in Table 25. Overall, the AESIs were manageable. No grade 5 AESI were reported. One AESI led to treatment discontinuation (PPE syndrome, Grade 1). Hyperphosphataemia was manageable with phosphate-lowering therapy and dose modification.

Table 25: Overview of AESIs

AE of special interest by group term	Safety population (N = 103), n (%)		
	Any grade	Grade 3	Grade 4
Hyperphosphataemia[a]	94 (91.3)	32 (31.1)	0
Nail toxicities[b]	54 (52.4)	2 (1.9)	0
Increased ALT and AST[c]	28 (27.2)	12 (11.7)	1 (1.0)

PPE syndrome	23 (22.3)	6 (5.8)	0
Rash[d]	9 (8.7)	0	0
Retinal disorders[e]	8 (7.8)	0	0

Notes: No Grade 5 AESIs were reported; [a]Includes increased blood phosphorus; [b]Includes nail discoloration, disorder, dystrophy, hypertrophy, infection, pigmentation, or toxicity, and onychalgia, onycholasis, onycholysis, onychomadesis, onychomycosis, and paronychia; [c]Also includes 2 events of increased GGT; [d]Includes macular, maculopapular, or papular rash; [e]Includes chorioretinopathy, detachment of retinal pigment epithelium, maculopathy, serous retinal detachment, and subretinal fluid
Abbreviations: AE: adverse event; AESI: adverse event of special interest; ALT: alanine transaminase; AST: aspartate transaminase; PPE: palmar–plantar erythrodysesthesia
Source: Goyal et al. (ASCO 2022)[82]

B.2.11 *Ongoing studies*

Two studies of futibatinib in CCA are ongoing:

- A study of futibatinib in patients with advanced CCA with FGFR2 fusion or rearrangement (TAS-120-205, FOENIX-CCA4, NCT05727176), which is an open-label, multinational, randomised Phase II study confirming the clinical benefit of 20 mg futibatinib and evaluating the safety and efficacy of 16 mg futibatinib, is recruiting patients.[90]
- A clinical trial FOENIX-CCA3 (TAS-120-301, NCT04093362) is ongoing. FOENIX-CCA3 is a Phase III study comparing the efficacy and safety of futibatinib versus gemcitabine plus cisplatin chemotherapy as first-line treatment in adults with unresectable or metastatic CCA with FGFR2 rearrangement.[91]

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

Principal findings from the clinical evidence base

In the FOENIX-CCA2 clinical trial, futibatinib 20 mg QD was shown to result in a substantial and sustained response in patients with iCCA. At the final DCO, ORR was 41.7%; median PFS was 8.9 months and median OS was 20.0 months. The number of responders with DOR of ≥6 months was 32 (74.4%), and 8 (18.6%) patients had responses of at least 12 months; the DCR per IRC was 82.5%. In addition to this sustained clinical response, the patients' HRQoL was maintained while on treatment with futibatinib.

The only relevant comparator for futibatinib in UK clinical practice is pemigatinib. Since key clinical evidence for futibatinib and pemigatinib comes from single-arm trials (FOENIX-CCA2 and FIGHT-202, respectively), a MAIC was performed in order to compare the efficacy of these two treatments. The results across all analysed outcomes, supported by sensitivity analyses, showed that the efficacy of futibatinib and pemigatinib was comparable, with no statistically significant differences observed between the two treatments in any of the analyses considered. This conclusion of equal efficacy was supported by UK clinical experts, who highlighted that they would expect the efficacy profile of futibatinib to be at least equal to the efficacy profile of pemigatinib.[2]

Beyond these observed efficacy results, one consideration is the potential resistance profile associated with both futibatinib and pemigatinib. UK clinical experts in CCA highlighted the

potential importance of futibatinib in reducing the potential to treatment resistance with FGFR2 inhibitors based on *in vitro* study data (see Figure 1, Goyal *et al.* [2023]).[2] Unlike the co-alteration profile (Section B.2.7.2), resistance mutations arise during treatment with FGFR2 inhibitors, and can only be detected ~6 months after the beginning of treatment. To this extent, preclinical experiments in murine cells provide supplementary evidence which highlights that futibatinib results in fewer resistance mutations than pemigatinib.[6]

The issue of resistance mutations and the possibility that futibatinib may offer an advantage with regard to treatment resistance compared with older FGFR2 inhibitors such as pemigatinib was also noted in the BSG 2023 guidelines. The guidelines note that futibatinib may be able to provide an advantage compared with pemigatinib with regard to treatment resistance, however it is highlighted that these observations are currently based on molecular data from a small number of patients supported by *in vitro* studies, and therefore need to be supported by randomised clinical trial data.[25]

UK clinical experts highlighted that they consider the potential benefit with regard to treatment resistance to be a key favourable characteristic of futibatinib, and that, given the comparable efficacy of the two treatments, they would prefer to prescribe futibatinib over pemigatinib to their patients in order to potentially reduce the emergence of resistance mutations.[2]

The AE profile of futibatinib observed in the FOENIX-CCA2 trial were generally tolerable and aligned with the clinical expectations for an FGFR2 inhibitor.[2, 76] The clinical experts noted that the side effect profiles of futibatinib and pemigatinib were extremely similar, based on their clinical experience.[2]

B.3 Cost effectiveness

Summary of the cost-effectiveness analysis

- A *de novo* cost-effectiveness model was developed to assess the cost-effectiveness of futibatinib versus pemigatinib in adult patients with previously treated locally advanced or metastatic CCA with FGFR2 gene rearrangements, including gene fusions
- The patient population was informed by data from the efficacy population (N=103) of the FOENIX-CCA2 trial
- The model adopted a cohort-based partitioned survival model (PSM) approach, in line with the NICE appraisal of pemigatinib (TA722).[61] It comprised three mutually exclusive health states: progression-free (PF), progressed disease (PD) and death. Patients were redistributed among the three health states at each model cycle; the length of one cycle was equal to 21 days
- Parametric survival functions were applied in order to extrapolate progression-free survival (PFS) and overall survival (OS) data. NICE TSD14 guidance was followed to determine the most appropriate extrapolations, including seeking expert clinical opinion for clinical plausibility[92]
- Costs included in the model were drug acquisition, health state costs, adverse events (AEs) and end of life costs. Utility inputs were derived from the FOENIX-CCA2 trial data
- The suitability of the PSM approach for this model and the key model inputs and assumptions were validated by both UK clinical and health economic experts at an Advisory Board[2]

Base-case results

- In the base-case deterministic analysis using futibatinib and pemigatinib list prices, futibatinib was found to be dominant versus pemigatinib, yielding an incremental net health benefit (INHB) of [redacted]. Incremental costs were [redacted] and incremental QALYs were [redacted]

Sensitivity and scenario analyses

- Since the results of the matching-adjusted indirect comparison (MAIC) showed no statistically significant difference between futibatinib and pemigatinib, a cost-comparison scenario analysis was carried out. For this analysis, it was assumed that futibatinib and pemigatinib have equal efficacies, and therefore the futibatinib PFS and OS curves were also used to calculate PFS and OS for pemigatinib. In this scenario, futibatinib was found to be cost-saving compared with pemigatinib
- Both probabilistic sensitivity analyses (PSA) and deterministic sensitivity analyses (DSA) were conducted in order to explore the uncertainty surrounding the base case economic model results
- Overall, the results of the sensitivity and scenario analyses showed that that all relevant uncertainties have been adequately accounted for, and the base case results were found to be robust to uncertainty in the key model inputs and assumptions. Futibatinib showed a positive or neutral INHB versus pemigatinib in all scenario analyses, ranging from [redacted] in the cost-comparison scenario (where futibatinib was slightly cost-saving) to [redacted]

Conclusion

- The cost-effectiveness analysis illustrates that futibatinib represents a cost-effective use of NHS resources versus pemigatinib, which is the only targeted treatment approved by NICE in the indication of interest to this submission

B.3.1 *Published cost-effectiveness studies*

A systematic literature review (SLR) was conducted in October 2023 to identify all relevant literature published on previous economic models for futibatinib and pemigatinib, and to review appraisals and criticisms of these models by health technology assessment (HTA) agencies. Full details of the economic SLR search strategy, study selection process and results are reported in Appendix G.

In total, seven publications reporting on five unique economic evaluations were identified by the SLR, the details of which are presented in Table 26.

Table 26: Summary list of published cost-effectiveness studies

Study and year	Summary of model	Intervention	Comparator	QALYs	ICER (per QALY gained)
Chen 2023[93]	Three-state PSM	Pemigatinib	• mFOLFOX • 5-FU	**QALYs** Total QALYs (overall): • Pemigatinib: 1.15 • mFOLFOX: 0.56 • 5-FU: 0.47 Incremental QALYs (pemigatinib vs. comparator; overall): • mFOLFOX: 0.59 • 5-FU: 0.68 Total QALYs (PF health state): • Pemigatinib: 0.61 • mFOLFOX: 0.33 • 5-FU: 0.26 Incremental QALYs (pemigatinib vs. comparator; PF health state): • mFOLFOX: 0.28 • 5-FU: 0.35 **LYs** Total LYs (overall): • Pemigatinib:1.61 • mFOLFOX: 0.80 • 5-FU:0.67 Incremental LYs (pemigatinib vs. comparator; overall): • mFOLFOX: 0.81 • 5-FU: 0.94	**ICER (per QALY gained, NT$)** • mFOLFOX: 5,814,700 • 5-FU: 5,380,241 **ICER (per LY gained, NT$)** • mFOLFOX: 4,238,063 • 5-FU: 3,888,175

				Total LYs (PF health state): • Pemigatinib: 0.81 • mFOLFOX: 0.46 • 5-FU: 0.36 Incremental LYs (pemigatinib vs. comparator; PF health state): • mFOLFOX: 0.35 • 5-FU: 0.45	
CADTH 2022[94]	Five-state PSM	Pemigatinib	• ASC alone • mFOLFOX + ASC	**QALYs** Total QALYs: • Pemigatinib: 1.65 • ASC: 0.42 • mFOLFOX + ASC: 0.41 Incremental QALYs (pemigatinib vs. comparator): • ASC: 1.23 • mFOLFOX + ASC: NR **LYs** Total LYs: • Pemigatinib: 2.56 • ASC: 0.61 • mFOLFOX + ASC: 0.67	**ICER (per QALY gained, CAD$)** • ASC: 143,604 • mFOLFOX + ASC: 127,359
Tzanetakos 2023[95]	Five-state PSM	Pemigatinib	• mFOLFOX + ASC • ASC	**QALYs** Total QALYs: • Pemigatinib: 1.66 • mFOLFOX + ASC: 0.44 • ASC: 0.41 **LYs** Total LYs were NR	**ICER (per QALY gained, €):** • mFOLFOX +ASC: 69,928 • ASC: 69,345 **ICER (per LY gained, €):** • mFOLFOX +ASC: 46,626 • ASC: 45,935

				Incremental LYs (pemigatinib vs. comparator): • mFOLFOX + ASC: 1.78 • ASC: 1.84	
NICE 2021[96]	Five-state PSM	Pemigatinib	• mFOLFOX + ASC • ASC	QALYs and LYs were not reported in the NICE final appraisal document. **LYs**[a] Total LYs: • Pemigatinib: 2.44 • mFOLFOX + ASC: 0.66 • ASC: 0.60 Incremental LYs (pemigatinib vs. comparator): • mFOLFOX + ASC: 0.06 • ASC: 1.84	*Company's base-case* **ICER (per QALY gained, £; PAS price):**[b] • mFOLFOX + ASC: 42,076 • ASC: 45,029 *Based on Committee's preferred assumptions* **ICER (per QALY gained, £; PAS price):**[b] • mFOLFOX + ASC: 45,051–45,808 • ASC: 44,354–45,010
SMC 2022[97]	Four-state PSM	Pemigatinib	• mFOLFOX + ASC • ASC	**QALYs** Total and incremental QALYs were not reported. **LYs** Total LYs were not reported. Incremental LYs (pemigatinib vs. comparator): • mFOLFOX + ASC: 1.78 • ASC: 1.84	**ICER (per QALY gained, £; PAS price):** • mFOLFOX+ ASC: 37,645 • ASC: 45,033

Abbreviations: 5-FU: fluorouracil; AE: adverse event; ASC: active symptom control; CAD$: Canadian dollar; ICER: incremental cost-effectiveness ratio; LY: life year; MAIC: matching-adjusted indirect comparison; mFOLFOX: A combination of oxaliplatin, folinic acid and fluorouracil; NICE: National Institute for Health and Care Excellence; NR: not reported; NT$: New Taiwan dollar; OS: overall survival; PAS: patient access scheme; PD: progressed disease; PF: progression-free; PSM: partitioned survival model; QALY: quality adjusted life year; SLR: systematic literature review; SMC: Scottish Medicines Consortium

B.3.2 *Economic analysis*

The economic SLR found no economic evaluations investigating futibatinib versus pemigatinib for the treatment of adult patients with previously treated locally advanced or metastatic CCA with FGFR2 gene rearrangements, including gene fusions, and therefore a *de novo* cost-effectiveness analysis has been conducted for the purpose of this appraisal and is described below. The cost-effectiveness model employed for this economic analysis was built in Microsoft Excel®.

The objective of this economic analysis was to assess the cost-effectiveness of futibatinib versus pemigatinib within its marketing authorisation for the treatment of adults with locally advanced or metastatic CCA with FGFR2 fusion or rearrangement that has progressed after at least one prior systemic therapy.

In line with the NICE reference case the analysis was conducted from the perspective of the NHS and Personal Social Services (PSS) in the United Kingdom (UK) and included direct medical costs over a lifetime horizon.[98]

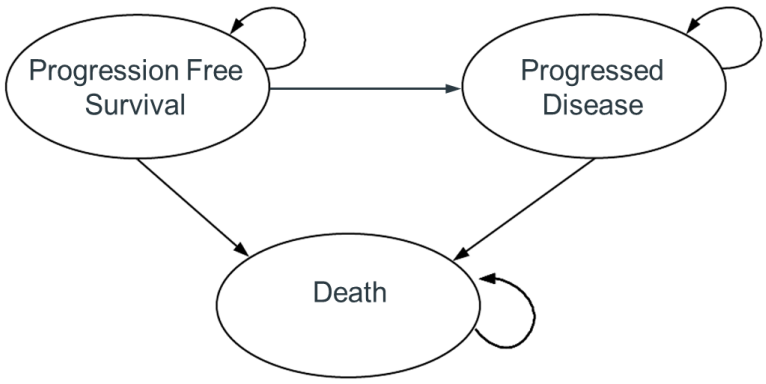
B.3.2.1 Patient population

The economic analysis considered adult patients with previously treated locally advanced or metastatic CCA with FGFR2 gene rearrangements, including gene fusions, informed by data from the FOENIX-CCA2 trial (N=103). The FOENIX-CCA2 trial population is reflective of the decision problem defined in Section B.1.1 and the license for futibatinib.

B.3.2.2 Model structure

The cost-effectiveness model was constructed in Microsoft Excel and adopted a cohort-based partitioned survival model (PSM) approach, in line with the NICE appraisal of pemigatinib in CCA (TA722).[61] Figure 16 provides a schematic of the model structure. Arrows in the schematic represent transitions that a patient can make within one model cycle.

Figure 16: Schematic of the PSM structure



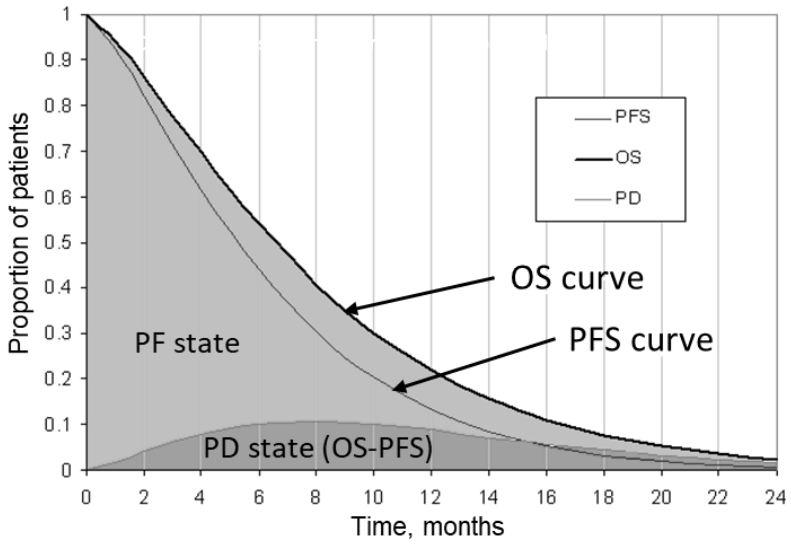
Abbreviations: PSM: partitioned survival model

The model comprised three mutually exclusive health states, as follows:

- Progression-free (PF): Patients' disease is in a stable or responding state and not actively progressing. Patients in this state are assumed to incur costs associated with treatment acquisition, administration, treatment monitoring, medical management of the condition and the management of Grade 3/4 AEs. Patients also experience a higher utility compared with progressed disease
- Progressed disease (PD): Patients have met the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria for disease progression. Patients in this state may incur costs associated with medical management of the condition and terminal care. Patients experience a lower utility compared with progression-free disease
- Dead: Patients no longer incur costs, life years or utilities

A graphical depiction of the health states used in the PSM is presented in Figure 17 below.

Figure 17: Schematic of the PSM health states



Notes: The data in the figure are fictitious and used for illustrative purposes only. The proportion of patients in the PD state is calculated as the proportion of patients alive (based on the OS estimates) minus proportion of patients progression-free (based on the PFS estimates); this is shown in the figure with grey shading, and with orange shading when plotted against the axis
Abbreviations: OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival; PSM: partitioned survival model

Patients were modelled to enter the PSM in the PF health state and to receive either futibatinib or pemigatinib. The proportion of patients in each heath state at each model cycle for futibatinib and pemigatinib was then determined from cumulative survival probabilities from PFS and OS parametric survival functions, as follows:

- The proportion of patients occupying the PF state was calculated as the proportion of patients who are progression-free (based on PFS parametric survival functions)
- The proportion of patients occupying the PD state was calculated as one minus the proportion of patients in the PF state minus the proportion of patients in the death health state
- The proportion of patients occupying the death state was calculated as one minus the proportion of patients alive (based on OS parametric survival functions)

Patients were redistributed among the three health states at each model cycle; the length of each model cycle was 21 days. The PFS health state was constrained to be equal or lower than OS at the beginning of each model cycle and OS was constrained by the age and gender matched general population survival in order to ensure the plausibility of the results.

The model structure does not allow for patients to improve their health state, which reflects the progressive nature of the condition. The death health state is an absorbing health state.

A PSM approach was selected over a state transition model (STM), such as a Markov model. While the STM approach has certain advantages, such as the ability to include additional health states to capture the disease in more detail, or to allow for more complex modelling of subsequent treatments, this level of detail was deemed unnecessary for this submission: three health states were confirmed by UK clinical and health economic experts to be sufficient for the indication of interest, and subsequent treatments were not modelled (see Section B.3.3).

On the other hand, PSMs make for intuitively appealing models that replicate within-study data with relative ease given that there is direct correspondence between reported time-to-event endpoints (PFS and OS) and the survival functions. This means that the model is expected to accurately reflect disease progression and the observed survival profile of patients treated with futibatinib and pemigatinib. Importantly, the PFS and OS curves can be constructed from summary Kaplan-Meier data in the absence of patient-level data; given the reliance on published summary data rather than patient-level data for pemigatinib, this was an important benefit of this model structure.

Further, use of a PSM in this submission has the potential to reduce uncertainty compared with STM. Utilisation of a STM approach would require strong assumptions, which can lead to an increased risk that the model will not accurately represent outcomes within the period covered by the clinical evidence. For example, it would be challenging to identify inputs to inform the probability of transitioning from the PD health state to the death health state for pemigatinib, given the absence of published post-progression survival data from FIGHT-202. In comparison, the published summary data from FIGHT-202 can be directly implemented in a PSM, reducing the need for strong structural assumptions.

In addition, the PSM model structure and the included disease states are expected to reflect locally advanced or metastatic CCA, as it is a progressive disease that, in advanced stages, typically leads to death. The PSM approach also aligns with TA722, the only previous NICE appraisal in CCA with FGFR2 fusion or rearrangement, in which the use of a PSM was accepted by the NICE committee.

As such, a PSM model was considered the most appropriate model structure for this submission. The suitability of the PSM approach for this model was confirmed by UK health economic experts.[2]

Features of the cost-effectiveness analysis

Costs and health state utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and quality-adjusted life years (QALYs) per cycle, which were totalled at the end of the time horizon. Effectiveness measures included life years (LYs) and QALYs. Cost components considered included: drug acquisition, treatment monitoring,

medical management of the condition, AEs and terminal care. The incremental cost-effectiveness ratio (ICER) of futibatinib versus pemigatinib was assessed.

In line with the NICE reference case, the analysis was conducted from the perspective of the National Health Service (NHS) and Personal Social Services (PSS).[98] A lifetime time horizon of 40 years was chosen based on the mean age of the FOENIX-CCA2 trial (56 years) and average life expectancy of patients with CCA. This was the same as the value used in the NICE appraisal of pemigatinib (TA722), the only treatment recommended by NICE in the indication of relevance to this submission, and was confirmed to be a suitable time horizon to cover the remaining lifetime of the patients in the model by UK clinical experts in CCA.[2, 61] A 21 day cycle length was considered in the base case as this was deemed sufficiently granular to accurately represent the movement of patients between health states and capture the dosing schedules of the treatments included in the model. Additionally, it corresponds with the licensed treatment cycle length of futibatinib. Owing to the relatively long cycle length, half-cycle correction was applied in the model.

In line with the NICE reference case, costs and effects were discounted at a rate of 3.5% annually.[98] The economic analysis was conducted using recent estimates of resource use and treatment costs available from published sources, including NHS reference costs for 2021/22, electronic market information tool (eMIT) 2022/23 and the British National Formulary 2023.[99]

The features of the analysis were informed by the previous NICE appraisal of pemigatinib (TA722). A summary of the key features of this appraisal and justification for the design of the economic analysis for futibatinib is provided in Table 27.

Table 27: Features of the economic analysis

	Previous evaluation	Current evaluation	
Factor	**TA722[61]**	**Chosen values**	**Justification**
Model structure	Partitioned survival model	Partitioned survival model	A partitioned survival model accurately reflects disease progression and the observed survival profile of patients with CCA treated with futibatinib and pemigatinib, and is in line with the previous NICE appraisal in CCA with FGFR2 fusion or rearrangement (TA722)[61]
Time horizon	Lifetime horizon (40 years)	Lifetime horizon (40 years)	A time horizon of 40 years was deemed sufficient to cover the remaining lifetime of the patients in the model serve as a lifetime horizon in the CCA indication; this was validated by UK experts in CCA[2]
Cycle length	1 week	21 days	A 21-day cycle length was deemed appropriate given the rate at which relevant clinical events may occur, and the frequency at which

			the futibatinib treatment regimen is administered; this was confirmed by UK clinical experts[2]
Half cycle correction	No	Yes	Owing to the slightly longer cycle length compared to TA722, half cycle correction was included in the economic model. This helps to reduce systemic over/underestimation of costs and other outcomes, and is in line with the recommended best practice[100]
Treatment waning effect?	No	No	As both futibatinib and pemigatinib are administered until disease progression or unacceptable toxicity, treatment waning was not included in the economic model. If treatment waning were to happen, it would have been implicitly captured in the survival curves in the FOENIX-CCA2 and FIGHT-202 trials. The exclusion of treatment waning is in line with the accepted approach adopted in TA722[61]
Source of utilities	Not reported	• Progression-free health state: [redacted] • Progressed disease health state: [redacted]	The utility data were derived from the FOENIX-CCA2 clinical trial. These data were aligned with the population of interest to this submission and were EQ-5D-3L, in line with the NICE reference case[98]
Source of costs	• NHS reference costs[101] • Previous NICE appraisals[102, 103]	• NHS reference costs 2021/22[99] • eMIT 2022/23 • BNF 2023	The best available evidence was used for the costs, in line with the NICE reference case[98]

Abbreviations: BNF: British National Formulary; CCA: cholangiocarcinoma; eMIT: electronic market information tool; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSS: Personal Social Services; TA: technology appraisal
Source: NICE TA722[61]

In addition to the base-case cost-effectiveness analysis, a scenario analysis was conducted in which the efficacy of futibatinib and pemigatinib (and subsequently their associated QALYs) were assumed to be equal, corresponding to a cost-comparison approach. This assumption was informed by the results of the MAIC, which found no statistically significant differences in efficacy between futibatinib and pemigatinib for either PFS or OS (Section B.2.9.2). It was also confirmed by UK clinical experts in CCA, who noted that they expected the efficacy of futibatinib to be

similar to that of pemigatinib, and potentially even better for some patients due to the smaller potential for treatment resistance (see Section B.2.12).

In this cost-comparison scenario analysis, the base case extrapolations of futibatinib PFS and OS (Section B.3.3) were also used to calculate PFS and OS data for pemigatinib, respectively.

B.3.2.3 Intervention technology and comparators

Intervention

The intervention of interest is futibatinib (20 mg), administered orally once daily (QD) as a continuous therapy. This is in line with the existing licensed dose of futibatinib in adult patients with locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy.[1] It is advised that futibatinib is administered until disease progression or unacceptable toxicity occurs.

Comparator

As noted in Section B.1.3.3, the only relevant comparator to futibatinib in UK clinical practice for the indication of interest to this submission is pemigatinib. In the UK, pemigatinib is the only mutation-specific therapy recommended by NICE for the treatment of patients with locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement that has progressed after prior systemic therapy.[61] UK clinical experts in CCA confirmed that in UK clinical practice all eligible adult patients with previously treated locally advanced or metastatic CCA harbouring FGFR2 gene rearrangements, including gene fusions, would be treated with pemigatinib, since it can offer notable gains in survival compared to chemotherapy, which is not mutation-specific.[2]

Pemigatinib is administered 13.5 mg QD on a 14 day-on, 7 day-off schedule.[61] Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity.[61]

The administration and dosing regimens for futibatinib and pemigatinib are summarised in Table 28.

Table 28: Details of administration of interventions included in the model

Intervention	Planned dosage per treatment cycle	Duration of treatment	Administration route	Source
Futibatinib	• 20 mg per day • 420 mg per 21 day treatment cycle (continuous)	Until disease progression or unacceptable toxicity	Oral	Futibatinib SmPC[1]
Pemigatinib	• 13.5 mg per day • 189 mg per 21 day treatment cycle (14 days on, 7 days off)	Until disease progression or unacceptable toxicity	Oral	Pemigatinib SmPC[104]

Abbreviations: SmPC: summary of product characteristics
Source: MHRA. Lytgobi SmPC;[1] EMA. Pemigatinib SmPC[104]

B.3.3 *Clinical parameters and variables*

B.3.3.1 Baseline characteristics

The baseline characteristics for the model population are provided in Table 29. These inputs were based on the baseline characteristics of patients who received futibatinib in the FOENIX-CCA2 trial. UK clinical experts in CCA confirmed that the baseline characteristics of patients in the FOENIX-CCA2 trial were in line with the patient population in which futibatinib is anticipated to be used in in UK clinical practice.[2]

Table 29: Baseline characteristics for the model population

Model parameter	Value	Source
Percentage female	56.3%	FOENIX-CCA2
Starting age, years	55.7	FOENIX-CCA2
Body weight, kg	[redacted]	FOENIX-CCA2
Body surface area, m^2	[redacted]	FOENIX-CCA2

Source: Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data Cut-Off 29 May 2021[76]

B.3.3.2 Progression free survival

As described in Section B.3.2.2, the proportion of patients in each heath state at each 21 day model cycle was determined for each therapy directly from cumulative survival probabilities for PFS.

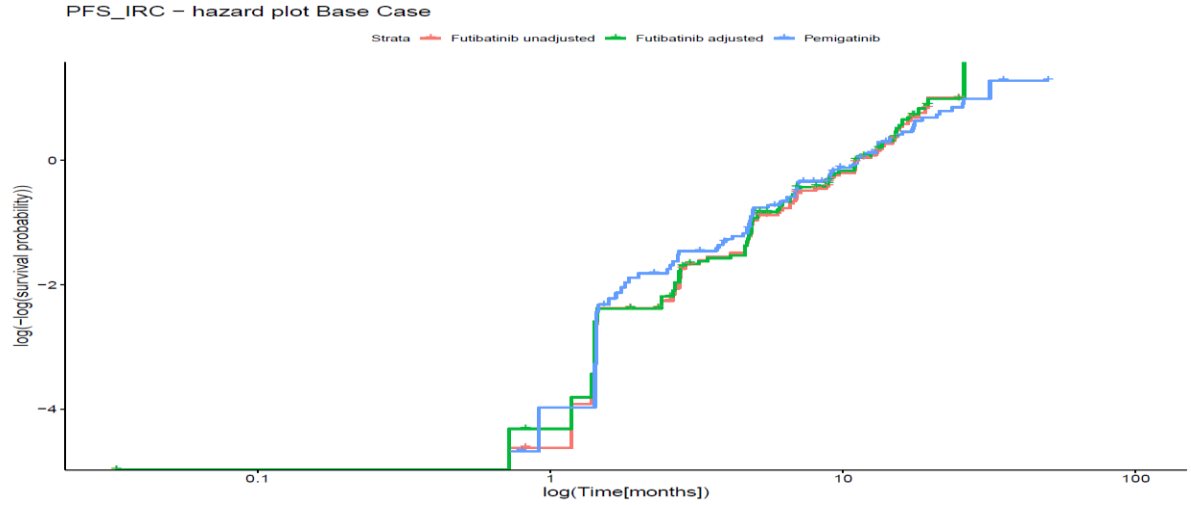
Approach to parametric survival function selection

To inform long-term estimates of PFS in the model for futibatinib and pemigatinib, it was necessary to extrapolate PFS data through the application of parametric survival functions.

Initially, in line with NICE TSD 14, the proportional hazards (PH) assumption was assessed. A log-cumulative hazard plot for futibatinib (unadjusted and MAIC adjusted) and pemigatinib is presented in Figure 18, and a Schoenfeld residual plot is presented in Figure 19.

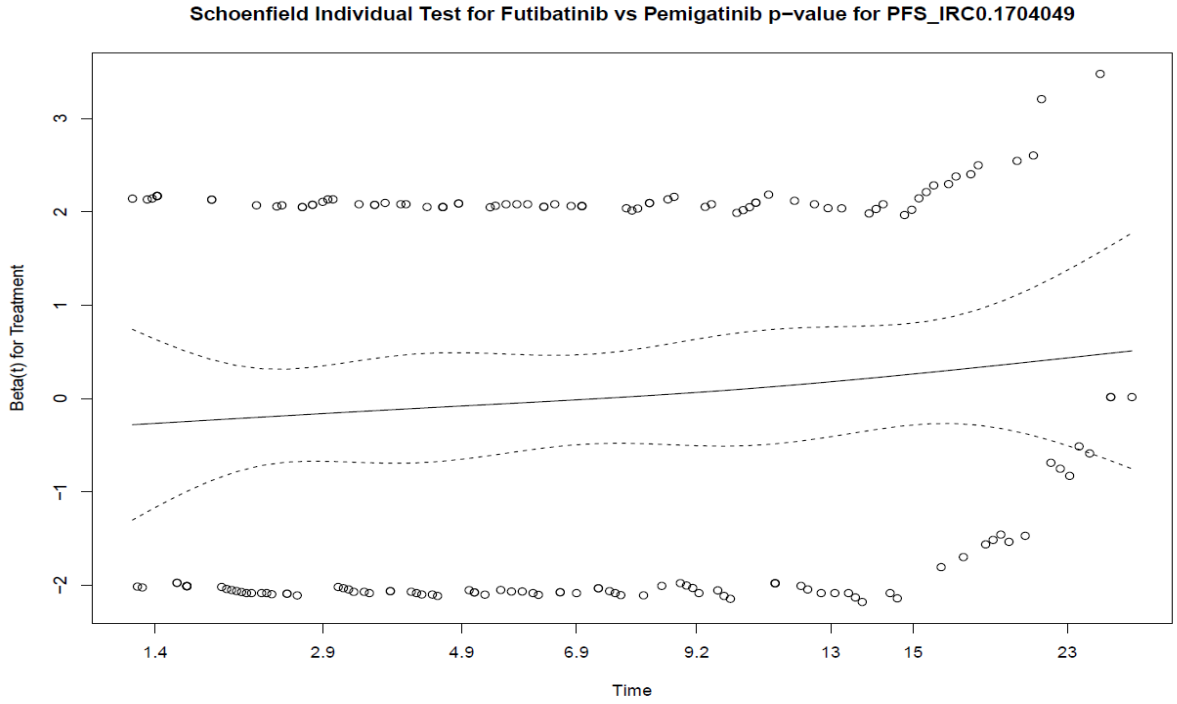
Overall, there was no evidence to suggest that the PH assumption was violated – the log cumulative hazard plot showed that the futibatinib curves (both unadjusted and adjusted) ran approximately parallel to the pemigatinib curve, while the Schoenfeld residual plot showed no evidence of the PH assumption being violated. Similarly, the Schoenfeld test reported a p-value of 0.225, suggesting that the PH assumption between futibatinib and pemigatinib for PFS is appropriate.

Figure 18: Log-cumulative hazard plot for futibatinib versus pemigatinib PFS



Abbreviations: PFS: progression-free survival.

Figure 19: Schoenfeld residual plot for futibatinib (adjusted) versus pemigatinib for PFS



Abbreviations: PFS: progression-free survival.

This appropriateness of the PH assumption is to be expected, given that futibatinib and pemigatinib, both FGFR2 inhibitors, are associated with extremely similar mechanisms of action and similar clinical efficacy based on the results of the MAIC (Section B.1.1). Feedback received from UK clinical experts indicated that they would expect futibatinib to be associated with at least equal efficacy, safety and quality of life benefits to that of pemigatinib in clinical practice, with potential for reduced treatment-resistance mutations for patients treated with futibatinib.[2]

Considering the above, in the base case economic analysis, futibatinib was modelled via extrapolation of the unadjusted Kaplan-Meier data obtained from the FOENIX-CCA2 trial, and pemigatinib was modelled via applying the inverse of the MAIC PFS HR (1.07) for futibatinib

versus pemigatinib in the base-case MAIC (Section B.2.9.2) – i.e. a HR of 0.93 – to the futibatinib extrapolation to derive a corresponding PFS extrapolation for pemigatinib.[82]

This approach permits the use of the MAIC results (which represent the least biased estimates of the relative effects between futibatinib and pemigatinib), but also allows the futibatinib extrapolations to be based on the maximum sample size; avoiding the reduction in effective sample size that would be associated with extrapolation of the MAIC-adjusted FOENIX-CCA2 data. This modelling approach also easily facilitates the consideration of scenario analyses to explore the impact of population adjustment by utilising alternative HRs, which are considered in Section B.3.11.3.

The selection of the most appropriate extrapolation for futibatinib PFS was informed by the recommendations of NICE DSU TSD 14.[92] Specifically, goodness-of-fit statistics were calculated and assessed to understand which parametric form had the best statistical fit to the Kaplan Meier data, assessment of visual fit was conducted, and clinical expert opinion was sought regarding the plausibility of the long-term extrapolations of each function.[2] The explored extrapolations included log-logistic, lognormal, exponential, Weibull, Gompertz and generalised gamma.

Internal validity of PFS parametric survival functions: futibatinib

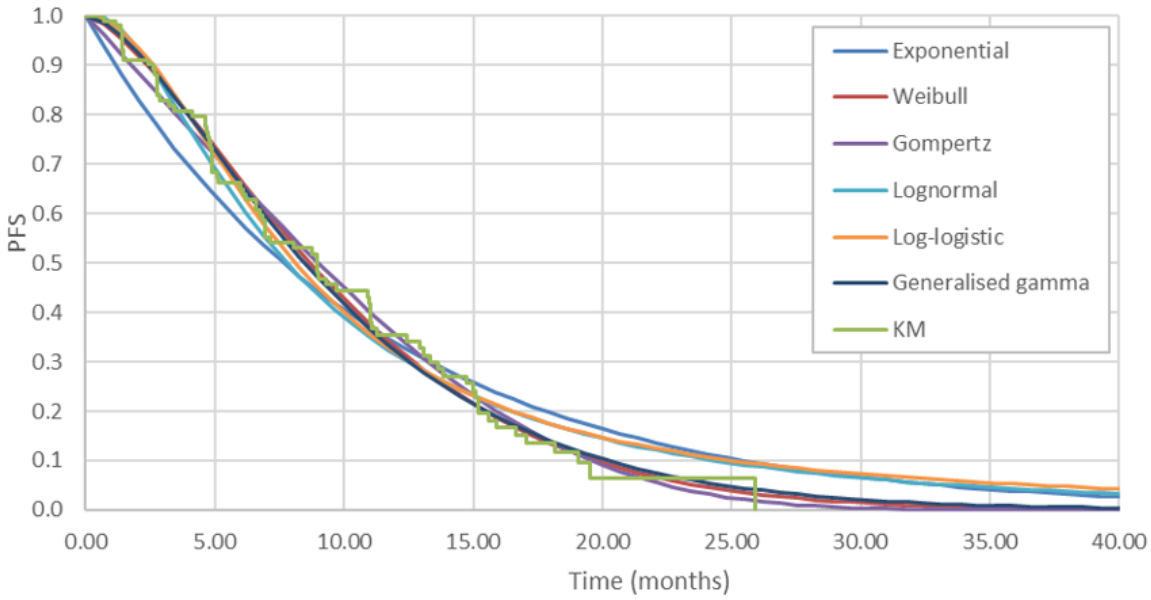
The model fit statistics (Akaike information criterion [AIC] and Bayesian information criterion [BIC]) for the parametric survival functions explored for the futibatinib PFS data are presented in Table 30. Visual assessment of the parametric survival functions to the Kaplan-Meier data for futibatinib was performed through the extrapolations presented in Figure 20.

Table 30: Model fit statistics for PFS parametric survival functions for futibatinib

Function	PFS			
	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	532.94	6	535.57	6
Weibull	520.09	1	525.36	1
Gompertz	523.90	3	529.17	2
Lognormal	523.97	4	529.24	3
Log-logistic	524.92	5	530.19	5
Generalised gamma	521.84	2	529.75	4

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; PFS: progression-free survival

Figure 20: Futibatinib PFS parametric survival function extrapolations



Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival

The difference between AIC and BIC values among the fitted PFS curves was not substantial, suggesting a similar goodness of fit to the KM data for all curves (difference in points <5 within AIC and BIC values, which is generally accepted to indicate similar fit,[105, 106] between all curves except for the exponential). This was also reflected in the visual assessment of the fit of functions to the observed Kaplan-Meier data, which all appeared to provide a similar fit, with the exception of the exponential curve; while the lognormal and log-logistic curves appeared to have worse visual fit after ~15 months, this distinction was not considered meaningful due to the small numbers of patients at risk remaining at that point (as detailed in Section B.2.6.4).

Owing to the similarity in values in AIC/BIC statistics, it was not possible to specify an optimal curve choice based on statistical fit alone. Furthermore, AIC/BIC statistics only provide information on the goodness of fit of the survival curve to the observed Kaplan-Meier data and do not provide information on the validity of the curves beyond the follow-up time of the trial data. As such, the external validity of the survival curves was an important consideration when selecting the most appropriate survival curve.

External validity of PFS parametric survival functions: futibatinib

Due to the lack of availability of long-term PFS data for futibatinib, expert elicitation was sought from UK experts in CCA on the long-term clinical validity of the survival curves.[2] The clinical experts were presented with the PFS curves for futibatinib and were asked to rank the curves from 1 to 6 to indicate which curves were most clinically plausible. These results are presented in Table 31 below.

Table 31: Expert rankings of futibatinib PFS survival curves

Curve	Expert 1 Ranking (1–6; 1 = most appropriate)	Expert 2 Ranking (1–6; 1 = most appropriate)
Exponential	2	3
Weibull	5	4–6
Log-logistic	3	1
Lognormal	1	2
Gompertz	4	4–6
Generalised gamma	6	4–6

Abbreviations: PFS: progression-free survival
Source: Taiho Oncology. Data on File. FOENIX-CCA2 Advisory Board Report. 22 May 2023[2]

Clinical experts noted that all PFS extrapolations showed similar visual fit to Kaplan-Meier data and therefore that the selection of the most appropriate extrapolation would rely on long-term PFS estimates at 5 years, as this is where the curves diverge. In particular, it was highlighted that, based on the experts' clinical experience in CCA, 5 year PFS is expected to be small but above 0%.[2] Based on this, the lognormal, log-logistic and exponential curves were selected as the top three most clinically plausible curve choices by both clinical experts.

Of the three curves considered to be most clinically plausible by the clinical experts, the lognormal and log-logistic curves provided substantially improved statistical fit to the adjusted futibatinib PFS data, compared to the exponential curve.

As such, the lognormal curve was selected in the base case economic analysis, as the PFS estimates associated with the lognormal curve were slightly lower at all timepoints, and therefore the lognormal could be considered a slightly more conservative choice versus the log-logistic curve. The lognormal was selected as the first and second most appropriate curve by the two clinicians.

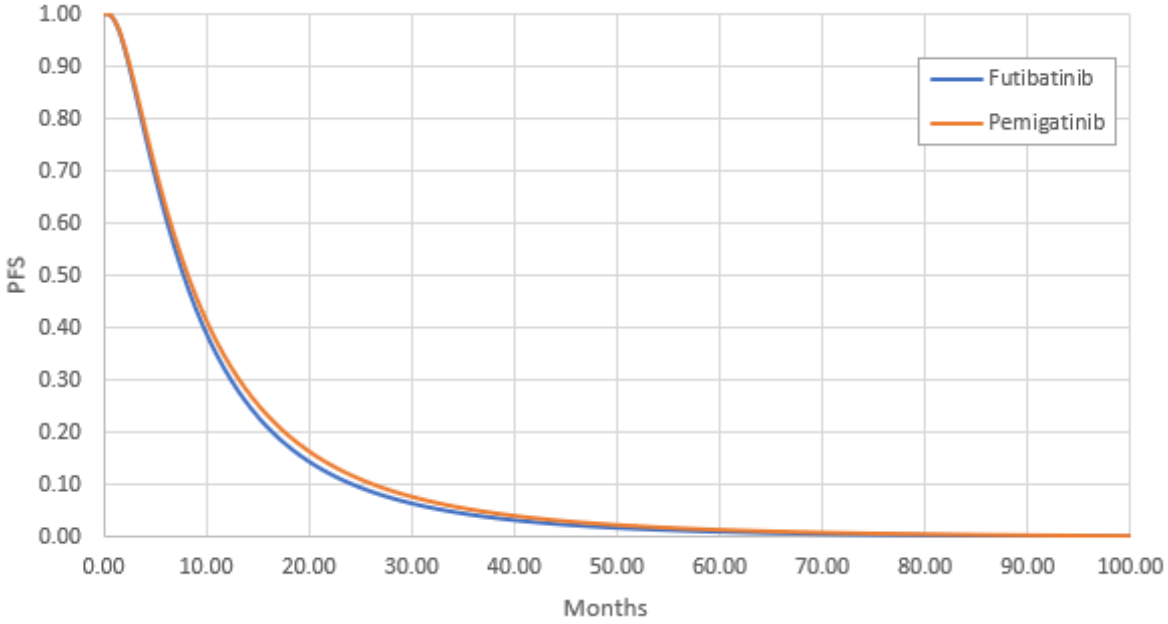
In order to explore uncertainty associated with the choice of futibatinib PFS extrapolation, the log-logistic and Weibull extrapolations were explored in scenario analyses (see Section B.3.11.3).

PFS parametric survival functions: pemigatinib

As discussed above, the extrapolated pemigatinib PFS curve was obtained from the chosen futibatinib extrapolation by adjusting it by the HR calculated in the MAIC (see Section B.2.9.2). The resulting extrapolation, compared with the futibatinib PFS extrapolation, is shown in Figure 21.

In order to explore any uncertainty associated with the MAIC PFS HR, the PFS HR from the unadjusted comparison of futibatinib and pemigatinib (HR: 1.02) and the sensitivity analysis MAIC (HR: 1.11) were both explored in sensitivity analyses, as well as an assumption of equal PFS between futibatinib and pemigatinib (HR: 1.00) (Section B.3.11.3). These MAIC PFS HRs are presented for futibatinib versus pemigatinib; therefore, the inverse of these HRs were applied to the futibatinib PFS extrapolation in each case to derive the corresponding pemigatinib PFS extrapolation.

Figure 21: Pemigatinib PFS extrapolation



Abbreviations: KM: Kaplan-Meier, PFS: progression-free survival.

Cost-comparison scenario analysis

The results of the MAIC showed no statistically significant difference for PFS (or OS) between futibatinib and pemigatinib. For this reason, in addition to the scenarios detailed above which explored the use of alternative HRs for PFS, a cost-comparison scenario analysis was conducted, in which the futibatinib PFS and OS extrapolations were used to represent PFS and OS for both futibatinib and pemigatinib – i.e. PFS and OS were modelled to be equal for both treatments, reflecting an assumption of equal efficacy, and additionally, AEs were assumed to be equal between the two treatments, assuming that there were no QALY differences between the two treatments.

B.3.3.3 Overall survival

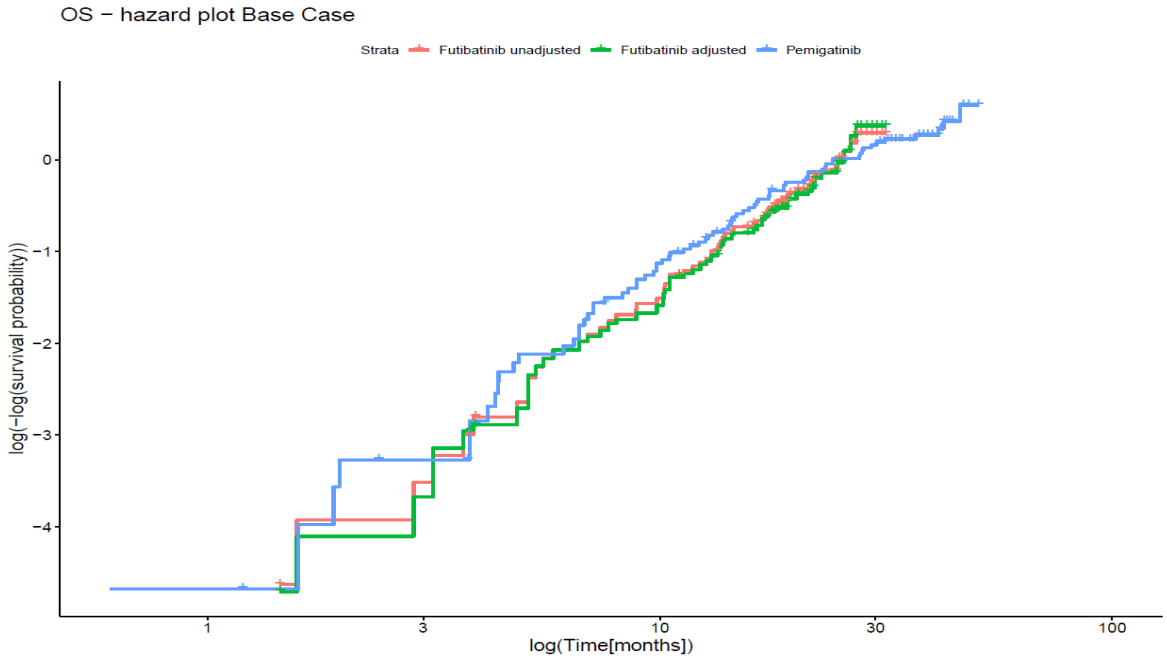
As described in Section B.3.2.2, the proportion of patients in each heath state at each 21 day model cycle was determined for each therapy directly from cumulative survival probabilities for OS. Mortality for patients with CCA is expected to be higher than the mortality of the general population when matched for age and gender. To ensure that the hazard of death is at least equal to general-population mortality (GPM) at any timepoint, age- and gender-matched GPM (based on life tables for England from the Office for National Statistics 2017-2019) was used in any cycle where the predicted rate of death was lower than general population mortality. The 2017-2019 life tables were used in favour of more recent estimates in order to avoid the data being skewed by COVID-19 excess mortality.

Approach to parametric survival function selection

As with PFS, in order to inform long-term estimates of OS in the model, it was necessary to extrapolate the OS data through the application of parametric survival curves. Initially, the PH assumption was assessed for OS – a log-cumulative hazard plot for futibatinib and pemigatinib is presented in Figure 22, and a Schoenfeld residual plot is presented in Figure 23. As with PH, there was no evidence to suggest that the PH assumption was violated – the log-cumulative

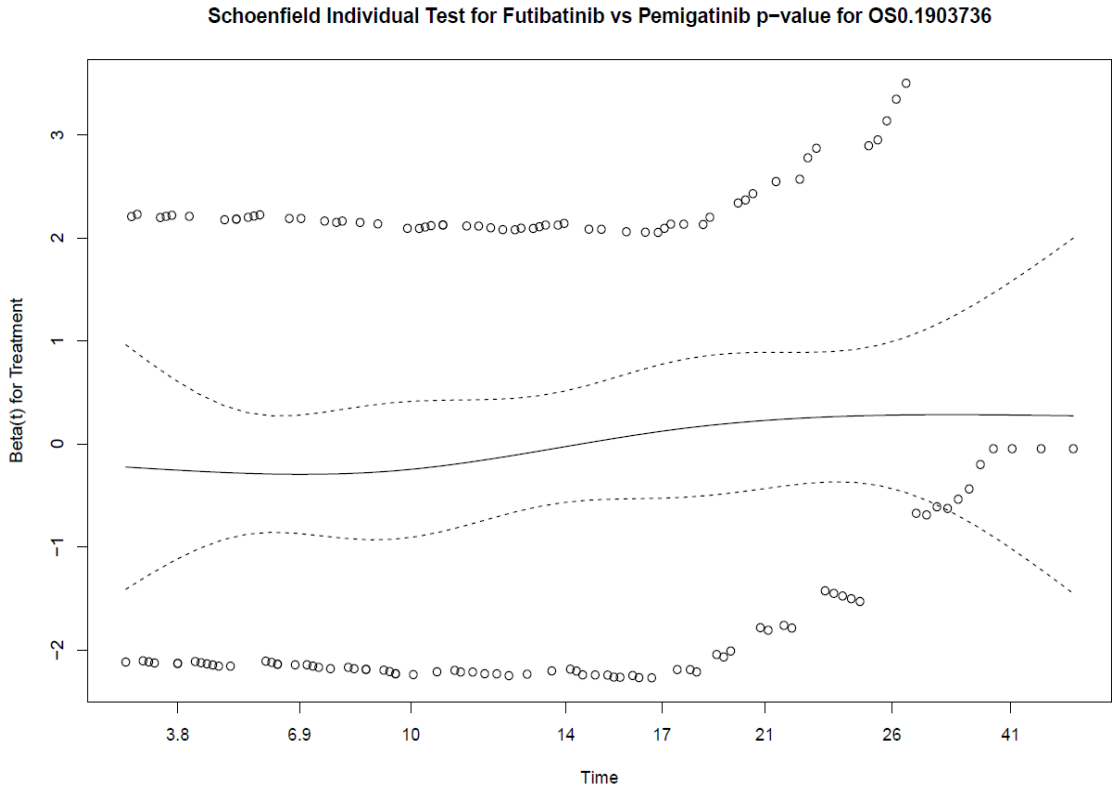
hazard plot showed that the futibatinib and pemigatinib curves run approximately parallel to each other – the two curves do across at log (30 months), although this must be interpreted with caution given the low numbers of patients at risk at this timepoint (Section B.3.3.3). The Schoenfeld residuals showed no evidence of the PH assumption being violated, and the Schoenfeld test reported a p-value of 0.190, suggesting that overall, the PH assumption between futibatinib and pemigatinib for OS is appropriate.

Figure 22: Log-cumulative hazard plot for futibatinib versus pemigatinib for OS



Abbreviations: OS: overall survival.

Figure 23: Schoenfeld residual plot for futibatinib (adjusted) versus pemigatinib for OS



Abbreviations: OS: overall survival.

Therefore, for the same reasons as previously detailed for PFS (Section B.3.3.2), futibatinib was modelled via extrapolation of the unadjusted Kaplan-Meier data obtained from the FOENIX-CCA2 trial, and pemigatinib was modelled via applying the inverse MAIC OS HR (0.95) for futibatinib versus pemigatinib in the base case MAIC (Section B.2.9.2) – i.e. a HR of 1.05 – to the futibatinib extrapolation to derive a corresponding OS extrapolation for pemigatinib.[82]

This approach was taken to allow the unadjusted futibatinib data to be used directly in the cost-effectiveness model, as individual patient data were available from the FOENIX-CCA2 trial, and this is considered to be the most generalisable source of evidence to patients receiving futibatinib in UK clinical practice.

The approach to selecting appropriate OS curves for futibatinib was the same as was used for the PFS data, described in Section B.3.3.2.

Internal validity of OS parametric survival functions: futibatinib

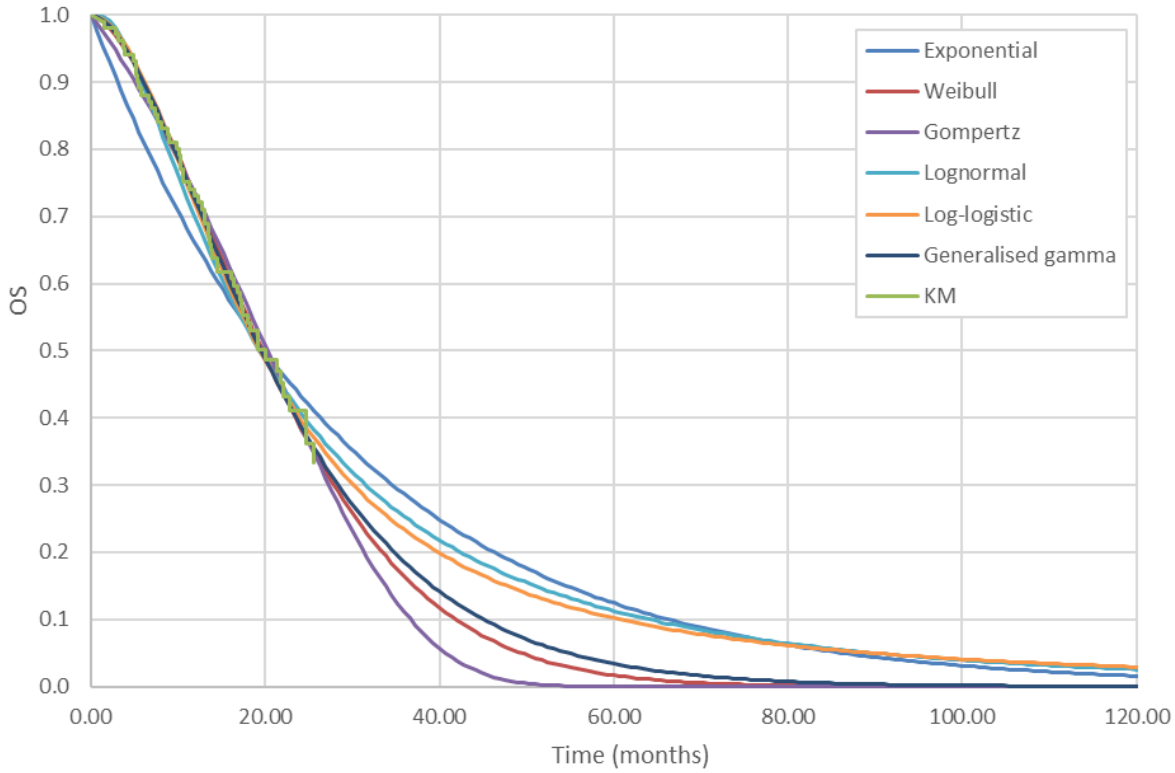
The AIC and BIC model fit statistics for the parametric survival functions explored for the futibatinib OS data are presented in Table 32. Visual assessment of the parametric survival functions to the Kaplan-Meier data for futibatinib was performed through the extrapolations presented in Figure 24.

Table 32: Model fit statistics for OS parametric survival functions for futibatinib

Function	OS			
	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	507.65	6	510.29	6
Weibull	495.96	1	501.23	1
Gompertz	499.24	5	504.51	4
Lognormal	497.94	4	503.21	3
Log-logistic	496.66	2	501.93	2
Generalised gamma	497.78	3	505.68	5

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival

Figure 24: Futibatinib OS parametric survival function extrapolations



Abbreviations: KM: Kaplan-Meier; OS: overall survival

The difference between AIC and BIC values among the fitted OS curves was not substantial, suggesting a similar goodness of fit to the KM data for all curves (difference in points <5 between all curves aside from the exponential). This was also reflected in the visual assessment of the fit of functions to the observed Kaplan-Meier data, which all, aside from the exponential, appeared to provide a similar fit. Slight differences in the best fitting curves between AIC and BIC are present, which is expected, however the AIC and BIC rankings did not differ substantially.

Owing to the similarity in values in AIC/BIC statistics, it was not possible to specify an optimal curve choice based on statistical fit alone. Furthermore, AIC/BIC statistics only provide information on the goodness of fit of the survival curve to the observed Kaplan-Meier data and do not provide information on the validity of the curves beyond the follow-up time of the trial data. As

such, the external validity of the survival curves was an important consideration when selecting the most appropriate survival curve.

External validity of OS parametric survival functions: futibatinib

Due to the lack of availability of long-term OS data for futibatinib, expert elicitation was sought from UK experts in CCA on the long-term clinical validity of the survival curves, similar to the process used for the PFS curve selection (Section B.3.3.2).2 The clinical experts were presented with the OS curves for futibatinib (as presented in Figure 24) and were asked to rank the curves from 1 to 6 to indicate which curves were most clinically plausible. These results are presented in Table 33 below.

Table 33: Expert rankings of futibatinib OS survival curves

Curve	Expert 1 Ranking (1–6; 1 = most appropriate)	Expert 2 Ranking (1–6; 1 = most appropriate)
Exponential	6	2
Weibull	4	4–6
Log-logistic	1	3
Lognormal	2	1
Gompertz	5	4–6
Generalised gamma	3	4–6

Abbreviations: OS: overall survival

Clinical experts noted that the log-normal and log-logistic curves were considered to be the most clinically plausible choices between the two expert rankings, with the lognormal curve receiving a slightly higher overall rating.

As both the log-logistic and lognormal curves were associated with a very similar statistical fit (<2 points difference, see Table 32), the lognormal survival curve was selected in the base case analysis, as it was associated with lower OS predictions compared to the log-logistic extrapolation, and therefore could be considered to represent a conservative choice.

In order to explore uncertainty associated with the extrapolation curve choice, log-logistic and Weibull extrapolations were also explored in scenario analyses (see Section B.3.11.3).

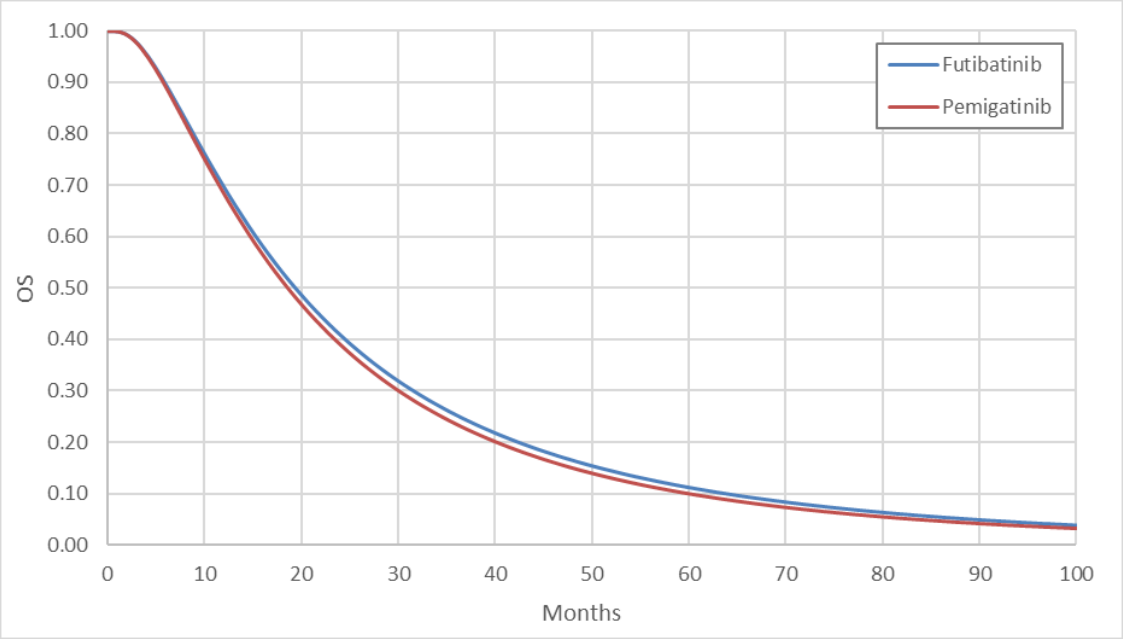
OS parametric survival functions: pemigatinib

As discussed above, the extrapolated pemigatinib OS curve was obtained from the chosen futibatinib extrapolation by adjusting it by the HR calculated in the MAIC (see Section B.2.9.2). The resulting extrapolation, compared with the pemigatinib OS Kaplan-Meier data from the FIGHT-202 trial, is shown in Figure 25.

Alternative OS HRs from the unadjusted comparison of futibatinib and pemigatinib (HR: 0.96) and the sensitivity analysis MAIC (HR: 0.96) were explored in scenario analyses, as well as an assumption of equal OS between futibatinib and pemigatinib (OS HR: 1), as described in Section B.3.11.3. A scenario analysis was explored whereby both PFS and OS were assumed to be equal between futibatinib and pemigatinib (PFS and OS HRs: 1). These MAIC OS HRs are presented for futibatinib versus pemigatinib; therefore, the inverse of these HRs were applied to

the futibatinib OS extrapolation in each case to derive the corresponding pemigatinib OS extrapolation.

Figure 25: Pemigatinib OS extrapolation (compared with the futibatinib OS extrapolation)



Abbreviations: KM: Kaplan-Meier, OS: overall survival

Cost-comparison scenario analysis

The results of the MAIC showed no statistically significant difference for OS (or PFS) between futibatinib and pemigatinib. For this reason, in addition to the scenarios detailed above which explored the use of alternative HRs for OS, a cost-comparison scenario analysis was conducted, in which the futibatinib PFS and OS extrapolations were used to represent PFS and OS for both futibatinib and pemigatinib – i.e. PFS and OS were modelled to be equal for both treatments, reflecting an assumption of equal efficacy, and additionally, AEs were assumed to be equal between the two treatments, assuming that there were no QALY differences between the two treatments.

B.3.3.4 Time to treatment discontinuation

In the base case analysis it was assumed that time on treatment (ToT) is equal to PFS for both treatments. Therefore, the selected PFS curves for futibatinib and pemigatinib informed ToT for these respective treatments.

This assumption is aligned with the data from the FOENIX-CCA2 trial, where the median PFS for futibatinib was 8.9 months, compared to a median duration of treatment of 9.07 months.

Furthermore, this assumption was validated by UK clinical experts in CCA. It was highlighted that whilst this was a suitable assumption for both futibatinib and pemigatinib, there could be a short delay from disease progression to treatment discontinuation due to practical reasons for some patients, however there was no evidence to suggest that ToT and PFS differ substantially in clinical practice.[2]

Cost-comparison scenario analysis

The results of the MAIC showed no statistically significant difference for PFS and OS between futibatinib and pemigatinib. For this reason, a cost-comparison scenario analysis was conducted, in which the futibatinib PFS extrapolation was used to represent ToT for both futibatinib and pemigatinib – i.e. both PFS and ToT were modelled to be equal for both treatments, reflecting an assumption of equal efficacy.

B.3.3.5 Summary of curve selections

The summary of extrapolation curves for futibatinib and pemigatinib PFS, OS and ToT data chosen for the base case analysis is provided below in Table 34.

Table 34: Summary of extrapolation curve choices in the base case analysis

	Futibatinib curve	Pemigatinib curve: base-case	Pemigatinib curve: cost-comparison scenario	Section
PFS	Lognormal	Derived by applying the inverse of the MAIC HR to the futibatinib PFS curve	Assumed equal to futibatinib PFS	Section B.3.3.2
OS	Lognormal	Derived by applying the inverse of the MAIC HR to the futibatinib OS curve	Assumed equal to futibatinib OS	Section B.3.3.3
ToT	Assumed equal to PFS	Assumed equal to PFS	Assumed equal to PFS	Section 0

Abbreviations: CCA: cholangiocarcinoma; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; OS: overall survival; PFS: progression-free survival; ToT: time on treatment

B.3.3.6 Adverse events

The economic model considered adverse events associated with both futibatinib and pemigatinib.

In the base case analysis, Grade 3+ AEs observed in >5% of patients in either the FOENIX-CCA2 trial and in the FIGHT-202 trial were applied in the model for futibatinib and pemigatinib, respectively, as detailed in Table 35 below. Grade 2+ hyperphosphataemia was additionally included, given the high proportion of patients experiencing hyperphosphataemia in the FOENIX-CCA2 trial. In the cost-comparison scenario analysis, which assumed equal efficacy between futibatinib and pemigatinib, AEs for pemigatinib were assumed to be the same as those for futibatinib. UK clinical experts confirmed that the safety profiles of futibatinib and pemigatinib were very similar, and that they would not expect any substantial differences in AEs between these two treatments.[2]

Table 35: Summary of AEs included in the economic model in the base case analysis

Adverse Event	Futibatinib (based on FOENIX-CCA2)	Pemigatinib (based on FIGHT-202)
	% patients	% patients
Arthralgia	0.0%	5.6%
Aspartate aminotransferase increased	6.8%	0.0%
Fatigue	5.8%	4.6%
Hyperphosphataemia (Grade 2+)	82.5%	51.9%

Hypophosphataemia	0.0%	0.0%
Stomatitis	5.8%	8.3%

Abbreviations: AE: adverse event.

Cost-Comparison Scenario Analysis

Feedback received from UK clinical experts indicated that they would expect futibatinib to be associated with at least equal efficacy, safety and quality of life benefits to that of pemigatinib in UK clinical practice. Therefore, a cost-comparison scenario analysis was conducted, where PFS, OS and AEs for pemigatinib were set equal to PFS, OS and AEs for futibatinib – assuming that incremental QALYs were equal between the two treatments and the only differences were related to costs. The results of this scenario analysis are presented in Section B.3.11.3.

B.3.4 *Measurement and valuation of health effects*

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

As described in Section B.2.6.6, patient-reported outcomes (PROs) collected in the FOENIX-CCA2 trial included the EORTC QLQ-C30 (5 functional and 9 physical measures) and the EQ-5D-3L (utility index and 5 dimensions: anxiety/depression, mobility, pain/discomfort, self-care, and usual activity).[76, 80]

Patient-reported outcomes were collected at Screening, Cycles 2 and 4, every 3 cycles after Cycle 4, and at the end of treatment. Change in mean score from baseline was assessed using predefined clinically meaningful thresholds for each time point with at least 19 observations (through Cycle 13).

PRO data collection and results are described in Section B.2.6.6. The utility values used in the model were derived from the FOENIX-CCA2 trial, as detailed in Section B.3.4.5 below.

B.3.4.2 Mapping

Since EQ-5D-3L outcomes were collected in the FOENIX-CCA2 trial, no mapping was required.

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

An SLR was conducted in October 2023 to identify all relevant literature published on HRQoL outcomes in adult patients treated with futibatinib or pemigatinib. The SLR identified one relevant study, reporting health state utility values from the ABC-06 trial.[107, 108] However, the ABC-06 trial did not include a population of patients with FGFR2 gene rearrangements or fusions, while utility values were only reported at Baseline and Month 4. As such, these utilities were not considered relevant for inclusion in the economic model.

Full details of the HRQoL SLR search strategy, study selection process and results are reported in Appendix H.

B.3.4.4 Adverse reactions

It is well accepted that adverse events (AEs) have a negative impact on patients' HRQoL. As such, disutility values were applied to those experiencing AEs to estimate the reduction in HRQoL due to the event for its duration.

Treatment related grade ≥3 AEs which had an incidence rate >5% for either futibatinib or pemigatinib in the FOENIX-CCA2 and FIGHT-202 trials were included in the economic model. AEs were applied upon initiation of treatment. Disutilities were applied as one-off events. These model assumptions were verified by UK economic experts.[2]

Utility decrements for adverse events and associated duration were based on values from previous NICE technology appraisals.[61, 109, 110] Decrements, duration and QALY losses for each adverse event as applied in the model are presented in Table 36.

Table 36: Adverse event disutility decrements applied in the cost-effectiveness model

Adverse event	Disutility	Duration (days)	Source
Arthralgia	-0.069	18.7	• Disutility: NICE TA391[110] • Duration: NICE TA722[61]
Aspartate aminotransferase increased	0[a]	6.8	• Disutility: NICE TA722[61] • Duration: NICE TA722[61]
Fatigue	-0.085	2.625	• Disutility: NICE TA439[109] • Duration: NICE TA722[61]
Hyperphosphatemia (grade 2+)	0[a]	15.5	• Disutility: NICE TA722[61] • Duration: NICE TA722[61]
Hypophosphataemia	0[a]	29.3	• Disutility: NICE TA722[61] • Duration: NICE TA722[61]
Stomatitis	-0.038	9.8	• Disutility: NICE TA439[109] • Duration: NICE TA722[61]

Notes: [a]Assumed to have no effect on HRQoL
Abbreviations: HRQoL: health-related quality of life; NICE: National Institute for Health and Care Excellence; QALY: quality-adjusted life year

UK clinical experts in CCA were asked to validate the provided values and overall considered the proposed durations and disutility values to be accurate.[2] They noted that the proposed duration of hypophosphataemia was longer than normally seen in clinical practice, however it was highlighted that this would not influence model outcomes, as this AE was assumed to have no impact on patient HRQoL. In addition, the experts noted that the duration of arthralgia was slightly higher than expected as it is not usually seen in clinical practice, although, this was modelled in line with NICE TA722 in the absence of more appropriate data.

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

Utility values were applied to the PF and PD states to estimate HRQoL. These values were derived from the EQ-5D-3L data from the FOENIX-CCA2 trial, as it was the most relevant source of information for the population of interest to this submission. The utilities were derived from the FOENIX EQ-5D-3L data using a mixed model for repeated measures (MMRM) approach, considering progression status as the sole covariate in the base case analysis; additional analyses were also conducted exploring additional covariates, such as treatment status, but were not considered to generate plausible results.

In the base-case analysis, health state utility values were age-adjusted over the model time horizon using the UK population norm values for EQ-5D as reported in the HSE 2014 dataset by the NICE DSU.[111]

The utility values used in the economic model are presented in Table 37.

Table 37: Summary of utility values for cost-effectiveness analysis

Health state	Utility value	Source
Progression-free	[redacted]	FOENIX-CCA2[76]
Progressed disease	[redacted]	FOENIX-CCA2[76]

The presented value for PF disease was verified by UK CCA clinical experts. Clinical and economic experts noted that the PD utility value derived from FOENIX-CCA2 may be slightly higher than expected, which may be explained by highly symptomatic patients not completing the questionnaire regularly following disease progression.[2] In the absence of alternative utility data, the base case economic analysis used the PD utility value derived from FOENIX-CCA2, however, this was explored as part of sensitivity and scenario analyses (Section B.3.11.3).

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

An SLR was conducted in October 2023 to identify all relevant literature published on cost and HCRU in adult patients treated with futibatinib or pemigatinib. The methods and results of the HCRU SLR are reported in Appendix I.

The economic model included drug acquisition, AE, end of life and disease management costs.

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs

The price for futibatinib is provided by Taiho Oncology. Futibatinib is provided at a PAS discount of [redacted] on the list price of [redacted] per pack. Drug acquisition costs for pemigatinib were based on its list price, which was extracted from the British National Formulary (BNF). Drug acquisition costs included in the cost-effectiveness analysis are presented in Table 38.

Table 38: Drug acquisition costs for futibatinib and pemigatinib

Treatment	Form	Strength/unit	Pack size	Cost per pack (list)	Cost per pack (PAS)	Source
Futibatinib						
Futibatinib	Tablet	4 mg	35	[redacted]	[redacted]	Taiho Oncology. Data on file
Futibatinib	Tablet	4 mg	28	[redacted]	[redacted]	Taiho Oncology. Data on file
Futibatinib	Tablet	4 mg	21	[redacted]	[redacted]	Taiho Oncology. Data on file
Pemigatinib						

Pemigatinib	Tablet	4.5 mg	14	£7,159	NR	BNF
Pemigatinib	Tablet	9 mg	14	£7,159	NR	BNF
Pemigatinib	Tablet	13.5 mg	14	£7,159	NR	BNF

Abbreviations: BNF: British National Formulary; NR: not reported; PAS: patient access scheme
Source: BNF. Pemigatinib[112]

Treatment costs were modelled based on time on treatment (ToT). The recommended dosing intensity (RDI) of 100% was applied in the model. Since the safety profile of futibatinib was pemigatinib was found to be similar, as confirmed by trial data and clinical expert opinion,[2] it was assumed that both treatments are associated with an RDI of 100% as a simplifying assumption. As both futibatinib and pemigatinib are associated with a flat price per pack, dose reductions do not result in a reduced cost per pack.

In the base case analysis, drug wastage was included; it was assumed that half a pack of futibatinib or pemigatinib is wasted per patient. This was based on the assumption that, on average, patients discontinue treatment halfway through a pack, which was validated by UK clinical experts.[2] Excluding drug wastage costs was explored in a scenario analysis (see Section B.3.11.3).

Table 39 summarises the costs of futibatinib and pemigatinib treatment.

Table 39: Treatment costs included in cost effectiveness model

Treatment	Cycle length, days	Cost per treatment cycle	Source
Futibatinib 20 mg daily (PAS price)	21 (continuous)	[redacted]	Taiho Oncology. Data on file.
Futibatinib 16 mg daily (PAS price)	21 (continuous)	[redacted]	Taiho Oncology. Data on file.
Futibatinib 12 mg daily (PAS price)	21 (continuous)	[redacted]	Taiho Oncology. Data on file.
Pemigatinib 13.5 mg daily	21 (14 on, 7 off)	£7,159.00	BNF

Abbreviations: PAS: patient access scheme; QD: once daily
Source: BNF. Pemigatinib[112]

Administration costs

No administration costs were applied for futibatinib or pemigatinib, due to them both being oral treatments.

Subsequent treatments

PFS and OS between futibatinib and pemigatinib are expected to be very similar, as confirmed by the results of the MAIC (see Section B.2.9.2) and expert clinical opinion.[2] Subsequent treatments following both treatments are also expected to be identical (usually consisting of the mFOLFOX chemotherapy regimen for the patients who are able to tolerate it, or BSC) based on UK clinical expert feedback.[2]

Therefore, it is expected that patients would be receiving the same subsequent treatment regimens, at the same time and for the same duration following either futibatinib or pemigatinib. Consequently it is anticipated that subsequent treatments would be associated with equal costs

in both treatment arms. For this reason, subsequent treatments have been excluded from the model as a simplifying assumption.

B.3.5.2 Health-state unit costs and resource use

The types of resource and frequency of use in the PF and PD health states included in the cost-effectiveness analysis were based on TA722, and verified with UK clinical experts in CCA.[2, 61] Costs were based on the 2021/22 NHS reference costs.[99]

The resource use frequencies were overall validated by UK clinical experts.[2] The experts added that use of phosphate binders (daily as a continuous treatment) would also be expected for patients in the PF state, which was explored in a scenario analysis.[2]

Resource use estimates and associated unit costs are reported per health state in Table 40.

Table 40: Resource use per 21 day cycle by health state: base-case

Resource	PF	PD	Unit cost, £
Clinical examination	0.23	0.23	221.48
CT scan	0.23	0.06	181.82
OCT (retinal scan)	0.25	0	158.18
Blood test	0.23	0.23	2.96
Pain medication	0	20.97	0.46

Abbreviations: CT: computer tomography; OCT: optical coherence tomography; PD: progressed disease; PF: progression-free
Source: Costs: NHS 2021/22 Reference Costs;[99] Frequencies: TA722;[61] Taiho Oncology Data on File. FOENIX-CCA2 Advisory Board report[2]

B.3.5.3 Adverse reaction unit costs and resource use

Mean cost per adverse event applied in the cost-effectiveness analyses are reported in Table 41. Adverse event costs were applied in the model according to the incidences presented in Section 2.10.3.

Table 41: Costs per adverse event applied in the cost-effectiveness model

Adverse event	Mean cost, £	Source
Aspartate aminotransferase increased	0.00	Watchful waiting (and thus no cost) assumed
Fatigue	770.29	NHS reference costs 2021/22: SA01G-K, Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, Non-elective short stay weighted average
Hyperphosphataemia (grade 2+)	19.75	BNF, 2023. One pack of phosphate binders - Calcium acetate, Renacet 950 mg tablets
Hypophosphataemia	19.39	BNF, 2023. One pack of oral phosphate supplements - Phosphate Sandoz effervescent tablet
Stomatitis	827.18	NHS reference costs 2021/22: FD10E-H, Non-malignant Gastrointestinal Tract Disorders with Single Intervention, Non-elective short stay weighted average

B.3.5.4 Miscellaneous unit costs and resource use

A one-off terminal care cost of £6,870.13 was applied upon death to account for the cost associated with the additional intensive disease management in the months prior to death.[113] The reference for this cost was aligned to that used in the pemigatinib NICE appraisal, inflated to the latest cost year.[61]

As genetic testing forms part of routine clinical practice for CCA in the UK, it is not anticipated the introduction of futibatinib to clinical practice would incur any additional genetic testing costs. As such, no FGFR2 genetic testing cost was included in the base case analysis. UK clinical experts consulted as part of an Advisory Board confirmed that FGFR2 genetic testing is currently a part of standard clinical pathway in the UK, and FGFR2 rearrangement fluorescent in situ hybridisation (FISH) testing is included in the 2024/2025 National Genomic Test Directory for patients with CCA (test code M220.7).[2, 10] The addition of genetic testing costs was explored in a scenario analysis, confirming that it had no substantial impact on the ICER (Section B.3.11.3); the cost of genetic testing used in this analysis (£34) was aligned with the cost of testing outlined in the Final Appraisal Document (FAD) for the NICE pemigatinib submission (TA722).[114]

B.3.6 *Severity*

A summary of the features of the QALY shortfall analysis is provided in Table 42. The expected quality-adjusted life expectancy (QALE) for the general population was calculated in line with the methods provided by Schneider et al. (2022).[115] The total life expectancy for the modelled population was calculated using population mortality data from the ONS for 2017-2019 – as previously detailed, 2017-2019 life tables were used to avoid the analyses being skewed by COVID-19 excess mortality. The total life expectancy was quality-adjusted using UK population norm values for EQ-5D as reported by Hernández Alava et al. (2022) through the NICE DSU.[116]

The results of the QALY shortfall analysis are summarised in Table 43. With an absolute QALY shortfall of [redacted] and a proportional QALY shortfall of [redacted], futibatinib is eligible for a 1.2x severity modifier.

As the guidance for the only prior appraisal in this indication [TA722] was published in 2021, no prior appraisals in the indication of interest to this submission used severity modifiers.[61]

In the cost-comparison scenario analysis, given the assumption of equal efficacy between futibatinib and pemigatinib, there is no difference in incremental QALYs between the two treatments. The application of a severity modifier therefore has no impact on the modelled results in the cost-comparison scenario.

Table 42: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Female, %	56.3	Section B.2.3.3, Table 4
Starting age (years)	55.7	Section B.2.3.3, Table 4
Utility value for PF health state	[redacted]	Section B.3.4.5, Table 37
Utility value for PD health state	[redacted]	Section B.3.4.5, Table 37

Abbreviations: PD: progressed disease; PF: progression-free
Source: Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 29 May 2021[76]

Table 43: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with the condition would be expected to have with current treatment (pemigatinib)	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
14.13	[redacted]	[redacted]	[redacted]	1.2

Abbreviations: QALY: quality-adjusted life year
Source: University of York. QALY shortfall calculator[117]

B.3.7 *Uncertainty*

CCA with FGFR2 fusions or rearrangements is a rare disease, with UK clinical experts estimating a prevalence of 2,500–3,000 patients in UK clinical practice (see Section B.1.3.1).[2] As such, no direct data on the efficacy of futibatinib compared to relevant treatments in UK clinical practice (pemigatinib) were available. Relative efficacy estimates for futibatinib compared to pemigatinib therefore had to be obtained indirectly via a MAIC. Indirect comparisons are associated with inherent uncertainty, however, where possible, all potential prognostic factors and effect modifiers were adjusted for in the analyses. Clinical experts in CCA confirmed that the variables adjusted for in the analysis were sufficient.[2] In addition, sensitivity analyses were performed to assess the uncertainty surrounding the MAIC results (see Section B.1.1). The results of the sensitivity analyses showed that the MAIC conclusions were robust to uncertainty surrounding the race covariate. Therefore, despite any uncertainty, the ITCs provide clear evidence for the similar efficacy between futibatinib and pemigatinib, and for the assumption of equal efficacy in the cost-comparison scenario.

Another potential source of uncertainty is the long-term survival extrapolations, in particular considering that OS data from the FOENIX-CCA2 trial were relatively immature at the time of the final data-cut. This was mitigated through conducting detailed consultations with UK clinical experts in CCA to generate as clinically valid long-term survival extrapolations as possible.[2] Additionally, the PFS data at the final data cut-off could be considered relatively mature, as over 75% of patients had experienced a PFS event (see Section B.2.6.4). Therefore, the long-term survival extrapolations are not expected to represent a substantial source of uncertainty for the base case analysis.

B.3.8 *Managed access proposal*

Since no further data cuts are planned in the FOENIX-CCA2 trial, a managed access proposal is not applicable for futibatinib.

B.3.9 *Summary of base-case analysis inputs and assumptions*

B.3.9.1 Summary of base-case analysis inputs

The base-case analysis inputs used in the model are summarised in Table 44.

Table 44: Summary of variables applied in the economic model (base case analysis)

Variable	Value	Reference to section in submission
Model settings		
Discount rate (costs)	3.5%	Section B.3.2.2
Discount rate (benefits)	3.5%	
Time horizon	Lifetime: 40 years	
Patient characteristics		
Percentage female	56.3%	Section B.3.3.1
Starting age, years	55.7	
Body weight, kg	[redacted]	
Body surface area, m^2	[redacted]	
Clinical inputs		
PFS for futibatinib	Lognormal	Section B.3.3
PFS for pemigatinib	The inverse of the MAIC HR of 1.07 – i.e. a HR of 0.93 was applied to the futibatinib PFS curve	
OS for futibatinib	Lognormal	
OS for pemigatinib	The inverse of the MAIC HR of 0.95 – i.e. a HR of 1.05 was applied to the futibatinib OS curve	
Utility inputs		
Utility for PF health state	[redacted]	Section B.3.4.5
Utility for PD health state	[redacted]	
AE disutilities	Various (Table 36)	Section B.3.4.4
Drug acquisition costs		
Futibatinib price (with PAS): 35 x 4 mg tablets	[redacted]	Section B.3.5.1
Futibatinib price (with PAS): 28 x 4 mg tablets	[redacted]	
Futibatinib price (with PAS): 21 x 4 mg tablets	[redacted]	
Pemigatinib price: 14 x 4.5 mg tablets	£7,159.00	
Pemigatinib price: 14 x 9 mg tablets	£7,159.00	
Pemigatinib price: 14 x 13.5 mg tablets	£7,159.00	
Health state unit costs		

Resource	PF	PD	Unit cost	
Clinical examination	0.23	0.23	£221.48	Section B.3.5.2
CT scan	0.23	0.06	£181.82	
OCT (retinal scan)	0.25	0	£158.18	
Blood test	0.23	0.23	£2.96	
Pain medication	0	20.97	£0.46	
Adverse events costs				
Aspartate aminotransferase increased	£0.00			Section B.3.4.4
Fatigue	£770.29			
Hyperphosphataemia (grade 2+)	£19.75			
Hypophosphataemia	£19.39			
Stomatitis	£827.18			
Miscellaneous costs				
End of life cost	£6,870.13			Section B.3.5.4

Abbreviations: CI: confidence interval; CT; computer tomography; OCT: optical coherence tomography; OS: overall survival; PAS: patient access scheme; PD: progressed disease; PF: progression-free; PFS: progression-free survival; RDI: recommended dose intensity

B.3.9.2 Assumptions

A summary of all the model assumptions and justifications is provided in Table 45.

Table 45: Base-case assumptions

Subject	Base-case assumption	Justification
Model settings		
Perspective	NHS and PSS	NICE reference case[98]
Discounting of outcomes	3.5% per annum for costs and effects	NICE reference case[98]
Time horizon	40 years	Lifetime time horizon is consistent with NICE reference case;[98] time horizon of 40 years was considered to be sufficient to capture the expected lifespan of the patient population and aligned with the previous NICE appraisal in CCA with FGFR2 fusion or rearrangement (TA722),[61] as well as was confirmed to be suitable by UK clinical experts[2]
Efficacy		
ToT	ToT is equal to PFS	Verified as a reasonable simplifying assumption by UK experts, as patients are not likely to continue receiving futibatinib or pemigatinib for a considerable time after disease progression.[2] This aligns with the data from the FOENIX-CCA2 trial, where median PFS was 8.9 months and median duration of treatment was 9.1 months[82]
Survival curves		
Futibatinib OS	Lognormal	The most appropriate extrapolations for futibatinib PFS and OS were based on a combination of statistical and visual fit and long-term clinical plausibility, guided by UK clinical experts in CCA.[2] Log-logistic and Weibull extrapolation curves for PFS and OS were explored in scenario analyses (see Section B.3.11.3)
Futibatinib PFS	Lognormal	
Pemigatinib OS	Futibatinib OS curve adjusted by the reverse of the OS HR calculated in the MAIC	PH assessments found that the PH assumption held between futibatinib and pemigatinib for both PFS and OS. Therefore, as a simplifying assumption and to allow the use of the FOENIX-CCA2 trial data directly, pemigatinib OS and PFS were modelled by applying the OS and PFS HRs from the MAIC to the chosen futibatinib PFS and OS extrapolations to derive PFS and OS extrapolations for pemigatinib. Varying the value of the HR (PFS HR=1, OS HR=1 or both PFS HR=1 and OS HR=1), as well as applying HR values from unadjusted comparisons or the MAIC sensitivity analysis, were explored in scenario analyses (see Section B.3.11.3)
Pemigatinib PFS	Futibatinib PFS curve adjusted by the reverse of the PFS HR calculated in the MAIC	
Safety		

AEs grade and incidence	Treatment related grade ≥3 AEs which have an incidence rate >5% for either futibatinib or pemigatinib have been modelled. AEs grade <3 and those with an incidence rate of ≤5% for both futibatinib and pemigatinib were excluded.	The AEs of grade <3 and/or incidence rate ≤5% for both futibatinib and pemigatinib were assumed to incur low costs and have a limited impact on the economic analysis results; this was verified as a reasonable simplifying assumption by UK experts[2]
AE costs	AEs were applied upon initiation of treatment and costs were applied as one-off events.	Verified as a reasonable simplifying assumption by UK experts[2]
Utilities		
Health state utility values (HSUVs)	HSUVs were applied directly to health states (PF and PD) and were assumed to be constant over time and not treatment specific	All relevant effects of treatment on HRQoL were assumed to have been captured separately via the consideration of disease progression and AE disutilities. Additionally, considered of treatment specific utilities is not feasible, as HSUVs for pemigatinib based on FIGHT-202 are not publicly available. The choice of HSUVs is expected to have minimal effect on the modelling conclusions due to the similar safety profiles of these two treatments. This was verified as a reasonable simplifying assumption by UK experts[2]
AE disutilities	One-off AE disutilities (accounting for the incidence rate, utility decrement and duration of each adverse events included in the model) are applied upon initiation of either futibatinib or pemigatinib	Verified as a reasonable simplifying assumption by UK experts[2]
Costs		
FGFR genetic testing	Cost of FGFR genetic testing has not been included in the model in the base case analysis, as it is assumed that FGFR testing is part of routine clinical practice in the UK	UK experts in CCA confirmed that in line with European guidelines, FGFR2 genetic testing is part of routine care for patients with CCA in the UK.[2] Adding a genetic testing cost was explored in a scenario analysis (see Section B.3.11.3)
Wastage	Half a pack of futibatinib or pemigatinib wasted per patient	It was assumed that, on average, patients discontinue treatment halfway through a pack. Excluding drug wastage was explored in a scenario analysis (see Section B.3.11.3)

Abbreviations: AE: adverse event; CCA: cholangiocarcinoma; FGFR: fibroblast growth factor receptor; HR: hazard ratio; HSUV: health-state utility value; MAIC: matching-adjusted indirect comparison; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PFS: progression-free survival; PSS: Personal Social Services; ToT: time on treatment
Source: Taiho Oncology. Data on File. FOENIX-CCA2 Advisory Board Report. 22 May 2023[2]

B.3.10 *Deterministic base-case results*

B.3.10.1 Base-case deterministic pair-wise cost-effectiveness analysis results

The base case deterministic cost-effectiveness results for futibatinib versus pemigatinib and incremental net health benefits are presented in Table 46. In the deterministic analysis with both treatments at list price, futibatinib was found to be dominant compared to pemigatinib at a willingness to pay (WTP) threshold of £30,000 per QALY, yielding an INHB of [redacted]. These results do not include a severity modifier; the analysis including the severity modifier is presented in Table 48 and Table 49 below.

The clinical outcomes and disaggregated base case cost-effectiveness results (by cost category, including health states) and QALYs (by health state) are presented in Appendix J.

Table 46: Deterministic base-case results (futibatinib list price versus pemigatinib list price, excluding severity modifier)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental NHB at £30,000
Futibatinib	[redacted]	2.36	[redacted]	[redacted]	0.11	[redacted]	Dominant	[redacted]
Pemigatinib	140,130	2.25	[redacted]	-	-	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years

Table 47: Deterministic base-case results (futibatinib PAS price versus pemigatinib list price, excluding severity modifier)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental NHB at £30,000
Futibatinib	[redacted]	2.36	[redacted]	[redacted]	0.11	[redacted]	Dominant	[redacted]
Pemigatinib	140,130	2.25	[redacted]	-	-	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years

Table 48: Deterministic base-case results (futibatinib list price versus pemigatinib list price; including severity modifier)

Intervention	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental NHB at £30,000
Futibatinib vs pemigatinib	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years

Table 49: Deterministic base-case results (futibatinib PAS price versus pemigatinib list price, including severity modifier)

Intervention	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental NHB at £30,000
Futibatinib vs pemigatinib	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years

B.3.11 *Exploring uncertainty*

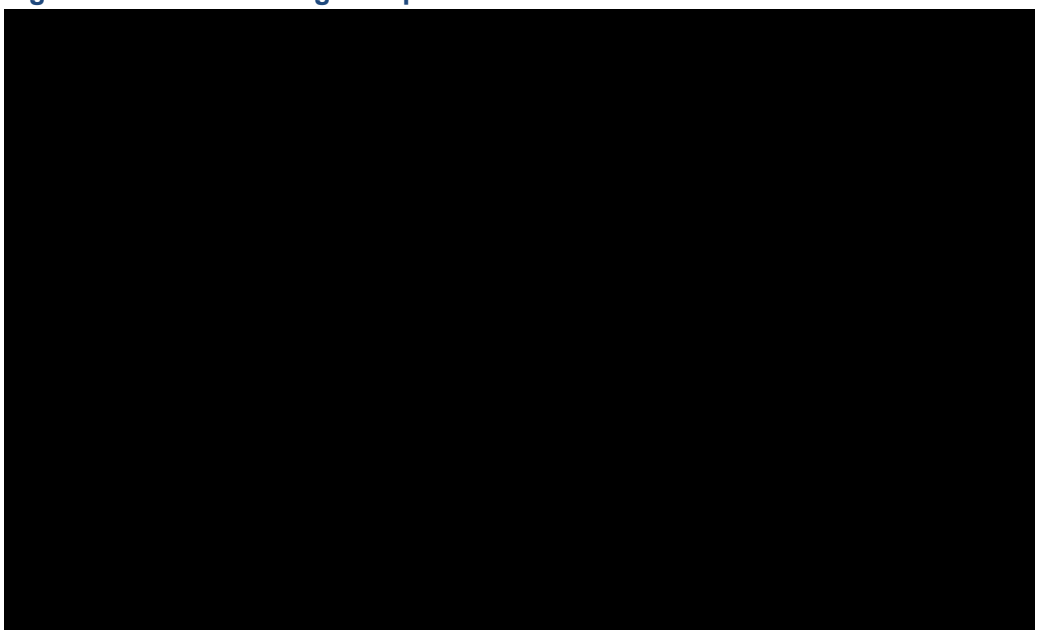
Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses the results of which are presented in Sections B.3.11.1 and B.3.11.2, respectively. In addition, key assumptions in the model were explored in several probabilistic scenario analyses, the results of which are presented below.

Overall, it is considered that all relevant uncertainties included in the analyses have been adequately accounted for and the base case results were found to be robust to uncertainty in the key model inputs and assumptions.

B.3.11.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were run with 1,000 iterations, with estimates of model parameters based on the uncertainty in the source data (where data availability permitted) as detailed in the Model Parameters tab of the CEM. Where no such data were available, the model applied a user-defined percentage of the mean value as the standard error. An INHB convergence plot is provided in Figure 26 below.

Figure 26: INHB convergence plot



Abbreviations: INHB: incremental net health benefit

The base case probabilistic cost-effectiveness results for futibatinib versus pemigatinib and net health benefits are presented in Table 50. Closely aligned with the deterministic base case results, in the probabilistic analysis futibatinib was found to remain dominant compared to pemigatinib at a willingness to pay (WTP) threshold of £30,000 per QALY, yielding an INHB of [redacted]. These results do not include a severity modifier.

Table 50: Probabilistic base-case results (futibatinib list price versus pemigatinib list price, excluding severity modifier)

Intervention	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental NHB at £30,000
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Pemigatinib	145,211	[redacted]	-	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years

The probabilistic cost-effectiveness plane for futibatinib versus pemigatinib is presented in Figure 27. The cost-effectiveness acceptability curves for futibatinib versus pemigatinib are presented in Figure 28. The PSA found the probability of futibatinib being cost-effective to be [redacted]% and [redacted]% at a WTP threshold of £20,000 and £30,000 per QALY, respectively (using futibatinib list price and excluding the severity modifier).

Figure 27: Probabilistic cost-effectiveness plane for futibatinib versus pemigatinib (list price, excluding severity modifier)

Abbreviations: CE: cost-effectiveness; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Figure 28: Cost-effectiveness acceptability curve for futibatinib versus pemigatinib

Abbreviations: WTP: willingness-to-pay.

B.3.11.2 Deterministic sensitivity analysis

In order to assess the robustness of the base case cost-effectiveness results, deterministic sensitivity analyses (DSA) were conducted by varying all parameters for which there were single input values in the model by ±20% of their mean value. The tornado diagrams for futibatinib versus pemigatinib are presented in Figure 29, Figure 30 and Figure 31; please note that the INHB is presented as the ICER is extremely sensitive to changes in costs due to the limited difference in QALYs between futibatinib and pemigatinib. The top ten most influential parameters on the base case are presented in each case.

A small number of inputs had a significant impact on the INHB when varied to their limits across all pairwise comparisons. The HR for PFS for futibatinib vs pemigatinib had the greatest impact on the INHB, as this is both a key factor in determining the time spent in the progression-free health state, which in turn has a considerable impact on both QALYs and treatment acquisition costs (as time to treatment discontinuation is assumed to align with time to progression). The HR for OS also has a considerable impact on the INHB, although this is less pronounced than the HR for PFS, as this does not affect the treatment acquisition costs. Other inputs have a very little impact on the calculated INHB.

Figure 29: DSA tornado diagram for futibatinib and pemigatinib (INHB)

Abbreviations: DSA: deterministic sensitivity analysis; HR: hazard ratio; INHB: incremental net health benefit; OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival.

Figure 30: DSA tornado diagram for futibatinib and pemigatinib (incremental costs)

Abbreviations: DSA: deterministic sensitivity analysis; HR: hazard ratio; OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival.

Figure 31: DSA tornado diagram for futibatinib and pemigatinib (incremental QALYs)

Abbreviations: DSA: deterministic sensitivity analysis; HR: hazard ratio; OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival; QALY: quality-adjusted life year.

B.3.11.3 Scenario analysis

Several scenario analyses were conducted to assess the impact of the uncertainty associated with key inputs and assumptions in the economic model. Given the small incremental QALYs observed in the comparison of futibatinib and pemigatinib and the resulting sensitivity of the ICER and INHB, scenarios were run deterministically to clearly demonstrate the impact of the changes in inputs or assumptions in isolation (i.e. excluding the impact random variation that would be introduced in a probabilistic analysis). As probabilistic base case results were similar to deterministic base case results, as shown in B.3.11.1, this should not be considered to represent a source of uncertainty.

Scenario analyses included a cost-comparison scenario with an assumption of equal efficacy between futibatinib and pemigatinib, based on the results of the MAIC showing no statistically significant difference in efficacy between futibatinib and pemigatinib. A summary of the scenario analysis results for futibatinib versus pemigatinib are presented in Table 51.

In all explored scenarios, INHB was positive for futibatinib, or neutral in the case of the cost-comparison scenario where futibatinib was found to be a cost-saving treatment option when compared to pemigatinib. Overall, the sensitivity analysis results demonstrate the base-case results to be robust to uncertainties in inputs and assumptions.

Table 51: Scenario analysis results for futibatinib versus pemigatinib

Scenario		Futibatinib versus pemigatinib			
		Incremental costs, £	Incremental QALYs	ICER (£/QALY)	INHB
Base case		[redacted]	[redacted]	Dominant	[redacted]
1	Cost-comparison analysis	[redacted]	[redacted]	Dominant	[redacted]

PFS					
2	Futibatinib PFS curve choice: log-logistic	[redacted]	[redacted]	Dominant	[redacted]
3	Futibatinib PFS curve choice: Weibull	[redacted]	[redacted]	Dominant	[redacted]
4	Futibatinib versus pemigatinib PFS HR is equal to 1	[redacted]	[redacted]	£1,053	[redacted]
5	Futibatinib versus pemigatinib PFS HR is based on the unadjusted comparison between FOENIX-CCA2 and FIGHT-202 (HR: 1.02 for futibatinib versus pemigatinib)	[redacted]	[redacted]	Dominant	[redacted]
6	Futibatinib versus pemigatinib PFS HR is based on the sensitivity analysis MAIC (HR: 1.11 for futibatinib versus pemigatinib)	[redacted]	[redacted]	Dominant	[redacted]
OS					
7	Futibatinib OS curve choice: log-logistic	[redacted]	[redacted]	Dominant	[redacted]
8	Futibatinib OS curve choice: Weibull	[redacted]	[redacted]	Dominant	[redacted]
9	Futibatinib versus pemigatinib OS HR is set equal to 1	[redacted]	[redacted]	£1,361,250	[redacted]
10	Futibatinib versus pemigatinib OS HR is set equal to the unadjusted comparison between FOENIX-CCA2 and FIGHT-202 (HR: 0.96)	[redacted]	[redacted]	Dominant	[redacted]
11	Futibatinib versus pemigatinib OS HR is based on the sensitivity analysis MAIC (HR: 0.96)	[redacted]	[redacted]	Dominant	[redacted]
OS and PFS					
8	Set PFS and OS HR to 1	[redacted]	[redacted]	Dominant	[redacted]
Costs					
9	Exclude drug wastage costs	[redacted]	[redacted]	Dominant	[redacted]
10	Include genetic testing cost	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

B.3.12 *Subgroup analysis*

N/A – No subgroups were considered relevant to this appraisal. Consequently, no subgroup analyses were included in the economic analysis.

B.3.13 *Benefits not captured in the QALY calculation*

As highlighted in Section B.2.12, treatment resistant mutations can arise over the course of treatment with FGFR2 inhibitors, including futibatinib and pemigatinib.[28] Futibatinib has been

shown to lead to significantly fewer resistance mutations than pemigatinib *in vitro* (see Section B.2.12).[3, 7]

UK clinical experts in CCA highlighted that, although this difference is not likely to be reflected in the survival results from the clinical trial, for individual patients this distinction may be important. In particular, the experts noted that, considering the comparable efficacy of futibatinib and pemigatinib, they would prefer to use futibatinib over pemigatinib in order to reduce the potential for the development of treatment resistance.[2] As such, in addition to the value associated with increased patient choice via the addition of futibatinib to the UK treatment pathway, it is plausible that futibatinib would be associated with additional improved efficacy versus pemigatinib that is not captured in the QALY calculation.

B.3.14 *Validation*

B.3.14.1 Validation of cost-effectiveness analysis

Model validations were performed in alignment with best practices.[118] The model structure, source date and key assumptions and inputs were reviewed by UK clinical and health economic experts.[2] Of note, and as discussed in Section B.3.3, in light of the relatively immature OS data available from the FOENIX-CCA2 trial, a thorough clinical validation process was conducted in order to inform the most robust PFS and OS extrapolations for futibatinib and pemigatinib.

Once fully developed, the model underwent two independent quality control and technical validation processes which included checking of all model calculations including standalone formulae, equations and Excel macros programmed in VBA. The correct functioning of the sensitivity and scenario analyses was also reviewed, and two checklists (for technical and stress test checks), based on the published TECH-VER checklist,[119] were completed to ensure that the model generated accurate results which were consistent with input data and robust to extreme values.

Quality-control procedures for verification of input data and coding were performed by health economists not involved in the model development and in accordance with a pre-specified test plan. These procedures included verification of all input data with original sources and programming validation. Verification of all input data was documented in the relevant worksheets of the model. Any discrepancies were discussed, and the model input data was updated where required. Programming validation included checks of the model results, calculations, data references, model interface, and VBA code.

B.3.15 *Interpretation and conclusions of economic evidence*

Summary of the cost-effectiveness evidence

In order to conduct the analysis, a *de novo* PSM was constructed from the perspective of the NHS and PSS in England.

In the deterministic base-case analysis futibatinib was found to be cost-effective versus pemigatinib at the WTP threshold of £30,000, with a positive INHB of [redacted] ([redacted] when considering the 1.2x severity modifier). Thus, futibatinib can be considered a cost-effective use of NHS

resources for patients with previously treated locally advanced or metastatic CCA with FGFR2 gene rearrangements, including gene fusions.

To assess the robustness of the base case analysis to key inputs and assumptions, a number of additional scenario analyses were explored. These scenario analyses proved that the base case results were robust to the uncertainty surrounding key inputs and assumptions of the economic analysis.

Due to the results of the MAIC showing no statistically significant difference in effectiveness between futibatinib and pemigatinib, a cost-comparison scenario analysis was also conducted. This analysis showed futibatinib to be cost-saving compared with pemigatinib.

Sensitivity analyses, including PSA and DSA, were conducted in order to verify the robustness of the model results. The PSA found the probability of futibatinib being cost-effective to be [redacted]% and [redacted]% at a WTP threshold of £20,000 and £30,000 per QALY, respectively. The DSA found that the model was most sensitive to the PFS and OS HRs between futibatinib and pemigatinib, however scenario analyses exploring alternative HRs (including HRs derived from unadjusted comparisons, HRs from the MAIC sensitivity analyses and scenarios where HR=1) all found that futibatinib still resulted in a positive or neutral INHB versus pemigatinib.

Strengths

Robust validation of the key model assumptions and parameters was conducted by two UK economic experts and by two clinical experts with extensive experience of treating patients of CCA in the UK.[2] The validation included discussion around the most plausible long-term extrapolations of of PFS and OS for futibatinib and pemigatinib.

In addition, clinical experts in CCA reviewed the baseline characteristics of patients enrolled in the FOENIX-CCA2 trial, which were deemed to be representative of UK clinical practice. The choice of pemigatinib as the only relevant comparator to futibatinib in UK clinical practice was also verified.[2] The results of the economic analysis are therefore considered highly relevant to decision-making in NHS clinical practice.

Furthermore, the model closely aligns to the NICE reference case, adopting an NHS and PSS perspective, as well as utilising a lifetime time horizon to ensure all costs and QALY gains associated with the interventions are fully capture and discounting costs and benefits at a rate of 3.5% per annum.[98] Where possible, the parameters and assumptions used in the model were also aligned to the NICE appraisal of pemigatinib [TA722], which is the only targeted treatment recommended by NICE in the indication of interest to this submisison.[61]

Limitations

The key limitations of the economic analysis include the single-arm nature of the FOENIX-CCA2 and FIGHT-202 trials, dictated by the rare nature of the disease, which led to the lack of direct data comparing futibatinib and pemigatinib in UK clinical practice. Another limitation was the immaturity of the OS data available at the final data cut-off of FOENIX-CCA2.

As discussed in Section B.1.1, a MAIC was conducted in order to obtain relative efficacy estimates for futibatinib versus pemigatinib, due to the single-arm nature of FOENIX-CCA2 and FIGHT-202 trials. The MAIC approach has a number of inherent limitations, however efforts were

made to adjust for all relevant parameters. UK clinical and economic experts confirmed that all relevant treatment effect modifiers were adjusted for in the analysis, and that the conclusions of the MAIC were suitable for the decision-making in the UK.

With regard to the immaturity of OS data, this was mitigated by discussing the choice of long-term survival extrapolations with UK clinical experts and aligning with their preferred extrapolation in the base case economic analysis.[2] An expert elicitation approach was adopted in order to obtain the clinical feedback on the relevant extrapolations in a rigorous manner.[2]

Conclusions

In the UK, there is currently only one targeted treatment option available to adult patients with previously treated locally advanced or metastatic CCA with FGFR2 gene rearrangements, including gene fusions – the FGFR inhibitor pemigatinib. Based on the results of the FOENIX CCA-2 trial and an ITC versus FIGHT-202, futibatinib is associated with comparable efficacy to pemigatinib. MAICs found that futibatinib slightly extended restricted mean PFS and OS when compared to pemigatinib; no statistically significant differences were observed between the two treatments across any of the analyses considered.

In addition, futibatinib has been shown to lead to the development of fewer treatment-resistant mutations than pemigatinib *in vitro*.[2, 3, 7] Therefore, futibatinib may have the potential to address the unmet need in this patient population for a treatment which is less susceptible to the emergence of treatment resistance compared with pemigatinib. UK clinical experts highlighted that they may prefer to use futibatinib over pemigatinib due to this distinction.

Overall, the base case analysis found futibatinib to be cost-effective versus pemigatinib at a WTP of £30,000 per QALY, resulting in a positive or neutral INHB across all sensitivity and scenario analyses that were considered. This finding was supported by the results of the cost-comparison scenario analysis which demonstrated futibatinib to be cost-saving versus pemigatinib. Consequently, futibatinib can be considered a cost-effective use of NHS resources.

References

1. MHRA. Summary of product characteristics. Lytgobi. Available at: https://mhraproducts4853.blob.core.windows.net/docs/fb49eac7d9ca87a7e57a0df17095e2db95a12a55 [Accessed 17 November 2023].
2. Taiho Oncology. Data on File. FOENIX-CCA2 Advisory Board Report. 22 May 2023.
3. Goyal L, Shi L, Liu LY, et al. TAS-120 Overcomes Resistance to ATP-Competitive FGFR Inhibitors in Patients with FGFR2 Fusion-Positive Intrahepatic Cholangiocarcinoma. Cancer Discov 2019;9:1064-1079.
4. Sootome H, Fujita H, Ito K, et al. Futibatinib Is a Novel Irreversible FGFR 1-4 Inhibitor That Shows Selective Antitumor Activity against FGFR-Deregulated Tumors. Cancer Res 2020;80:4986-4997.
5. Vogel A, Segatto O, Stenzinger A, et al. FGFR2 Inhibition in Cholangiocarcinoma. Annu Rev Med 2023;74:293-306.
6. Goyal L, Meric-Bernstam F, Hollebecque A, et al. Futibatinib for FGFR2-Rearranged Intrahepatic Cholangiocarcinoma. N Engl J Med 2023;388:228-239.
7. Sootome H, Kato S, Kato M, et al. Abstract 1117: Acquired resistance to ATP-competitive and irreversible FGFR inhibitors (FGFRi's): A library-based approach. Cancer Research 2021;81:1117-1117.
8. European Medicines Agency. Lytgobi. Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/lytgobi-epar-product-information_en.pdf [Accessed 1 February 2024].
9. Futibatinib. Summary of product characteristics. Taiho Oncology Data on File.
10. National Health Service. National genomic test directory. Available at: https://www.england.nhs.uk/publication/national-genomic-test-directories/ [Accessed on 17 May 2023].
11. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology 2013;145:1215-29.
12. Genus T, Tataru D, Morement H, et al. (late submission poster) Incidence and mortality rates of cholangiocarcinoma in England. Annals of Oncology 2019;30:iv155.
13. Banales JM, Marin JJG, Lamarca A, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol 2020;17:557-588.
14. Valle JW, Kelley RK, Nervi B, et al. Biliary tract cancer. Lancet 2021;397:428-444.
15. Farshidfar F, Zheng S, Gingras MC, et al. Integrative Genomic Analysis of Cholangiocarcinoma Identifies Distinct IDH-Mutant Molecular Profiles. Cell Rep 2017;19:2878-2880.
16. Israel MA, Danziger N, McGregor KA, et al. Comparative Genomic Analysis of Intrahepatic Cholangiocarcinoma: Biopsy Type, Ancestry, and Testing Patterns. Oncologist 2021;26:787-796.
17. Lee H, Wang K, Johnson A, et al. Comprehensive genomic profiling of extrahepatic cholangiocarcinoma reveals a long tail of therapeutic targets. J Clin Pathol 2016;69:403-8.
18. Neumann O, Burn TC, Allgäuer M, et al. Genomic architecture of FGFR2 fusions in cholangiocarcinoma and its implication for molecular testing. Br J Cancer 2022;127:1540-1549.
19. Boerner T, Drill E, Pak LM, et al. Genetic Determinants of Outcome in Intrahepatic Cholangiocarcinoma. Hepatology 2021;74:1429-1444.
20. Izquierdo-Sanchez L, Lamarca A, La Casta A, et al. Cholangiocarcinoma landscape in Europe: Diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. J Hepatol 2022;76:1109-1121.
21. National Comprehensive Cancer Network. NCCN Guidelines. Biliary Tract Cancers Version 2.2023 (May 10, 2023). Available at: https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf [Accessed 10th May 2023].
22. Vogel A, Bridgewater J, Edeline J, et al. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2023;34:127-140.

23. Blechacz B. Cholangiocarcinoma: Current Knowledge and New Developments. Gut Liver 2017;11:13-26.
24. Valle JW, Lamarca A, Goyal L, et al. New Horizons for Precision Medicine in Biliary Tract Cancers. Cancer Discov 2017;7:943-962.
25. Rushbrook SM, Kendall TJ, Zen Y, et al. British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma. Gut 2023.
26. National Institute for Health and Care Excellence. Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [TA944]. Available at: https://www.nice.org.uk/guidance/ta944 [Accessed 22 January 2024].
27. National Institute for Health and Care Excellence. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement. Technology appraisal guidance. Recommendaitons. Available at: https://www.nice.org.uk/guidance/ta722/chapter/1-Recommendations [Accessed 11th May 2023].
28. Rizzo A, Ricci AD, Brandi G. Pemigatinib: Hot topics behind the first approval of a targeted therapy in cholangiocarcinoma. Cancer Treat Res Commun 2021;27:100337.
29. Banales JM, Cardinale V, Carpino G, et al. Expert consensus document: Cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). Nat Rev Gastroenterol Hepatol 2016;13:261-80.
30. Rizvi S, Khan SA, Hallemeier CL, et al. Cholangiocarcinoma - evolving concepts and therapeutic strategies. Nat Rev Clin Oncol 2018;15:95-111.
31. Genus T, Tataru D, Morement H, et al. THU508 - Cholangiocarcinoma in England - a national study examining changes in incidence, diagnostic routes and overall survival. Journal of Hepatology 2020;73:S393-S394.
32. Burton A, Tataru D, Driver RJ, et al. Primary liver cancer in the UK: Incidence, incidence-based mortality, and survival by subtype, sex, and nation. JHEP Rep 2021;3:100232.
33. Florio AA, Ferlay J, Znaor A, et al. Global trends in intrahepatic and extrahepatic cholangiocarcinoma incidence from 1993 to 2012. Cancer 2020;126:2666-2678.
34. Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: Epidemiology and risk factors. Liver Int 2019;39 Suppl 1:19-31.
35. Zabron A, Edwards RJ, Khan SA. The challenge of cholangiocarcinoma: dissecting the molecular mechanisms of an insidious cancer. Dis Model Mech 2013;6:281-92.
36. Clements O, Eliahoo J, Kim JU, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: A systematic review and meta-analysis. J Hepatol 2020;72:95-103.
37. Goyal L, Kongpetch S, Crolley VE, et al. Targeting FGFR inhibition in cholangiocarcinoma. Cancer Treat Rev 2021;95:102170.
38. Kelley RK, Bridgewater J, Gores GJ, et al. Systemic therapies for intrahepatic cholangiocarcinoma. J Hepatol 2020;72:353-363.
39. Lamarca A, Ross P, Wasan HS, et al. Advanced Intrahepatic Cholangiocarcinoma: Post Hoc Analysis of the ABC-01, -02, and -03 Clinical Trials. J Natl Cancer Inst 2020;112:200-210.
40. Babina IS, Turner NC. Advances and challenges in targeting FGFR signalling in cancer. Nat Rev Cancer 2017;17:318-332.
41. Farrell B, Breeze AL. Structure, activation and dysregulation of fibroblast growth factor receptor kinases: perspectives for clinical targeting. Biochem Soc Trans 2018;46:1753-1770.
42. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol 2020;21:671-684.
43. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated locally advanced/metastatic cholangiocarcinoma (CCA): Update of FIGHT-202. Journal of Clinical Oncology 2021;39:4086-4086.
44. 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;38:108-108.
45. Jain A, Borad MJ, Kelley RK, et al. Cholangiocarcinoma With FGFR Genetic Aberrations: A Unique Clinical Phenotype. JCO Precis Oncol 2018;2:1-12.
46. Javle MM, Roychowdhury S, Kelley RK, et al. Final results from a phase II study of infigratinib (BGJ398), an FGFR-selective tyrosine kinase inhibitor, in patients with previously treated advanced cholangiocarcinoma harboring an FGFR2 gene fusion or rearrangement. Journal of Clinical Oncology 2021;39:265-265.
47. Murugesan K, Necchi A, Burn TC, et al. Pan-tumor landscape of fibroblast growth factor receptor 1-4 genomic alterations. ESMO Open 2022;7:100641.
48. Borad MJ, Conner T, He L, et al. Real-world genomic testing, treatment, and outcomes in patients with cholangiocarcinoma with FGFR2 fusions/rearrangements. Journal of Clinical Oncology 2022;40:e16168-e16168.
49. Rizzato M, Brignola S, Munari G, et al. Prognostic impact of FGFR2/3 alterations in patients with biliary tract cancers receiving systemic chemotherapy: the BITCOIN study. Eur J Cancer 2022;166:165-175.
50. Churi CR, Shroff R, Wang Y, et al. Mutation profiling in cholangiocarcinoma: prognostic and therapeutic implications. PLoS One 2014;9:e115383.
51. Javle M, Bekaii-Saab T, Jain A, et al. Biliary cancer: Utility of next-generation sequencing for clinical management. Cancer 2016;122:3838-3847.
52. Shroff RT, Avogadri F, Weng R, et al. Natural history of patients with advanced cholangiocarcinoma and FGFR2 gene fusions/rearrangements. Journal of Clinical Oncology 2022;40:391-391.
53. Buckarma E, De La Cruz G, Truty M, et al. Impact of FGFR2 gene fusions on survival of patients with intrahepatic cholangiocarcinoma following curative intent resection. HPB (Oxford) 2022;24:1748-1756.
54. Abou-Alfa GK, Bibeau K, Schultz N, et al. Effect of FGFR2 Alterations on Overall and Progression-Free Survival in Patients Receiving Systemic Therapy for Intrahepatic Cholangiocarcinoma. Target Oncol 2022;17:517-527.
55. Saha SK, Zhu AX, Fuchs CS, et al. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S.: Intrahepatic Disease on the Rise. Oncologist 2016;21:594-9.
56. Uhlig J, Sellers CM, Cha C, et al. Intrahepatic Cholangiocarcinoma: Socioeconomic Discrepancies, Contemporary Treatment Approaches and Survival Trends from the National Cancer Database. Ann Surg Oncol 2019;26:1993-2000.
57. Lamarca A, Santos-Laso A, Utpatel K, et al. Liver Metastases of Intrahepatic Cholangiocarcinoma: Implications for an Updated Staging System. Hepatology 2021;73:2311-2325.
58. Liu J, Zhong M, Feng Y, et al. Prognostic Factors and Treatment Strategies for Intrahepatic Cholangiocarcinoma from 2004 to 2013: Population-Based SEER Analysis. Transl Oncol 2019;12:1496-1503.
59. Kommalapati A, Tella SH, Goyal G, et al. Association between treatment facility volume, therapy types and overall survival in patients with intrahepatic cholangiocarcinoma. HPB (Oxford) 2019;21:379-386.
60. Bertuccio P, Malvezzi M, Carioli G, et al. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. J Hepatol 2019;71:104-114.
61. National Institute for Health and Care Excellence. Single Technology Appraisal. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations [ID3740]. Committee Papers. Available at: https://www.nice.org.uk/guidance/ta722/documents/committee-papers [Accessed 28th April 2023].
62. Moschopoulou E, Deane J, Duncan M, et al. Measuring quality of life in people living with and beyond cancer in the UK. Support Care Cancer 2021;29:6031-6038.
63. Bottomley A. The cancer patient and quality of life. Oncologist 2002;7:120-5.
64. Bibeau K, Bachini M, Lindley A, et al. Exploring the diagnostic journey and life impact of patients with cholangiocarcinoma (CCA): Results from a large patient survey in the United States. Journal of Clinical Oncology 2021;39:277-277.

65. Kaupp-Roberts SD, Yadegarfar G, Friend E, et al. Validation of the EORTC QLQ-BIL21 questionnaire for measuring quality of life in patients with cholangiocarcinoma and cancer of the gallbladder. Br J Cancer 2016;115:1032-1038.
66. Woradet S, Songserm N, Promthet S, et al. Health-Related Quality of Life and Survival of Cholangiocarcinoma Patients in Northeastern Region of Thailand. PLoS One 2016;11:e0163448.
67. Patel N, Lie X, Gwaltney C, et al. Understanding Patient Experience in Biliary Tract Cancer: A Qualitative Patient Interview Study. Oncol Ther 2021;9:557-573.
68. Sangruangake M, Summart U, Methakanjanasak N, et al. Psychometric Properties of the Thai Version of Supportive Care Needs Survey-Partners and Caregivers (T- SCNS-P&C) for Cholangiocarcinoma Caregivers. Asian Pac J Cancer Prev 2022;23:1069-1076.
69. Summart U, Sangruangake M, Songthamwat M, et al. Factors Associated with the Quality of Life among Family Caregivers of Cholangiocarcinoma Survivors in Northeastern Thailand. Asian Pac J Cancer Prev 2023;24:1249-1255.
70. Chamberlain CX, Faust E, Goldschmidt D, et al. Burden of illness for patients with cholangiocarcinoma in the United States: a retrospective claims analysis. J Gastrointest Oncol 2021;12:658-668.
71. Parasuraman S, Thiel E, Park J, et al. Productivity loss outcomes and costs among patients with cholangiocarcinoma in the United States: an economic evaluation. J Med Econ 2023;26:454-462.
72. Darbà J, Marsà A. Analysis of hospital incidence and direct medical costs of intrahepatic cholangiocarcinoma in Spain (2000-2018). Expert Rev Pharmacoecon Outcomes Res 2021;21:425-431.
73. Ransome E, Tong L, Espinosa J, et al. Trends in surgery and disparities in receipt of surgery for intrahepatic cholangiocarcinoma in the US: 2005-2014. J Gastrointest Oncol 2019;10:339-347.
74. Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol 2014;60:1268-89.
75. National Institute for Health and Care Excellence. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement. Technology appraisal guidance. Committee discussion. Available at: https://www.nice.org.uk/guidance/ta722/chapter/3-Committee-discussion [Accessed 11th May 2023].
76. Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 29 May 2021.
77. Dissemination C. Systematic reviews: CRD's guidance for undertaking reviews in healthcare. York: University of York NHS Centre for Reviews & Dissemination 2009.
78. ClinicalTrials.gov. A Study of TAS-120 in Patients With Advanced Solid Tumors. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT02052778 [Accessed 21 June 2023].
79. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
80. Taiho Oncology. Data on File. FOENIX-CCA2 Clinical Study Protocol Amendment 10.
81. Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 1 October 2020.
82. Goyal L, Meric-Bernstam F, Hollebecque A, et al. Updated results of the FOENIX-CCA2 trial: Efficacy and safety of futibatinib in intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 fusions/rearrangements. Journal of Clinical Oncology 2022;40:4009-4009.
83. A. Vogel et al. Pemigatinib for previously treated locally advanced or metastatic cholangiocarcinoma: final results from FIGHT-202. ESMO. 29 June 2022.
84. Goyal L et al. Oral presentation at the AACR Annual Meeting 2021; April 10-15, 2021. Abstract CT010.
85. National Institute for Health and Care Excellence. NICE TSD 18. Available at: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list [Accessed 19 April 23].
86. Subbiah V, Iannotti NO, Gutierrez M, et al. FIGHT-101, a first-in-human study of potent and selective FGFR 1-3 inhibitor pemigatinib in pan-cancer patients with FGF/FGFR alterations and advanced malignancies. Ann Oncol 2022;33:522-533.

87. Rodon J DS, Furqan M, Garcia-Donas J, Imai H, Italiano A, Spanggaard I, Ueno M, Yokota T, Veronese L, Oliveira N, Li X, Gilmartin A, Goyal L. Abstract CT016: Clinical and translational findings of pemigatinib in previously treated solid tumors with activating FGFR1-3 alterations in the FIGHT-207 study. Cancer Res 2023;82:CT016.
88. Shi GM, Huang XY, Wen TF, et al. Pemigatinib in previously treated Chinese patients with locally advanced or metastatic cholangiocarcinoma carrying FGFR2 fusions or rearrangements: A phase II study. Cancer Med 2023;12:4137-4146.
89. Vogel A, Sahai V, Hollebecque A, et al. O-2 Pemigatinib for previously treated locally advanced or metastatic cholangiocarcinoma: Final results from FIGHT-202. Annals of Oncology 2022;33:S379.
90. ClinicalTrials.gov. Study of Futibatinib in Patients With Advanced Cholangiocarcinoma With FGFR2 Fusion or Rearrangement (FOENIX-CCA4). Available at: https://clinicaltrials.gov/study/NCT05727176 [Accessed 30 June 2023].
91. ClinicalTrials.gov. Futibatinib Versus Gemcitabine-Cisplatin Chemotherapy as First-Line Treatment of Patients With Advanced Cholangiocarcinoma Harboring FGFR2 Gene Rearrangements (FOENIX-CCA3). Available at: https://clinicaltrials.gov/study/NCT04093362 [Accessed 30 June 2023].
92. University of Sheffield. NICE Decision Support Unit. Full list of technical support documents. Available at: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list [Accessed 16 August 2023].
93. Chen ZR, Chueh, C. H., Chiang, N. J. and Tsai, Y. W. Cost-effectiveness of pemigatinib as a second-line treatment for advanced intrahepatic cholangiocarcinoma with fibroblast growth factor receptor 2 fusions in Taiwan: from the evidence of the phase II trial and the perspective of Taiwan's National Health Insurance Administration. Cost Eff Resour Alloc. 2023;21.
94. Canadian Journal of Health Technologies. CADTH Reimbursement Review: Pemigatinib (Pemazyre). Available at: https://www.cadth.ca/sites/default/files/DRR/2022/PC0252-Pemazyre.pdf. [Last accessed: 20 October 2023]. 2022.
95. Tzanetakos C, Psarra M, Batsi M, et al. Cost-Effectiveness Analysis of Pemigatinib for the Treatment of Adult Patients with Locally Advanced or Metastatic Cholangiocarcinoma with a FGFR2 Fusion or Rearrangement That Have Progressed After Systemic Therapy in Greece. Value Health 2023;26.
96. National Institute for Health and Care Excellence. TA722: Pemigatinib for treating relapsed or refractory advanced CCA with FGFR2 fusion or rearrangement. Available at: https://www.nice.org.uk/guidance/ta722 [Last accessed: 02 November 2023]. 2021.
97. Scottish Medicines Consortium. SMC2399: Pemigatinib 4.5mg, 9mg and 13.5mg tablets. Available at: https://www.scottishmedicines.org.uk/media/6668/pemigatinib-pemazyre-final-jan-2022-for-website.pdf. [Last accessed: 02 November 2023]. 2022.
98. National Institute for Health and Care Excellence. NICE health technology evaluations Available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation [Accessed 02 August 2023].
99. 2021/22 National Cost Collection Data Publication. Available at: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/ [Accessed 12 December 2023].
100. O'Mahony JF, Newall AT, van Rosmalen J. Dealing with Time in Health Economic Evaluation: Methodological Issues and Recommendations for Practice. Pharmacoeconomics 2015;33:1255-68.
101. NHS Improvement. National schedule of reference costs. 2018; https://improvement.nhs.uk/resources/reference-costs/ [Accessed 6 November 2019].
102. National Institute for Health and Care Excellence. Nivolumab with ipilimumab for untreated advanced renal cell carcinoma; Committee papers 1. 2019; https://www.nice.org.uk/guidance/ta581/documents/committee-papers [Accessed 7 April 2020].
103. National Institute for Health and Care Excellence. TA476: Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer; Committee

papers. 2017; https://www.nice.org.uk/guidance/ta476/documents/committee-papers [Accessed 7 April 2020].
104. European Medicines Agency. Pemazyre. Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/pemazyre-epar-product-information_en.pdf [Accessed 17 August 2023].
105. Burnham KP, Anderson DR. Multimodel Inference:Understanding AIC and BIC in Model Selection. Sociological Methods & Research 2004;33:261-304.
106. Raftery AE. Bayesian Model Selection in Social Research. Sociological Methodology 1995;25:111-163.
107. Lamarca A, Palmer D, Wasan HS, et al. Quality of life (QoL) and value of health (V-He) in advanced biliary cancers (ABC) treated with second-line active-symptom-control (ASC) alone or ASC with oxaliplatin/5-FU chemotherapy (ASC+FOLFOX) in the randomised phase III, multi-centre, open-label ABC-06 trial. Ann Oncol. 2022;33:S564–S565.
108. Lamarca A, Palmer, D. H., Wasan, H. S., Ross, P. J., Ma, Y. T., Arora, A., Falk, S., Gillmore, R., Wadsley, J., Patel, K., Anthoney, A., Maraveyas, A., Iveson, T., Waters, J. S., Hobbs, C., Barber, S., Ryder, W. D., Ramage, J., Davies, L. M., Bridgewater, J. A, Valle, J.W. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol. 2021;22:690–701.
109. National Institute for Health and Care Excellence. Cetuximab and panitumumab for previously untreated metastatic colorectal cancer. Technology appraisal guidance [TA439]. Available at: https://www.nice.org.uk/guidance/ta439 [Accessed 02 August 2023].
110. National Institute for Health and Care Excellence. Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel. Technology appraisal guidance [TA391]. Available at: https://www.nice.org.uk/guidance/ta391 [Accessed 02 August 2023].
111. University of Sheffield. NICE Decision Support Unit. Estimating EQ-5D by age and sex for the UK. Available at: https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d [Accessed 14 August 2023].
112. British National Formulary. Pemigatinib [Specialist drug]. Medicinal forms. Available at: https://bnf.nice.org.uk/drugs/pemigatinib-specialist-drug/medicinal-forms/ [Accessed 03 August 2023].
113. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. Palliat Med 2015;29:899-907.
114. National Institute for Health and Care Excellence. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement. technology appraisal guidance. Available at: https://www.nice.org.uk/guidance/ta722 [Accessed 4th May 2023].
115. Schneider P et al. Quality-adjusted life expectancy norms for the English population. QALY Shortfall Calculator. 2022. Available at: https://github.com/bitowaqr/shortfall. [Last accessed: 17/05/22].
116. Hernández Alava M et al. NICE DSU. Estimating EQ-5D by age and sex for the UK. 2022. Available at: https://nicedsu.sites.sheffield.ac.uk/methods-development/estimating-eq-5d-by-age-and-sex-for-the-uk. [Last accessed: 10/03/2022].
117. University of York. QALY shortfall calculator. Available at: https://shiny.york.ac.uk/shortfall/ [Accessed 10th August 2023].
118. Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. Med Decis Making 2012;32:733-43.
119. Büyükkaramikli NC, Rutten-van Mölken M, Severens JL, et al. TECH-VER: A Verification Checklist to Reduce Errors in Models and Improve Their Credibility. Pharmacoeconomics 2019;37:1391-1408.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Futibatinib for Previously Treated Locally Advanced or Metastatic Cholangiocarcinoma with FGFR2 Fusion or Rearrangement [ID6302]

Summary of Information for Patients (SIP)

February 2024

File name	Version	Contains confidential information	Date
ID6302_Futibatinib_CCA_SIP	V.1	No	February 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Please note: Further explanations for the words and phrases highlighted in **bold underlined text** are provided in the glossary (**Section 4b**).

1a) Name of the medicine (generic and brand name):

Generic name: Futibatinib; **brand name**: Lytgobi®

1b) Population this treatment will be used by:

Please outline the main patient population that is being appraised by NICE:

The population that this treatment will be used for is: *Adult patients with locally advanced or metastatic cholangiocarcinoma (CCA) with fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy*

1c) Authorisation:

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The Medicines and Healthcare products Regulatory Agency (MRHA) has granted the marketing authorisation for futibatinib as a treatment for adult patients with locally advanced or

metastatic CCA with FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy in August 2023[2]

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Taiho Pharma Europe, Limited, has and is supporting various patient support groups. An overview of any existing collaborations between Taiho Pharma Europe, Limited and relevant patient groups to this medicines is provided in Table 1 below.

Table 1: Summary of support provided by Taiho to relevant patient groups

Patient group	Engagement/activity	Reason for engagement/activity	Financial support provided
AMMF	Taiho Pharma Europe, Limited, part-sponsored the AMMF conference in 2023	Grant requested by AMMF	£35,000

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is cholangiocarcinoma (CCA)?

Cholangiocarcinoma (CCA) is also known as bile duct cancer.[3] Bile ducts are a part of the digestive system and carry bile, which is a fluid that helps to break down fats in food. CCA develops when cells in the bile duct start growing uncontrollably, forming a tumour. These cells can eventually grow into surrounding healthy tissue and spread to other parts of the body.

Medical experts estimate that around 2,500–3,000 people in the UK live with CCA.[4] This means that CCA is a rare disease in the UK. However, it is becoming more common over time, both in the UK and worldwide.[5,6]

What causes CCA?

In most cases, the cause of CCA is not known. However, there are some known risk factors that can mean that a person is more likely to develop CCA. These include various conditions of bile ducts and liver (such as the presence of cysts or gallstones, liver cirrhosis, or bile ducts that are wider than normal).[6] Viral infections, parasites and exposure to certain chemicals may also lead to CCA.[6]

What are the different types of CCA?
CCA can develop in different parts of the bile duct. CCA which first develops in the bile duct within the liver is named "intrahepatic" CCA ("intra" means "inside", and "hepatic" refers to the liver). If CCA developed in the bile duct outside of the liver, it is called "extrahepatic" CCA ("extra" meaning "outside").[3]

Intrahepatic and extrahepatic CCA are similar in some ways, but they can have different symptoms and options for treatment.[3]

What are the signs and symptoms of CCA?
In the earlier stages, CCA often has no symptoms, or shows common signs that can be mistaken for other diseases. Because of this, CCA is often diagnosed late in the disease.[3]

The signs of CCA may arise due to the tumour growing and pressing on the tissues around it (for example, blocking bile ducts).[3,7] Symptoms can also be caused by other conditions that the patient may have along with CCA.[3,7]

Intrahepatic and extrahepatic CCA have different symptoms. Blocking of bile ducts and jaundice (yellowing of the skin or eyes) are common in patients with extrahepatic CCA.[3] Patients with intrahepatic CCA often show no signs until later in the disease, when they show common symptoms such as weight loss, feeling sick, tiredness and stomach ache.[3]

What is CCA with fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement?
Fibroblast growth factors are molecules which circulate in the body. Cells in the body use fibroblast growth factors to communicate to each other. Fibroblast growth factor **receptors** (**FGFRs**) are present on the surface of cells and can sense the presence, or absence of, fibroblast growth factor molecules around the cell. Through this ability, FGFRs control important processes in the cell.[8] FGFR2 is one of these FGFR receptors.

Genetic aberrations (mistakes) in the FGFR2 gene can results in FGFR2 working incorrectly. In some cases, this can cause cells to divide uncontrollably and turn into cancer.[9] One such aberration, is the joining together or 'fusion' of the FGFR2 gene with a different gene; this aberration is known as FGFR2 **fusion**. Sometimes, genetic tests cannot determine which other gene is fused to the FGFR2 gene. In these cases, the aberration in the FGFR2 gene is called a "**rearrangement**".

FGFR2 fusions and rearrangements can lead to the development of CCA, in particular intrahepatic CCA.[9] FGFR2 fusions and rearrangements are found in approximately 9 to 15 people out of 100 who have intrahepatic CCA.[10-14] FGFR2 fusions and rearrangements are almost never seen in extrahepatic CCA.

People with FGFR2 fusions or rearrangements may be eligible to receive treatments which specifically targets these fusions or rearrangements. These treatments are known as FGFR2 **inhibitors.**

What is the impact (burden) of CCA?
The life expectancy of patients diagnosed with CCA varies, and depends on how advanced the disease is (i.e., how large the tumour is and whether it is has spread to other parts of the body). In addition, life expectancy depends on when CCA was diagnosed, as well as the age of the patient at the time of diagnosis.

Although no UK-wide survival statistics for CCA are available, in the US around 25 out of 100 people survive intrahepatic CCA for 5 years or more after diagnosis if their cancer has not spread (metastasised) outside the bile duct.[15] Life expectancy is worse for more advanced cancer. If the tumour has spread outside the bile duct into lymph nodes or surrounding tissues (i.e., metastasised), approximately 10 out of 100 people survive intrahepatic CCA for 5 years or more after diagnosis.[15] Around 2 out of 100 people survive their cancer for 5 years or more if it has spread to other parts of the body, away from the bile duct.[15]

CCA is a serious disease. Patients with CCA may have reduced **quality of life**, in particular because of anxiety, depression and tiredness.[16,17] Symptoms get worse as the disease develops, making people with CCA increasingly unable to complete normal activities.

In addition to the large impact that CCA has on patients and their families, it also has an economic burden. CCA can cause large direct costs, for example due to hospital visits.[18,19] CCA can also have other effects, for example people not being able to work.[20] Since the numbers of CCA cases are growing, these costs are also increasing over time.[19,21]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is CCA diagnosed?
CCA often has common symptoms, or no symptoms at all. In addition, it is a rare disease. Because of this, CCA can be difficult to diagnose.

Some people are diagnosed with CCA after they see their General Practitioner (GP). If cancer is suspected, the GP will refer the patient to a specialist.[22] In addition, the patient may have various tests to diagnose CCA and to monitor the disease. These tests can include blood tests, ultrasound scans, computer tomography (CT) scans, magnetic resonance imaging (MRI), positron emission tomography (PET) and others.[22]

Sometimes, CCA is diagnosed only after the patient becomes very unwell and goes to a hospital's Accident and Emergency (A&E) department. In very rare cases, CCA may be diagnosed early. For example, some people who are at a high risk for developing CCA can have regular screening for the disease.[22]

What are the stages of CCA?
CCA is usually categorised in stages 1 to 4.[23] For intrahepatic CCA, stage 1 means the cancer (tumour) is only in the bile ducts. If CCA is categorised as stage 2 or 3, the tumour has grown into the surrounding organs and lymph nodes. Stage 4 means that the cancer has spread to other areas of the body such as the lungs, which means that it developed **metastases**.

Cancer at later stages (3–4) is sometimes called "advanced". This usually means cancer has spread outside the bile ducts or other parts of the body (metastasised) or returned after treatment, or that it is not likely to be cured.[24]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Can CCA be cured?

Some patients in the early stages of CCA can have surgery to remove the tumour.[25] Surgery is the only treatment option that may cure CCA. However, patients do not usually experience symptoms at the early stages of CCA. This means that most patients are diagnosed with advanced disease and their tumours are considered unsuitable for surgery (i.e. their tumours are not **resectable**). This is usually because the tumour is too big or it has spread to other parts of the body.

On average, only half of patients diagnosed with CCA are eligible to receive surgery at the time of diagnsois.[26] Surgery however is not always successful, and the disease can **relapse** (the tumour can return) after surgery.[26] Disease relapse following surgery occur in approximately 6 to 8 patients out of 10, depending on how successful the surgery was.[26]

What are the treatment options for patients who cannot have surgery?

For the patients who cannot have surgery, a number of other options are available. At this stage, the goal is to reduce the symptoms of CCA and to slow the growth and spread of the tumour.

For patients who have large tumours, or tumours which have spread to other areas of the body, the usual treatment is chemotherapy with the drugs gemcitabine and cisplatin (GEM + CIS). Another drug called durvalumab can be added to this treatment, which has been recently recommended by the National Institute for Health and Care Excellence (NICE) in this indication.[25,27]

What are the options after the GEM + CIS treatment?

Next steps depend on how the tumour reacts to the drugs. If the tumour does not respond or develops after the GEM + CIS treatment, patients have several options. Some receive other drugs, such as the combination of modified folinic acid, fluorouracil and oxaliplatin (mFOLFOX). Other patients may be invited to take part in a clinical trial for a new treatment, if the doctors decide that it may help.

Additionally, some drugs can help patients with certain genetic aberrations. This includes FGFR2 fusions or rearrangements.

What are the treatment options for patients with FGFR2 fusions or rearrangements?

There are several drugs that target processes in cells that are connected to the FGFR2 fusions or rearrangements. These drugs are called FGFR2 inhibitors.

Currently in the UK, the only FGFR2 inhibitor recommended by NICE (and therefore paid for by the NHS) is pemigatinib. It is recommended for the treatment of patients with locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement that has progressed (i.e. continued to grow or spread) after prior **systemic therapy** (in the UK this is usually GEM + CIS with or without durvalumab).[28-30]

UK clinical experts confirmed that in current practice, patients with advanced CCA with FGFR2 fusion or rearrangement who have progressed after GEM + CIS therapy almost always receive pemigatinib.[31]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

What is the impact of CCA from the patient perspective?

Because CCA is a rare disease, there is not much information on the specific challenges faced by patients in the UK with CCA.[1,32,33] Several studies show the patient perspective from other countries.[16,17,34,35] Based on these, patients with CCA highlight the impact of CCA, in particular, caused by anxiety, depression and tiredness from treatment.[16,17]

AMMF (The Alan Morement Memorial Fund) is the only CCA charity in the UK. Patient and caregiver experiences have been gathered by AMMF from online reports, such as social media surveys and their forum for people impacted by CCA.[36,37]

In addition, AMMF provided a patient organisation submission and referred patient experts during the NICE appraisal process for pemigatinib, a **targeted therapy** for patients with CCA with FGFR2 fusion or rearrangement.[1] These submissions illustrate the serious nature of CCA and the large impact that it can have on patients and their families and friends.

What are the patient views on targeted treatments for CCA?

One of the problems, highlighted by many patients and caregivers, is the limited treatment options for patients with CCA, especially in later stages of the disease.

Before the introduction of targeted treatments, the available chemotherapy regimens offered limited benefits and strong side effects. Undergoing chemotherapy meant possibly extending lifespan by a few months, but with a worse quality of life of patients and their families. Since

the life expectancy for patients with late stage CCA is very low, this presented a difficult choice for the patients on whether to accept the chemotherapy treatment.[1,37]

> "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"
>
> *Andrea Sheardown, Patient Expert nominated by AMMF for the NICE assessment of pemigatinib*[1]

The patient experts highlighted the potential benefits that a targeted therapy could bring, compared to the side effects from alternative chemotherapy treatments.[1]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

What is futibatinib?

FGFR2 is a receptor that controls important processes in the cell.[8] In patients with FGFR2 fusions or rearrangements, this receptor does not work as it should. This incorrect functioning plays an important part in the development of CCA.[9]

Futibatinib is an inhibitor of FGFR1–4, including FGFR2.[38,39] This means that futibatinib stops the activity that the "broken" FGFR2 causes in cancer cells. In turn, this leads to the tumour growing slower and cancer cells dying faster.

Resources providing additional information on futibatinib works are linked below:

- The Package Leaflet
- The Public Assessment Report

How is futibatinib different from pemigatinib?

During treatment with FGFR inhibitors, new genetic aberrations appear in tumour cells. Sometimes these changes help the cancer cells survive the treatment; in this case, CCA "acquires **resistance**" to the drug, and the drug becomes less effective.

Futibatinib and pemigatinib have a similar target: both these drugs block FGFR2. However, in vitro studies (studies conducted on cells) show that futibatinib may be less likely to lead to treatment resistance than pemigatinib.[29-31,39]

UK clinical experts noted that they consider the issue of treatment resistance to be important.[31] For this reason, the experts said that they may prefer to use futibatinib instead of pemigatinib.

It is important to note that, although studies in cells have found that futibatinib may lead to fewer cases of treatment resistance than pemigatinib, this has not been confirmed in humans.[40]

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / **No**

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the

main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Futibatinib is **not** intended to be used with any other treatment for adult patients with locally advanced or metastatic CCA with FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How should futibatinib be taken?

Futibatinib treatment should be started by a doctor who is experienced in the diagnosis and treatment of bile duct cancer. Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is 5 tablets of futibatinib (20 mg) taken orally once daily. Your doctor will adjust the dose or stop treatment if needed.

Method of administration: swallow the tablet whole with one glass of water at the same time every day. Futibatinib may be taken with food or between meals. Do not crush, chew, split or dissolve the tablets.

Duration of treatment: take futibatinib for as long as it is prescribed by the doctor.

If you take more futibatinib than you should: tell your doctor if you have taken more futibatinib than you should have.

If you forget to take futibatinib:

- If you miss a dose of futibatinib by 12 hours or less, take the missed dose as soon as you remember.
- If you miss a dose of futibatinib by more than 12 hours, or if you vomit after taking futibatinib, skip the missed dose. Take your next dose at the usual time.
- Do not take a double dose to make up for a missed dose

If you stop taking futibatinib: do not stop taking futibatinib without discussing it with your doctor, as this could reduce the success of therapy.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Detailed information on how to take futibatinib is available in the Summary of Product Characteristics (SmPC).[2]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Studies of futibatinib in CCA with FGFR2 fusion or rearrangement

Futibatinib has been studied in a clinical trial **TAS-120-101**. This was a single-arm non-randomised trial, meaning that patients were not randomly separated into groups receiving different treatments, and all patients simply received futibatinib. It was also an open-label trial, meaning that all patients knew they were receiving futibatinib.

TAS-120-101 was an international trial and it had three parts:

- **Phase 1 dose escalation study (FOENIX-101).** In this study, patients received futibatinib in escalating (increasing) doses (8–200 mg every other day and 4–24 mg once daily). The purpose of a dose escalation study is to find the highest dose of the drug at which the side effects are acceptable

- **Phase 1 dose expansion study (FOENIX-101).** This study evaluated the efficacy of futibatinib (its ability to treat CCA) and its safety at the dose of 16 mg or 20 mg taken once daily

- **Phase 2 (FOENIX-CCA2).** This study evaluated the efficacy of futibatinib 20 mg taken once daily in patients with intrahepatic CCA with FGFR2 gene rearrangements, including fusions. FOENIX-CCA2 also looked at the safety of futibatinib and at how it impacted the patients' quality of life

FOENIX-CCA2 is the main trial providing evidence for this NICE submission. In FOENIX-CCA2 trial, patients only received futibatinib (without a different treatment as a comparator), and all patients knew they were receiving futibatinib (the trial was not blinded).

FOENIX-CCA2 included patients with unresectable or metastatic intrahepatic CCA, with FGFR2 fusion or other rearrangement. For the included patients, disease should have progressed after one or more previous systemic therapy, and they should have previously taken gemcitabine with a platinum-based therapy, such as gemcitabine plus cisplatin.

The last data from FOENIX-CCA2 trial were collected on 29th of May 2021, and the trial is now completed.

More information about TAS-120-101 and FOENIX-CCA2 can be found here:

- Goyal L et al., 2023[38] (https://www.nejm.org/doi/full/10.1056/NEJMoa2206834)
- ClinicalTrials.gov (https://classic.clinicaltrials.gov/ct2/show/NCT02052778)

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Futibatinib trial results

The efficacy of futibatinib has been studied in the FOENIX-CCA2 clinical trial. This trial enrolled 103 patients with advanced or metastatic CCA with FGFR2 fusion or rearrangement who have been treated with at least one systemic therapy.[38] UK clinical experts confirmed that the patients in the FOENIX-CCA2 trial were overall similar to the patients who would be eligible to receive futibatinib in the UK.[4]

Results from the primary (first) data-cut of the FOENIX-CCA2 trial are published in a paper by Goyal *et al.* (2023). Results from the final data-cut were presented at the American Society for Clinical Oncology 2022 conference.[38,41]

One of the clinical **outcomes** used to assess the efficacy of futibatinib during the study was the objective response rate (ORR). The ORR refers to the proportion of patients whose tumour responded, i.e. partly reduced in size (or disappeared completely) in response to treatment. This is an important outcome for patients with cancer that is often used in clinical trials. In FOENIX-CCA2, 43 out of 103 patients responded to treatment with futibatinib, resulting in an ORR of 41.7%.[41]

Other outcomes measured in the FOENIX-CCA2 trial included the duration of response, progression-free survival (how long the patients live without the disease getting worse) and overall survival (how long the patients survived with CCA if they received futibatinib). On average, among the patients who responded, their responses lasted 9.5 months. Among all patients, average progression-free survival was 8.9 months and overall survival was 20.0 months.[38,41]

In addition to efficacy outcomes, the FOENIX-CCA2 trial also reported on the quality of life of patients and on the treatment side effects. These are described below in sections 3f and 3g, respectively.

Efficacy of futibatinib compared with pemigatinib

The efficacy of pemigatinib has been measured in the FIGHT-202 clinical trial.[42,43]

No clinical trial has yet compared futibatinib and pemigatinib to each other directly. In addition, both FOENIX-CCA2 and FIGHT-202 were single-arm trials, which means that patients received only one treatment. There was no common comparator treatment that could provide a reference point to compare futibatinib and pemigatinib. As a result, the efficacy of futibatinib and pemigatinib had to be compared using an indirect treatment comparison (ITC). ITC is a mathematical way of comparing efficacy data from two different clinical trials.

The results of the ITC showed that futibatinib and pemigatinib lead to similar progression-free survival and overall survival in patients with advanced CCA with FGFR2 fusions or rearrangements. An ITC is less reliable than a direct clinical trial comparing two treatments.

However, the results of the ITC agree with the opinion of UK clinical experts, who said that they expect the efficiency of these two treatments to be similar.[4]

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life impact of futibatinib

Quality of life outcomes describe the patients' physical and emotional state, as well as metrics such as social functioning and financial difficulties. In clinical trials, quality of life is measured by specifically developed and verified questionnaires. The goal of these is to capture patients' experiences with the disease and the treatment in addition to other outcomes measured in a trial.

The FOENIX-CCA2 trial used established questionnaires to measure quality of life. One of them is called the European Organisation of Cancer Research Quality of Life Questions C30 (EORTC QLQ-C30). Other questionnaires used were Euro-QoL-5 dimensions-3 levels (EQ-5D-3L) and EuroQol visual analogue scale (EQ-VAS). All of these questionnaires are commonly used in clinical trials including patients with cancer and are well accepted in the UK.

During the FOENIX-CCA2 trial, all quality of life outcomes remained stable over time. This indicates that patients experienced no decrease in their quality of life whilst receiving treatment with futibatinib.[41]

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Every medicine has its own **side effects** and the same medicine can produce different reactions in different people. In the FOENIX-CCA2 trial (the key trial for futibatinib), most patients experienced mild-to-moderate side effects which were manageable.

The most common treatment-related side effects seen in the FOENIX-CCA2 trial were the following:

- **Hyperphosphatemia** (high levels of phosphate in the blood): 88 out of 103 patients treated with futibatinib in the FOENIX-CCA2 trial had this side effect
- Hair loss (also called alopecia) was seen in 34 out of 103 patients
- Dry mouth was reported by 31 out of 103 patients
- Diarrhoea was reported by 29 out of 103 patients

Four patients had to stop (discontinue) treatment with futibatinib due to side effects related to the drug. Seven patients died while receiving futibatinib or within 30 days of their last dose. However, doctors did not consider any of these deaths to be related to futibatinib.

UK clinical experts confirmed that the side effects from futibatinib were very similar to those from pemigatinib, and that no new side effects compared with pemigatinib were observed.[31] Experts also said that the side effects of futibatinib were as expected for FGFR2 inhibitors, including futibatinib and pemigatinib, and were generally manageable.

If side effects do happen, the dose of futibatinib may be reduced. This can help to reduce side effects while allowing patients to possibly still receive some benefit from the treatment. Some side effects can be managed in different ways. For example, hyperphosphatemia can be managed with changes to the patient's diet or with treatment.

The common side effects that can occur during treatment with futibatinib are described in the Summary of Product Characteristics (SmPC), which can be accessed here.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration.

What are the key benefits of futibatinib for patients?

- **Patient choice:** Currently the only treatment targeting FGFR2 fusions or rearrangements in CCA that is approved in the UK is pemigatinib. When it was introduced, pemigatinib offered a notable improvement over other available therapies, however, it remains the only treatment available for these patients in the UK. The introduction of futibatinib would provide patients and their doctors an alternative treatment option, thereby allowing for patient choice, providing patients an increased sense of control over their own health.

- **Potential for reduced treatment resistance:** During treatment with FGFR inhibitors, new genetic aberrations can develop which result in the treatment not working as well as it should; this is known as treatment resistance. Treatment resistance is a known problem for patients receiving pemigatinib.[31] However, in vitro studies (studies

conducted on cells) show that futibatinib may potentially lead to fewer cases of treatment resistance than pemigatinib.[29-31,39] UK doctors who have experience of treating CCA in clinical practice noted that treatment resistance is an important issue, and therefore that if futibatinib does lead to fewer cases of resistance they may use it preferentially over pemigatinib.[31] It is important to note however, that although studies in cells have found that futibatinib may lead to fewer cases of treatment resistance, this has not been confirmed in humans.[40]

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Futibatinib is expected to have the same efficacy and safety as pemigatinib. However, some things that patients may want to consider before starting treatment include:

Efficacy

Futibatinib does not work for everyone, and some patients might not experience any improvement in CCA progression. This means that the tumour may still grow and spread to other organs despite the treatment. Patients for whom futibatinib does not work may still experience side effects, which are detailed further in Section 3g.

Side effects

Like all medicines, some patients may experience side effects while they are taking futibatinib. These are usually manageable, and most patients do not need to stop treatment because of side effects. UK clinical experts noted that the side effects of futibatinib are generally manageable.[31]

In addition, side effects of futibatinib are very similar to the side effects of pemigatinib, which is a treatment routinely used in clinical practice. UK clinical experts who have experience of prescribing both pemigatinib and futibatinib confirmed that there are no meaningful differences in the safety or side effects of these two treatments.[31]

Administration

Futibatinib should be taken every day for as long as it is prescribed by the doctor. Patients may receive a reduced dose of futibatinib in order to manage side effects. Futibatinib is taken as a tablet, similar to pemigatinib.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and

issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Healthcare administrators need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines. They will look at the costs of the new medicine and how the health of patients is likely to improve if they take it.

The pharmaceutical company that develops the medicines provides this information to healthcare administrators using a health economic model. The pharmaceutical company uses the health economic model to perform an analysis, which compares the costs and benefits of the new treatment (in the case of this submission, futibatinib) with the standard of care (pemigatinib).

How the model reflects CCA

The economic model was designed to reflect the key features of CCA and clinical practice in the UK. To do this, a model structure called a partitioned survival model (PSM) was used. In this model, patients moved between three states: no disease progression; disease progression (i.e. the tumour growing or spreading to other organs); and death.

To inform the model, it is necessary to use the data from clinical trials, in particular progression-free survival and overall survival, and to extrapolate it over longer time periods, i.e. estimate what survival data would look like if the clinical trials lasted much longer. This was done in line with NICE guidance, and the choice of extrapolations was confirmed by UK clinical experts, who confirmed that the data used in the model were similar to what they would expect in clinical practice.

The PSM used the data from the FOENIX-CCA2 and FIGHT-202 clinical trials, as well as a number of necessary assumptions. The structure of the model and the main inputs and assumptions were verified by UK clinical and health economic experts.[31]

Results of the economic model

One of the main outcomes of an economic model is the quality-adjusted life years (QALYs) of the patients receiving treatment. This reflects how long the patients survive with treatment, adjusted to account for quality of life. For example, one year of survival with low quality of life equals to less than one QALY. The resulting accumulation of costs and QALYs associated with each treatment, and the ratio between these values, indicates whether the treatments are cost effective or not. A ratio of £20,000 to £30,000 per QALY is considered cost-effective for a new treatment to be adopted by the NHS.

A **severity modifier** is a factor that takes into account the severity or impact of a disease when evaluating the cost-effectiveness of a particular treatment. In the CCA patients with FGFR2 fusions or rearrangements futibatinib is eligible for a severity modifier when compared with standard of care (pemigatinib).

Overall, the results of the economic analysis showed futibatinib to be associated with both increased QALYs and decreased costs when compared to pemigatinib. These results therefore suggest that futibatinib is both more effective and cheaper versus pemigatinib. As stated above, futibatinib is eligible for a severity modifier, these results do not take this severity modifier into account.

It is important to note that the Company's estimation of cost-effectiveness is not the only result considered by NICE. NICE may prefer some assumptions that are different from the assumptions that the company used in their model. In addition, pemigatinib may have a confidential discount that the Company do not have access to.

Because the efficiency of futibatinib and pemigatinib was similar (as shown by the ITC and confirmed by UK clinicians), an additional simplified economic model was built. This model assumed that futibatinib and pemigatinib resulted in the same progression-free survival and overall survival, and only considered the costs of each treatment – this is called a cost-comparison model. This model showed that treatment with futibatinib was cheaper versus pemigatinib.

Benefits of futibatinib not captured in the economic analysis

Currently the only treatment targeting FGFR2 fusions or rearrangements in CCA that is approved in the UK is pemigatinib. The introduction of futibatinib would provide patients and their doctors an alternative treatment option, thereby allowing for patient choice, providing patients an increased sense of control over their health.

Compared with pemigatinib, futibatinib may potentially lead to fewer cases of treatment resistance. UK clinical experts explained that this may not be seen in the overall trial results for all patients, however this still may make a difference to a number of patients on an individual basis.[31] As such, in addition to the value associated with increased patient choice via the addition of futibatinib to the UK treatment pathway, it is plausible that futibatinib would be associated with additional improved efficacy versus pemigatinib that is not captured in the QALY calculation

The issue of treatment resistance is described in more detail in section 3h.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Futibatinib is an innovative treatment which would represent an important advancement in the treatment of CCA

Currently the only treatment targeting FGFR2 fusions or rearrangements in CCA that is approved in the UK is pemigatinib. The introduction of futibatinib would provide patients and their doctors an alternative treatment option, thereby allowing for patient choice, providing patients an increased sense of control over their own health.

Additionally, treatment resistance is a known problem for some patients treated with pemigatinib;[29,44] during treatment with pemigatinib, genetic aberrations sometimes appear in

the tumour that help cancer cells to survive the drug, and as a result, the treatment is less effective. In vitro studies suggest that futibatinib may lead to fewer cases of treatment resistance than pemigatinib. It is important to note however that these results have not been confirmed in humans.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? 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.

Find more general information about the Equality Act and equalities issues here

There are no equality issues that are anticipated for the use of futibatinib in adult patients with locally advanced or metastatic CCA with FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on CCA:

- Cancer Research UK. Bile duct cancer: https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer
- Cancer Research UK. Bile duct cancer. Resources and support organisations: https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/living-with/resources-books
- Macmillan Cancer Support. Bile duct cancer: https://www.macmillan.org.uk/cancer-information-and-support/bile-duct-cancer
- AMMF – The cholangiocarcinoma charity: https://ammf.org.uk/

Further information on NICE and the role of patients:

- Public Involvement at NICE: Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs: Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- The European Patients' Academy on Therapeutic Innovation (EUPATI) guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- The European Federation of Pharmaceutical Industries and Associations (EFPIA) – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative: https://nationalhealthcouncil.org/issue/value/
- The International Network of Agencies for Health Technology Assessment (INAHTA): http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

This glossary explains terms highlighted in **bold and underlined** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Gene	A gene is a part of a molecule that contains information in the body. Each gene has a certain function, and genes are passed from parent to child. Genes contain "instructions" for biological processes in the body
Genetic aberration	A mistake that appears in the **gene**, usually when the cell tries to divide or is damaged. Often these mistakes are quickly repaired or have no bad consequences, but sometimes they may lead to disease
Clinical trial / clinical study	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a **clinical trial**
Fibroblast growth factor	Fibroblast growth factors are one type of molecules which circulate in the body and which cells in the body use to communicate to each other
Fibroblast growth factor receptor (FGFR)	Fibroblast growth factor receptors (FGFRs) are present on the surface of cells and can sense the presence, or absence of, fibroblast growth factor molecules around the cell. Through this ability, FGFRs control important processes in the cell. FGFR2 is one of the receptors in the FGFR family
Fusion / gene fusion	**Gene** fusion is a type of **genetic aberration** (mistake) when one gene joins (or "fuses" with) another gene, which stops it from working properly
Health economic model	A way to predict the costs and effects of a technology over time or in patient groups not covered in a **clinical trial**

Hyperphosphatemia	High level of phosphate in blood
Inhibitor	Drug that works by blocking some molecule in the body, for example a **receptor** on the surface of cells
In vitro	Performed or taking place in a test tube, culture dish, or elsewhere outside a living organism
Marketing authorisation	The legal approval by a **regulatory body** that allows a medicine to be given to patients in a particular country
Medicines and Healthcare products Regulatory Agency (MRHA)	The **regulatory body** that evaluates, approves and supervises medicines throughout the United Kingdom
Metastasis	Cancer that has spread from the other part of the body
Outcome	An outcome, or a clinical outcome, is the way that the efficiency of a treatment is measured in a clinical trial. For example, clinical outcomes can include the number of patients whose tumours stopped growing or became smaller after treatment, or how long on average patients survived with the disease
Quality of life	The overall enjoyment of life. Many **clinical trials** assess the effects of cancer and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living
Rearrangement / gene rearrangement	**Gene** rearrangement is a type of **genetic aberration** (mistake). Sometimes one gene joins (or "fuses" with) another gene, this is called gene **fusion**). If a genetic tests cannot determine which other gene is fused to the first gene the genetic aberration is called a gene rearrangement. A gene rearrangement can results in the gene not working properly and in some cases, can cause the cells to divide uncontrollably, resulting in cancer.
Receptor	Molecule on the surface of the cell that can sense the presence of a certain other

	molecule around the cell, and depending on this changing something in how the cell works
Regulatory bodies	These are legal bodies that review the quality, safety and **efficacy** of medicines and medical technologies
Relapse	When disease comes back after treatment, for example after surgery
Resectable	Suitable to be removed by surgery. For a tumour this usually means that it has not developed too much into surrounding tissues and other organs
Resistance	When a disease does not respond to a drug as expected
Severity modifier	A factor that takes into account the severity or impact of a disease or condition when evaluating the cost-effectiveness of the treatment
Side effect / adverse event	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe
Systemic therapy	Therapy that works on the entire body and not just the tumour, for example drugs that are received as a tablet or injection into blood. This is in contrast to local therapy, which only acts on the area of the tumour, for example surgery
Targeted therapy	Therapy that works on specific molecules or **mutations** that help cancer cells grow and spread
Tolerate	The ability of a patient to put up with the **side effects** of treatment

4c) References

1. National Institute for Health and Care Excellence. Single Technology Appraisal. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations [ID3740]. Committee Papers. Available at: https://www.nice.org.uk/guidance/ta722/documents/committee-papers [Accessed 28th April 2023].

2. MHRA. Summary of product characteristics. Lytgobi. Available at: https://mhraproducts4853.blob.core.windows.net/docs/fb49eac7d9ca87a7e57a0df17095e2db95a12a55 [Accessed 17 November 2023].

3. Banales JM, Marin JJG, Lamarca A, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol*. Sep 2020;17(9):557-588. doi:10.1038/s41575-020-0310-z

4. *Taiho Oncology. Data on File. FOENIX-CCA2 Advisory Board Report. 22 May 2023*.

5. Genus T, Tataru D, Morement H, Toledano M, Khan S. (late submission poster) Incidence and mortality rates of cholangiocarcinoma in England. *Annals of Oncology*. 2019;30:iv155. doi:10.1093/annonc/mdz183.007

6. Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: Epidemiology and risk factors. *Liver Int*. May 2019;39 Suppl 1:19-31. doi:10.1111/liv.14095

7. Valle JW, Kelley RK, Nervi B, Oh DY, Zhu AX. Biliary tract cancer. *Lancet*. Jan 30 2021;397(10272):428-444. doi:10.1016/s0140-6736(21)00153-7

8. Farrell B, Breeze AL. Structure, activation and dysregulation of fibroblast growth factor receptor kinases: perspectives for clinical targeting. *Biochem Soc Trans*. Dec 17 2018;46(6):1753-1770. doi:10.1042/bst20180004

9. Vogel A, Segatto O, Stenzinger A, Saborowski A. FGFR2 Inhibition in Cholangiocarcinoma. *Annu Rev Med*. Jan 27 2023;74:293-306. doi:10.1146/annurev-med-042921-024707

10. Boerner T, Drill E, Pak LM, et al. Genetic Determinants of Outcome in Intrahepatic Cholangiocarcinoma. *Hepatology*. Sep 2021;74(3):1429-1444. doi:10.1002/hep.31829

11. Farshidfar F, Zheng S, Gingras MC, et al. Integrative Genomic Analysis of Cholangiocarcinoma Identifies Distinct IDH-Mutant Molecular Profiles. *Cell Rep*. Jun 27 2017;19(13):2878-2880. doi:10.1016/j.celrep.2017.06.008

12. Israel MA, Danziger N, McGregor KA, et al. Comparative Genomic Analysis of Intrahepatic Cholangiocarcinoma: Biopsy Type, Ancestry, and Testing Patterns. *Oncologist*. Sep 2021;26(9):787-796. doi:10.1002/onco.13844

13. Lee H, Wang K, Johnson A, et al. Comprehensive genomic profiling of extrahepatic cholangiocarcinoma reveals a long tail of therapeutic targets. *J Clin Pathol*. May 2016;69(5):403-8. doi:10.1136/jclinpath-2015-203394

14. Neumann O, Burn TC, Allgäuer M, et al. Genomic architecture of FGFR2 fusions in cholangiocarcinoma and its implication for molecular testing. *Br J Cancer*. Nov 2022;127(8):1540-1549. doi:10.1038/s41416-022-01908-1

15. Cancer Research UK. Survival for bile duct cancer. Available at: https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/survival [Accessed 10 July 2023].

16. Bibeau K, Bachini M, Lindley A, Barkey NM, Lindsey S. Exploring the diagnostic journey and life impact of patients with cholangiocarcinoma (CCA): Results from a large patient survey in the United States. *Journal of Clinical Oncology*. 2021;39(3_suppl):277-277. doi:10.1200/JCO.2021.39.3_suppl.277

17. Kaupp-Roberts SD, Yadegarfar G, Friend E, et al. Validation of the EORTC QLQ-BIL21 questionnaire for measuring quality of life in patients with cholangiocarcinoma and cancer of the gallbladder. *Br J Cancer*. Oct 25 2016;115(9):1032-1038. doi:10.1038/bjc.2016.284

18. Chamberlain CX, Faust E, Goldschmidt D, et al. Burden of illness for patients with cholangiocarcinoma in the United States: a retrospective claims analysis. *J Gastrointest Oncol*. Apr 2021;12(2):658-668. doi:10.21037/jgo-20-544

19. Darbà J, Marsà A. Analysis of hospital incidence and direct medical costs of intrahepatic cholangiocarcinoma in Spain (2000-2018). *Expert Rev Pharmacoecon Outcomes Res*. Jun 2021;21(3):425-431. doi:10.1080/14737167.2021.1842201

20. Parasuraman S, Thiel E, Park J, Teschemaker A. Productivity loss outcomes and costs among patients with cholangiocarcinoma in the United States: an economic evaluation. *J Med Econ*. Jan-Dec 2023;26(1):454-462. doi:10.1080/13696998.2023.2187604

21. Ransome E, Tong L, Espinosa J, Chou J, Somnay V, Munene G. Trends in surgery and disparities in receipt of surgery for intrahepatic cholangiocarcinoma in the US: 2005-2014. *J Gastrointest Oncol*. Apr 2019;10(2):339-347. doi:10.21037/jgo.2018.12.07

22. Cancer Research UK. Bile duct cancer. Getting diagnosed. Available at: https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/getting-diagnosed [Accessed 14 June 2023].

23. Cancer Research UK. Bile duct cancer. Stages and grades of bile duct cancer. Available at: https://about-cancer.cancerresearchuk.org/about-cancer/bile-duct-cancer/stages-grades [Accessed 14 June 2023].

24. Macmillan Cancer Support. Advanced cancer. Available at: https://www.macmillan.org.uk/cancer-information-and-support/advanced-cancer [Accessed 10 July 2023].

25. Vogel A, Bridgewater J, Edeline J, et al. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. Feb 2023;34(2):127-140. doi:10.1016/j.annonc.2022.10.506

26. Izquierdo-Sanchez L, Lamarca A, La Casta A, et al. Cholangiocarcinoma landscape in Europe: Diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. *J Hepatol*. May 2022;76(5):1109-1121. doi:10.1016/j.jhep.2021.12.010

27. National Institute for Health and Care Excellence. Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [TA944]. Available at: https://www.nice.org.uk/guidance/ta944 [Accessed 22 January 2024].

28. National Institute for Health and Care Excellence. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement. Technology appraisal guidance. Recommendaitons. Available at: https://www.nice.org.uk/guidance/ta722/chapter/1-Recommendations [Accessed 11th May 2023].

29. Goyal L, Shi L, Liu LY, et al. TAS-120 Overcomes Resistance to ATP-Competitive FGFR Inhibitors in Patients with FGFR2 Fusion-Positive Intrahepatic Cholangiocarcinoma. *Cancer Discov*. Aug 2019;9(8):1064-1079. doi:10.1158/2159-8290.Cd-19-0182

30. Sootome H, Kato S, Kato M, Hirai H. Abstract 1117: Acquired resistance to ATP-competitive and irreversible FGFR inhibitors (FGFRi's): A library-based approach. *Cancer Research*. 2021;81(13_Supplement):1117-1117. doi:10.1158/1538-7445.Am2021-1117

31. Taiho Data on File. Advisory Board Report. 2023.

32. Moschopoulou E, Deane J, Duncan M, et al. Measuring quality of life in people living with and beyond cancer in the UK. *Support Care Cancer*. Oct 2021;29(10):6031-6038. doi:10.1007/s00520-021-06105-z

33. Bottomley A. The cancer patient and quality of life. *Oncologist*. 2002;7(2):120-5. doi:10.1634/theoncologist.7-2-120

34. Woradet S, Songserm N, Promthet S, Parkin DM. Health-Related Quality of Life and Survival of Cholangiocarcinoma Patients in Northeastern Region of Thailand. *PLoS One*. 2016;11(9):e0163448. doi:10.1371/journal.pone.0163448

35. Patel N, Lie X, Gwaltney C, et al. Understanding Patient Experience in Biliary Tract Cancer: A Qualitative Patient Interview Study. *Oncol Ther*. Dec 2021;9(2):557-573. doi:10.1007/s40487-021-00159-z

36. Morement H, Harrison R, Taylor-Robinson SD. The multidisciplinary team meeting in the UK from the patients' perspective: comments and observations from cholangiocarcinoma patients and their families. *International Journal of General Medicine*. 2017/12/31 2017;10:305-310. doi:10.2147/IJGM.S145029

37. AMMF Forum. Available at: https://ammf.org.uk/forum/ [Accessed 19 June 2023].

38. Goyal L, Meric-Bernstam F, Hollebecque A, et al. Futibatinib for FGFR2-Rearranged Intrahepatic Cholangiocarcinoma. *N Engl J Med*. Jan 19 2023;388(3):228-239. doi:10.1056/NEJMoa2206834

39. Sootome H, Fujita H, Ito K, et al. Futibatinib Is a Novel Irreversible FGFR 1-4 Inhibitor That Shows Selective Antitumor Activity against FGFR-Deregulated Tumors. *Cancer Res*. Nov 15 2020;80(22):4986-4997. doi:10.1158/0008-5472.Can-19-2568

40. Rushbrook SM, Kendall TJ, Zen Y, et al. British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma. *Gut*. Sep 28 2023;doi:10.1136/gutjnl-2023-330029

41. Goyal L, Meric-Bernstam F, Hollebecque A, et al. Updated results of the FOENIX-CCA2 trial: Efficacy and safety of futibatinib in intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 fusions/rearrangements. *Journal of Clinical Oncology*. 2022;40(16_suppl):4009-4009. doi:10.1200/JCO.2022.40.16_suppl.4009

42. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated locally advanced/metastatic cholangiocarcinoma (CCA): Update of FIGHT-202. *Journal of Clinical Oncology*. 2021;39(15_suppl):4086-4086. doi:10.1200/JCO.2021.39.15_suppl.4086

43. Vogel A, Sahai V, Hollebecque A, et al. O-2 Pemigatinib for previously treated locally advanced or metastatic cholangiocarcinoma: Final results from FIGHT-202. *Annals of Oncology*. 2022;33:S379. doi:10.1016/j.annonc.2022.04.443

44. Rizzo A, Ricci AD, Brandi G. Pemigatinib: Hot topics behind the first approval of a targeted therapy in cholangiocarcinoma. *Cancer Treat Res Commun*. 2021;27:100337. doi:10.1016/j.ctarc.2021.100337

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [ID6302]

Clarification questions

February 2024

File name	Version	Contains confidential information	Date
ID6302 futibatinib EAG clarification letter 27022024 IC final [CON].docx"	V1.0	Yes	13 March 2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

A: Clarification on effectiveness data

A1. Literature searches

Please provide full details of all clinical trial registry and conference proceedings searches (including dates searched and terms used) conducted in Appendix D.

The search terms, links and search dates for the conferences and clinical trials searched as part of the clinical SLR are presented in Table 1.

Table 1. Search strategy for conferences and clinical trials (clinical SLR)

Resource	Search Strategy	Date Searched
Conferences		
American Society of Clinical Oncology (ASCO)	Search for "futibatinib" or "pemigatinib" (separately) in the search bar and filter by "Year" for 2021, 2022 and 2023	6th September 2023
European Society of Medical Oncology (ESMO) and The ESMO World Congress on Gastrointestinal Cancer[a]	Search for "futibatinib" or "pemigatinib" (separately) in the search bar and filter by All Filters, Sections, Meeting Resources Sort by "Date newest to oldest" and select relevant entries dated 2021–2023	6th September 2023

Resource	Search Strategy	Date Searched
Conferences		
International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual Meetings	Search for “futibatinib OR pemigatinib” in the “Keywords” field and select relevant entries dated 2021–2023	6th September 2023
Clinical Trials		
ClinicalTrials.gov	Search for Intervention/Treatment: pemigatinib OR Pemazyre OR "INCB 054828" OR INCB054828 OR "IBI 375" OR IBI375 OR "INCB 54828" OR INCB54828 OR futibatinib OR TAS120 OR "TAS 120" or Lytgobi Additional filters: Study Phase: Phase 2/3/4/Not applicable Study results: “With results”	11th September 2023

Footnotes: [a]Conference proceedings from the European Society of Medical Oncology and the ESMO World Congress on Gastrointestinal Cancer and were searched simultaneously.

A2. Please confirm the date that Embase was searched in Appendix G, as the column header and footnote to Table 20 provide different search dates.

The correct date is 3rd October 2023 and the footer for Table 20 should read ‘Database: Embase 1974 to 3rd October 2023.’

A.3 The PRISMA flow diagram in Figure 3 of Appendix G.2 lists 'Cochrane CENTRAL' as one of the databases searched. Please confirm that this should read 'International HTA Database'.

The Company confirms that the 'Cochrane CENTRAL' label in Figure 3 is incorrect and should read ‘International HTA Database’.

A.4 Please provide full details of all grey literature and conference proceedings searches (including dates searched and terms used) conducted in Appendix G.

Full details of the grey literature and conference searches, including the search strategy and date searched, are presented in Table 2.

Table 2. Search strategy for conferences and grey literature (economic SLR)

Resource	Search Strategy	Date Searched
Conferences		
American Society of Clinical Oncology (ASCO)	Search for “cholangiocarcinoma” and apply filter for years 2021–2024 Search for “bile duct cancer” and apply filter for years 2021–2024 Search for “biliary tract cancer” and apply filter for years 2021–2024	11th October 2023

Resource	Search Strategy	Date Searched
European Society of Medical Oncology (ESMO) and ESMO World Congress on Gastrointestinal Cancer[a]	Search for "cholangiocarcinoma", filter by "Meeting resources", sort by date and select records for years 2021–2023 Search for "bile duct cancer" filter by "Meeting resources" and select records for years 2021–2023 Search for "biliary tract cancer" filter by "Meeting resources", and select records for years 2021–2023	11th October 2023
International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual Meetings	Search for "cholangiocarcinoma" and select records for years 2021–2023 Search for "bile duct cancer" and select records for years 2021–2023 Search for "biliary tract cancer" and select records for years 2021–2023	11th October 2023
Economic Databases		
The Cost-effectiveness Analysis (CEA) Registry, managed by Tufts Medical Center	Click on the yellow box titled 'View the CEA Registry'. In the search bar, paste in the first search term in the list below, with 'Methods' selected and hit search. 1. Cholangiocarcinoma 2. Bile duct cancer 3. Biliary tract cancer Repeat the above with 'Ratios' selected and then with 'Utility Weights' selected. Then repeat for each subsequent search term in the list.	24th October 2023
The School of Health and Related Research Health Utilities Database (ScHARRHUD), University of Sheffield	Select "search" in the menu at the top. In the first search bar, search for the following (in Abstract [AB]): 1. Cholangiocarcinoma 2. Bile duct cancer 3. Biliary tract cancer	24th October 2023
The EQ-5D Publications Database	Ensure the advanced search is presented. In the "type" dropdown, select "abstract" and in the "abstract" box enter the following terms: 1. Cholangiocarcinoma 2. Bile duct cancer 3. Biliary tract cancer	24th October 2023
HTA Body Websites		
All Wales Medicines Strategy Group (AWMSG)	In the search bar at the top right, enter the search term: 1. Cholangiocarcinoma 2. Pemigatinib 3. Futibatinib 4. Pemazyre 5. Lytgobi Screen the interventions against the list of relevant interventions in the eligibility table. For each relevant intervention, select these and review the "AWMSG Secretariat Appraisal Report (ASAR)" document for relevance.	12th October 2023

Resource	Search Strategy	Date Searched
	Restrict searches to documents published after 2013.	
Canadian Agency for Drugs and Technology in Health (CADTH)	Enter search term in top left search box: 1. Cholangiocarcinoma 2. Pemigatinib 3. Futibatinib 4. Pemazyre 5. Lytgobi Filter the results by "Reimbursement Review" and "Health Technology Review". Restrict searches to documents published after 2013.	12th October 2023
Scottish Medicines Consortium (SMC)	In the search bar, enter the search term: 1. Cholangiocarcinoma 2. Pemigatinib 3. Futibatinib 4. Pemazyre 5. Lytgobi Under the SMC advice bar, select the option at the bottom of the list "More results from the SMC Advice section". Screen the interventions against the list of relevant interventions in the eligibility table. For each relevant intervention, check to see which are "Full Submissions" and "Resubmissions". For those which are full and resubmissions, select these and review the "Detailed Advice (PDF)" document for relevance. Restrict searches to documents published after 2013.	12th October 2023
National Institute for Health and Care Excellence (NICE)	In the search bar, enter the search term: 1. Cholangiocarcinoma 2. Pemigatinib 3. Futibatinib 4. Pemazyre 5. Lytgobi Under the "Filter results by…" on the left-hand side of the screen, check the following boxes only: "Guidance", "NICE Advice" and "Published". Screen the titles of the results for relevance. Select relevant results and look for the "History" tab on the right-hand side of the screen. Download the "Final Appraisal Document" and "Committee papers" for each result. Within the "Committee papers" document, double click the "Submission from manufacturer" document and screen this for relevance. Restrict searches to documents published after 2013.	12th October 2023

Resource	Search Strategy	Date Searched
National Centre for Pharmacoeconomics (NCPE)	In the search bar, enter the search term: 1. Cholangiocarcinoma 2. Pemigatinib 3. Futibatinib 4. Pemazyre 5. Lytgobi Screen the interventions against the list of relevant interventions in the eligibility table. For each relevant intervention, select these and review the "Summary" document (where available) for relevance. If no summary document is available, use the information given on the screen (these will therefore always be excluded). Restrict searches to documents published after 2013.	12th October 2023
Pharmaceutical Benefits Advisory Committee (PBAC)	Use ctrl+f to search for each intervention in turn (note that only interventions can be searched for and not indications as not all titles contain the indication): 1. Pemigatinib 2. Futibatinib 3. Pemazyre 4. Lytgobi Open all links in turn and review the "summary" document (where available) for relevance. If no summary document is available, use the information given on the screen (these will therefore always be excluded). Restrict searches to documents published after 2013.	12th October 2023

Footnotes: [a]Conference proceedings from the European Society of Medical Oncology and the ESMO World Congress on Gastrointestinal Cancer and were searched simultaneously.

Decision problem

A.5 Priority question. The case made for omitting modified folinic acid, 5 fluorouracil and oxaliplatin (mFOLFOX) and BSC from the decision problem is that pemigatinib is recommended by NICE and that *"UK clinical experts highlighted that patients known to have an FGFR2 fusion or rearrangement would receive pemigatinib in clinical practice, given the magnitude of the survival benefit for pemigatinib versus chemotherapy."* (p. 23, company submission (CS)). However, although technology appraisal (TA) 722 recommended pemigatinib, the National Institute for Health and Care Excellence (NICE) scope states that pemigatinib is *"…an option for treating advanced cholangiocarcinoma with FGFR2* [Fusion growth factor receptor 2]

fusion or rearrangement after systemic therapy in adults. Alternatively, people may be offered modified folinic acid, fluorouracil and oxaliplatin (mFOLFOX) in the second line setting." **Also, the final appraisal document (FAD) for TA722 states that whether pemigatinib is more effective than current treatments is *"…uncertain because the study did not directly compare pemigatinib with symptom control or mFOLFOX."* It is explained that the evidence was based on an unanchored matching-adjusted indirect comparison (MAIC) with insufficient adjustment for possible effect modifiers and prognostic variables. Therefore, given the limitations of the evidence, further rationale needs to be given for the absence of mFOLFOX and best supportive care (BSC) from the decision problem. In particular, please provide evidence that neither mFOLFOX nor BSC are still be used in clinical practice in England and Wales. If not, then please include both of these comparators in all comparative clinical and cost effectiveness analyses.**

At the time of the NICE appraisal of pemigatinib, the most recent British Society of Gastroenterology (BSG) guidelines for the management of CCA (which, at the time, were published in 2012), recommended combination chemotherapy in patients with adequate performance status following failure of first-line chemotherapy.[1] In line with this, second-line chemotherapy regimens, in particular the modified folinic acid, fluorouracil and oxaliplatin (mFOLFOX) regimen with active supportive care (ASC), were considered to be relevant comparators in the NICE evaluation of pemigatinib (TA722). ASC (or best supportive care [BSC]) alone was also considered a relevant comparator: clinical experts in treating CCA consulted as part of TA722 highlighted that ASC could also be used in patients who had too poor a performance status, or who were otherwise unfit to receive systemic treatment with chemotherapy, which is associated with substantial toxicity and debilitating side effects.[2]

However, the introduction of targeted therapies, including pemigatinib, has changed the treatment landscape for advanced CCA with FGFR2 fusions or rearrangements, due to these treatments offering apparent substantial survival benefits compared with second-line chemotherapy. In the ABC-06 study which evaluated FOLFOX plus ASC versus ASC alone in patients with locally advanced or metastatic biliary tract cancer, FOLFOX plus ASC resulted in a median overall survival (OS) of 6.2 months (95% CI: 5.4–7.6) versus 5.3 months (4.1–5.8) in the ASC alone arm.[3, 4] In comparison, in the FIGHT-202 trial, patients with CCA with FGFR fusions or rearrangements with disease progression following at least one previous treatment receiving pemigatinib had a median OS of 17.5 months (95% CI: 14.4, 22.9).[5] These substantial survival gains resulted in a positive recommendation of pemigatinib from NICE in adult patients with locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement that has progressed after systemic therapy.

These developments are reflected in the most recent guidelines for the treatment of CCA. The European Society of Medical Oncology (ESMO) guidelines (2022) position FOLFOX as a second-line therapy for patients without targetable genetic aberrations only, and recommend the exclusive use of FGFR inhibitors in eligible patients with FGFR2 fusions or rearrangements.[4]

This aligns with the updated BSG (2023) guidelines: although, unlike the ESMO guidelines, they do not present a specific treatment pathway, these guidelines do however strongly recommend that CCA should be subjected to molecular profiling at the earliest opportunity, and that treatment options should be reviewed by clinicians with appropriate expertise.[6]

The exclusive use of pemigatinib in UK clinical practice in eligible patients with FGFR2 fusions or rearrangements was also supported by expert clinical opinion. As part of an Advisory Board, UK clinical experts in CCA highlighted that owing to the significant survival benefits associated with targeted treatment for patients with recognisable oncogenic mutations, in UK clinical practice, following one prior therapy, patients with CCA with FGFR2 fusions or rearrangements receive targeted treatment with pemigatinib (an FGFR2 inhibitor).[7] The experts additionally highlighted that response rates to treatment in patients with CCA with FGFR2 fusions or rearrangements increased from ~5% in patients receiving non-targeted chemotherapy to ~40% in patients receiving pemigatinib, an 8-fold increase. Due to these substantial differences in both response rates and survival, FOLFOX is not used in UK clinical practice in patients with FGFR2 fusions or rearrangements.[7] Clinical expert feedback and most recent guidelines therefore align in that mFOLFOX does not represent a relevant comparator to futibatinib in the indication of relevance to this submission.[7]

It is however acknowledged that there may be patients in UK clinical practice who are not fit enough to receive treatment with pemigatinib and who may therefore receive only ASC or BSC. However, as futibatinib is associated with a comparable safety profile to pemigatinib, it is reasonable to assume that patients who are not fit enough to receive pemigatinib, would also be unable to receive futibatinib. As such, patients with FGFR2 fusions or rearrangements receiving ASC or BSC in UK clinical practice represent a distinct subgroup of patients that is not relevant to this submission. Neither ASC nor BSC therefore represent a relevant comparator to futibatinib in this indication.

A.6 Please provide justification for the presence of the outcomes ‘duration of response’ and ‘disease control rate’ in the decision problem, even though these are not prescribed by the NICE scope.

The NICE scope specifies that response rate outcomes should be included in the evaluation. Disease control rate (DCR), based on confirmed CR, PR and stable disease (SD), was therefore included in the submission in addition to objective response rate (ORR) which is based on confirmed complete response (CR) and partial response (PR), to provide additional response rate data on futibatinib. The duration of response (DOR) outcome, in addition to providing further evidence related to patient responses, is considered to be an established and clinically important outcome in the field of oncology.[8, 9] As a result, both DCR and DOR were considered to be relevant outcomes for inclusion in the submission, alongside the main efficacy outcomes of overall survival (OS), progression-free survival (PFS) and ORR. The relevance of these outcomes in this indication is supported by the fact that both outcomes were included in the two most recent appraisals in CCA submitted to NICE.[2, 10]

Systematic review

A.7 Please describe the manner in which data extraction was conducted. How many reviewers were involved? Was extraction conducted independently? How were disagreements resolved?

For each included study, key information was extracted into a pre-specified data extraction grid in Microsoft Word – the variables to be extracted were pre-specified, to avoid data dredging. A single reviewer extracted data from each of the included studies. Each extraction was checked by an independent reviewer who verified the accuracy and completeness of the data extracted. Any discrepancies were discussed by the two reviewers until a consensus was reached or were referred to and resolved by a third independent reviewer not involved in the data collection process. In total, three independent reviewers were involved in data extraction.

A.8 Please describe the approach taken to conduct quality appraisal of the included evidence, by including number of reviewers involved, whether appraisals were conducted independently, and how disagreements were resolved. Please also provide justification for the quality appraisal method utilised.

The quality assessment of each included study was conducted by a single reviewer. The results of the quality assessment for each included study were verified by an independent reviewer. Any discrepancies were discussed by the two reviewers until consensus was reached or were referred to and resolved by a third independent reviewer not involved in the appraisal process. In total, three independent reviewers were involved in the quality appraisal process. As described in Section D.1.2 of the Company Appendices, in line with NICE's preferred checklist, the quality of all included RCTs, non-randomised comparative trials and single-arm trials was assessed using the University of York Centre for Reviews and Dissemination criteria.[11, 12]

Clinical effectiveness evidence

A.9 Priority question: It is stated in the CS that "UK clinical experts in CCA confirmed that the baseline characteristics of the FOENIX-CCA2 trial were broadly generalisable to UK clinical practice". Clinical expert guidance, though useful, may not be sufficient for this situation, because the similarity between trial and target populations in England and Wales has an important influence on the representativeness of trial results to the target population. Furthermore, if the characteristics that differ are amongst those included as variables in the pre-specified sub-group analyses, then it may be possible to infer how outcomes in clinical practice in England and Wales will be affected by these differences. Please provide objective information on the characteristics of the

target population. This should ideally cover the variables included in the pre-specified sub-group analyses.

Cholangiocarcinoma (CCA) is a relatively rare cancer, with an estimated age-standardised incidence rate of 4.3 per 100,000 in England.[13, 14] Thus, as is a common limitation in rare diseases, the evidence base for this disease area is limited and, in particular there is a paucity of evidence in the patient population of relevance to this submission in the UK. To the best of the Company's knowledge, there are no cohort studies reporting on the demographic and/or disease characteristics of patients with advanced and pretreated CCA with FGFR2 fusions or gene rearrangements in the UK. Therefore, where quantitative data are not available, UK clinical expert feedback presents an important evidence source, that reflects the most up-to-date information on patients with CCA in the UK. In the absence of alternatives, the Company considers clinical expert feedback to present the best available means of judging whether the data collected from the FOENIX-CCA2 trial is suitable for decision-making.

UK clinical experts in CCA consulted at a recent Advisory Board confirmed that the baseline characteristics of patients enrolled in the FOENIX-CCA2 trial were broadly generalisable to the relevant population in UK clinical practice.[7] In particular, median age and ECOG performance status were noted to be closely aligned.[7] Additionally, the baseline patient characteristics in FOENIX-CCA2 were in line with the patient population in the FIGHT-202 trial (Table 3). Of note, the FIGHT-202 trial population is aligned with the anticipated population that futibatinib would be used in UK clinical practice and was deemed appropriate for decision-making by the NICE Committee (Section 3.4 of the NICE FAD).[15] Furthermore, two separate clinical experts who submitted input into the NICE submission for pemigatinib confirmed that the FIGHT-202 trial was reflective of the population of CCA patients treated in UK clinical practice.[2]

Considering the variables included in the pre-specified subgroup analyses, all variables were aligned between trials except the proportion of white patients and the proportion of patients receiving >1 prior therapy line, which were both higher in the FIGHT-202 trial versus the FOENIX-CCA2 trial. As race was demonstrated to have no significant impact on OS and PFS outcomes in the sensitivity analyses performed on the ITC comparing futibatinib to pemigatinib (see Company submission Section B.2.9.2; Tables 21 and 23), the difference in proportion of white patients between trials is not anticipated to impact the generalisability of the results of the FOENIX-CCA2 trial to UK clinical practice. Furthermore, the only prior treatment variables that would be anticipated to impact efficacy and safety outcomes are FGFR2 treatments and prior surgery, and prior treatment with an FGFR2 treatment was a key exclusion criterion in both trials,[16, 17] whilst prior surgery rates were similar between trials (39.8% in FOENIX-CCA2 versus 35.5% in FIGHT-202, respectively). As such, this difference in prior treatments is not anticipated to reduce the generalisability of the FOENIX-CCA2 trial results to UK clinical practice. This view is supported by feedback received from UK clinical experts who noted that prognostic factors and treatment effect modifiers were "remarkably similar with no key differences" between the FIGHT-202 and FOENIX-CCA2 trials observed.[7] Finally, the similarities between the baseline characteristics between the FOENIX-CCA2 and the FIGHT-202 trial is supported by the fact that there were was no statistically significant differences between the results of the naïve and adjusted ITCs between futibatinib and pemigatinib presented in the Section B.2.9.2 of the Company submission.

Overall, in the absence of real-world data for CCA patients in UK clinical practice, the similarities in the baseline patient characteristics between the FOENIX-CCA2 and FIGHT-202 trials, which was deemed suitable for decision-making in the UK, provide confidence in the generalisability of

the results of the FOENIX-CCA2 trial to UK clinical practice.[2] A view which is supported by feedback received from UK clinical experts in CCA.

Table 3: Baseline patient characteristics for FOENIX-CCA2 and FIGHT-202

Characteristic	Futibatinib (FOENIX-CCA2)	Pemigatinib (FIGHT-202)[b]
Median age (range), years	58 (22–79)	56 (26–77)
Male (%)	43.7	39.3
ECOG PS 0 (%)	46.6	42.0
Albumin <35 g/L (%)	19.4	19.6
One prior therapy line	46.6	60.7
Prior surgery(%)	39.8	35.5
TP53 alteration(%)	12.6	8.4
White[a] (%)	49.5	73.8
Prior neoadjuvant treatment (%)	3.9	NR
Patients with solid tissue (%)	96.1	NR
Baseline FGFR2 status		
FGFR2 fusion (%)	77.7	95.3%
FGFR2 rearrangement (%)	22.3	4.7%

Footnotes: [a]Race (% white versus other) was used in a sensitivity analysis; [b]Informed by the Cohort A (n=107, FGFR2 fusions or rearrangements) of the FIGHT-202 trial.
Abbreviations: CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; ESS: estimated sample size; FGFR: fibroblast growth factor receptor 2; OS: overall survival; PFS: progression-free survival; TP53: tumour protein p53. **Source:** Taiho Oncology. Data on File. FOENIX-CCA2 CSR. Data cut-off 1 October 2020; Vogel et al. (2022).

A.10 Priority question. The company implies that the sub-group analyses suggest no effect modification from the chosen variables. However, this is not necessarily the case. The sub-group analyses show a trend for age to be an effect modifier, with older age being associated with a more robust response to treatment. For 'prior systemic therapy' there was an apparent dose-response effect, which supports the possibility that efficacy may increase with increased prior systemic therapy. It was unclear if other sub-grouping variables are effect-modifiers. The 95% confidence interval (CI) for the strata in all sub-grouping analyses overlap, but this does not necessarily mean that the differences are 'non-significant', as it is quite possible for overlapping 95% CIs to be consistent with significant difference at an alpha of 0.05.

In any event, the sub-group analysis is probably underpowered: the groups may be so small that detection of 'significant' differences will be difficult. This implies that any significant results are to be taken seriously, because they will probably require a large effect size to be so detected. On the other hand, there

may be a high risk of type II errors if the statistical analyses show a marginally 'non-significant' result, and therefore it would make sense to pay attention to strong but non-significant trends in the data. Normally the emphasis in statistical testing is conservative; that is, the null hypothesis will only be rejected if there is a low probability ($p<0.05$) that the sample could have been drawn from the null population. This is because the harms of falsely rejecting the null hypothesis (type I error) are often greater than the harms of falsely accepting the null hypothesis (type II error). However, in this case the harms of a type II error - of falsely accepting the null hypothesis - may be greater. The impact of possible effect modification by a variable on external validity is potentially important if that variable is also shown to differ between the trial and the UK target population. For example, a real effect modification for the variable of 'race', in conjunction with the target population in England and Wales having a different proportion of ethnic identities to the trial, might mean that results for the trial are not representative of the target population.

a) Please provide formal statistical analyses for the sub-group analyses.

Formal statistical subgroup analyses were not conducted for the FOENIX-CCA2 trial owing to the fact that any results would be associated with substantial uncertainty owing to the small sample sizes.[18] Furthermore, the power calculations conducted to identify the target enrolment number for the FOENIX-CCA2 trial were not powered for subgroup analyses. As a result, any formal statistical subgroup analyses conducted would be underpowered and therefore any resulting p-values would not be statistically meaningful. This is supported by Barraclough *et al.* (2010), who note that a key limitation of subgroup analyses is that they are often underpowered owing to the sample size of the clinical trial being calculated to evaluate the primary study objective as opposed to in specific subgroups. Barraclough (2010) goes on to highlight that unplanned subgroup analyses (subgroup analyses not pre-specified in the protocol) frequently lack statistical power and therefore results are often over interpreted and misused.[19] For these reasons, the conduct of formal statistical subgroup analyses on the FOENIX-CCA2 trial population was not considered appropriate.

b) Please comment on any trends that suggest possible effect modification.

N/A – No formal statistical subgroup analyses were conducted.

A.11 As shown in Figure 6 of the CS, five patients in the FOENIX-CCA2 trial discontinued treatment due to withdrawal of consent or investigator decision. These form a significant proportion of the whole cohort. Therefore, please clarify the precise reasons for withdrawal of consent and investigator decision.

Of these five patients, two patients discontinued treatment due to withdrawal of consent and three discontinued treatment due to investigator decision. Of the patients who discontinued treatment due to withdrawal of consent, one patient requested to stop taking the treatment due to overall deterioration/feeling unwell (SAE: clinical PD). No additional information was collected in terms of the precise reasons for the discontinuation for the other patient. Of the three patients who discontinued treatment due to investigator decision, no additional information was recorded for the precise reason for discontinuation, however the decision for one patient coincided with the date of radiological progression.

A.12 Only 10/11 of the pre-planned sub-group analyses are reported. The omitted analysis was defined by 'patients with solid tissue sample and report'.

a) Please explain this omission.

Per the primary analysis (DCO 1st October 2020) of ORR and DOR for patients with solid tissue sample and report, 96.1% (99/103) of patients were classified as having a solid tissue sample with a report available. Therefore, a subgroup analysis based on "patients with solid tissue sample and report" was not performed, as only four patients did not meet this criterion, therefore the results of any such subgroup analysis would be subject to substantial uncertainty resulting from the extremely imbalanced distribution of patient numbers.

b) Please provide the sub-group analysis for this outcome if appropriate.

N/A – No subgroup analysis for this characteristic were conducted.

A 13. 'Concomitant treatments' is not a sub-grouping variable, despite having the potential to be a powerful effect modifier.

a) Please explain why this variable was omitted.

Since the population of the FOENIX-CCA2 trial included patients with advanced CCA, most of the patients were expected to receive concomitant medications at the time of the trial design. Therefore, a subgroup analysis of patients based on whether they received concomitant treatments was not considered to be meaningful. Indeed, all patients in the FOENIX-CCA2 trial received at least one concomitant medication – therefore, a subgroup analysis split by patients receiving versus not receiving concomitant treatment would not be feasible.

It is also important to note that the concomitant medications permitted by the FOENIX-CCA2 protocol were principally intended for the mitigation of AEs, or in some cases, palliative treatment, and were not expected to have any significant anti-cancer activity. As per the FOENIX-CCA clinical trial protocol, the following concomitant medications were permitted:

- Bisphosphonate
- Denosumab
- Non enzyme-inducing anticonvulsants
- Gonadotropin-releasing hormone (GnRH) agonists, luteinizing hormone–releasing hormone (LH-RH) agonists, steroids and local or regional palliative cryotherapy or radiation were allowed for certain patients

- Guidelines were also provided for concomitant treatments for haematologic support and management of diarrhoea, nausea/vomiting and hyperphosphatemia

In addition, it was considered that concomitant treatments do not present an effect modifier by themselves, instead reflecting on other patient characteristics that do present treatment effect modifiers, and it was considered that all principal effect modifying variables were considered in subgroup analyses.

For all of the above reasons, a subgroup analysis based on concomitant medications was not considered feasible nor appropriate.

b) Please provide the sub-group analysis for this outcome if appropriate.

N/A – This analysis was not performed.

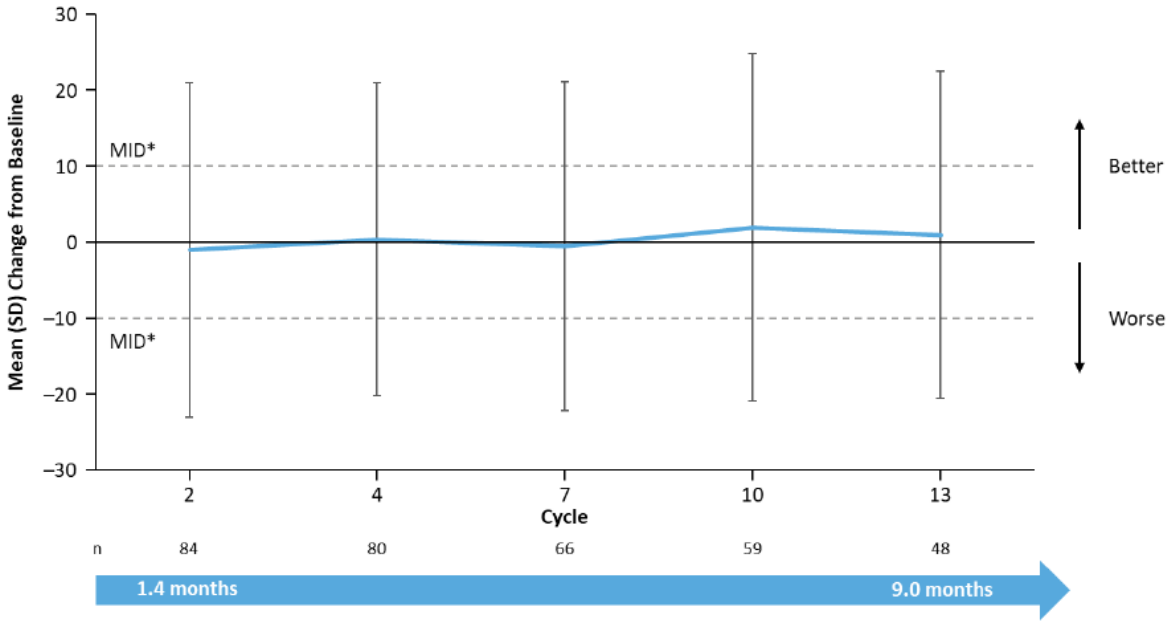
A 14. Three measures of Health-related quality of life (HRQoL) were reported to be measured - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), Euro-QoL-5 dimensions-3 levels (EQ-5D-3L), and EuroQol visual analogue scale (EQ VAS). However, only results for EQ-VAS were fully reported in the CS or appendices. This suggests possible reporting bias. Please report the QoL data for the EORTC QLQ-C30 and EQ-5D-3L measures in full.

As reported in Section B.2.6.6 of the submission document, HRQoL outcomes collected in the FOENIX-CCA2 trial included EORTC QLQ-C30 (5 functional and 9 physical measures), EQ-5D-3L (utility index and 5 dimensions: anxiety/depression, mobility, pain/discomfort, self-care, and usual activity) and EQ-VAS. Primary analysis for HRQoL outcomes was assessed using predefined clinically meaningful thresholds; since after Cycle 13 less than 50% of the patient population provided PRO data, the primary analyses were conducted up to Cycle 13.

The EORTC-QLQ-C30 Global Health Status Score change from baseline through Cycle 13 and EQ-5D-3L Dimensions Status change from baseline at Cycle 13 are presented in Figure 1 and Figure 2 respectively, reproduced from the Goyal et al. (2023)[17] publication reporting the results of the FOENIX-CCA2 trial. The change from baseline in the EORTC QLQ-C30 Scales are provided in Table 4.

Overall, the outcomes of EORTC-QLQ-C30 and EQ-5D-3L were consistent with the results for EQ-VAS, indicating stable quality of life for most patients. The HRQoL assessments for the final DCO (21 May 2021) were consistent with those from the preliminary DCO (1 October 2020).

Figure 1: EORTC-QLQ-C30 Global Health Status Score change from baseline through Cycle 13



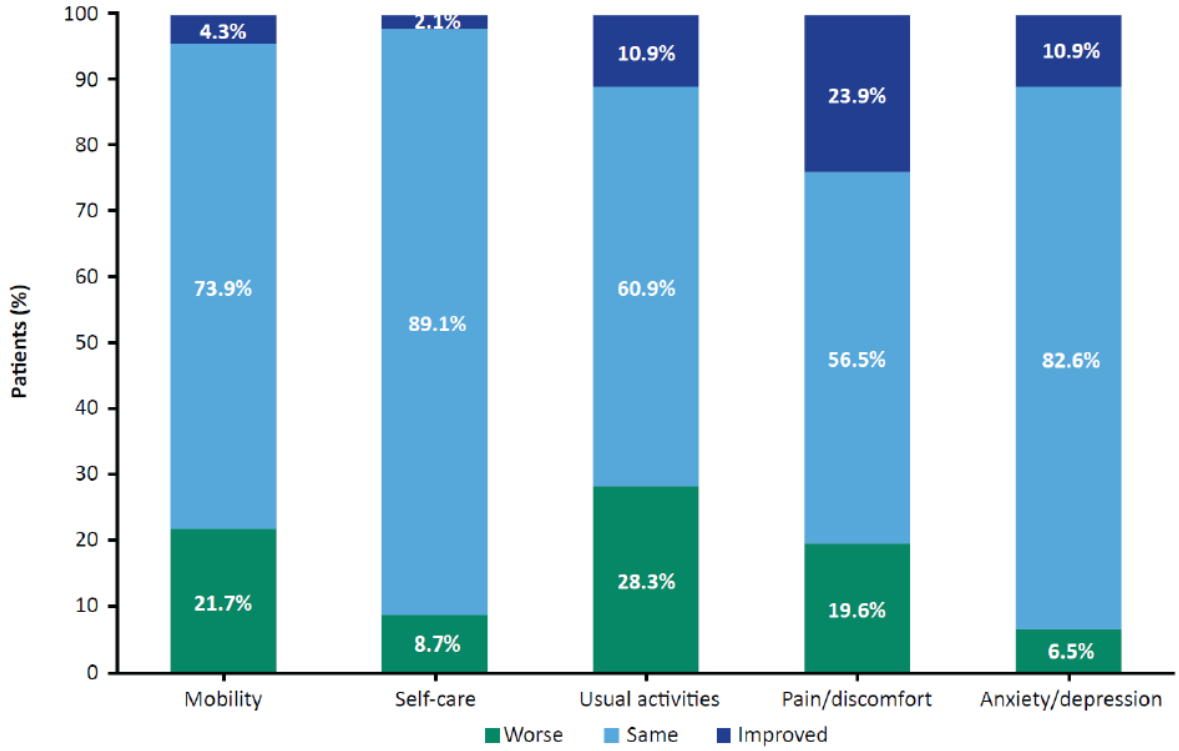
Footnotes: The error bars indicate one standard deviation, and the dashed lines MIDs; changes from baseline between the dashed lines were not considered clinically meaningful. *A ≥10-point change from baseline in QLQ-C30 scores was predefined as the MID to designate a change as clinically meaningful
Abbreviations: EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; MID: minimally important difference; SD: standard deviation
Source: Goyal et al. (2023)[17]

Table 4: EORTC QLQ-C30 Scales, Mean (SD) Change From Baseline

Scale[a]	Cycle 2 n=84	Cycle 4 n=80	Cycle 7 n=66	Cycle 10 n=59	Cycle 13 n=48
Global health status	−1.0 (22.0)	+0.4 (20.6)	−0.5 (21.6)	+1.9 (22.8)	+0.9 (21.5)
Functional scales					
Physical	−1.1 (17.9)	+0.8 (15.0)	−0.4 (14.1)	−1.4 (15.4)	−2.0 (14.0)
Role	−1.2 (26.0)	−2.3 (24.0)	−0.8 (24.2)	−3.7 (23.6)	−1.4 (25.7)
Cognitive	−3.8 (15.9)	−5.7 (15.1)	−3.3 (12.2)	−4.0 (14.1)	−5.2 (12.5)
Emotional	+3.0 (19.7)	+4.7 (17.6)	+3.7 (16.2)	+2.9 (16.6)	+4.9 (15.6)
Social	+4.4 (27.9)	+0.6 (23.9)	+0.8 (19.9)	+2.9 (23.6)	−0.3 (20.5)
Symptom scales/single items					
Appetite loss	+0.4 (30.6)	+0.8 (31.8)	0.0 (35.1)	−3.4 (30.1)	−5.6 (31.0)
Constipation	+9.6 (31.5)	**+10.0 (34.9)**	+9.1 (31.8)	+5.1 (35.5)	+7.1 (34.7)
Diarrhoea	+7.1 (26.9)	+5.4 (28.8)	+2.5 (25.0)	−0.6 (26.6)	+4.2 (21.3)
Dyspnoea	−4.0 (26.2)	−5.4 (24.6)	−7.1 (23.0)	−9.0 (22.2)	−6.3 (20.2)
Fatigue	−2.3 (23.7)	−2.4 (20.5)	−2.9 (22.6)	−5.2 (21.3)	−3.2 (20.9)
Insomnia	+0.8 (29.8)	−0.4 (27.1)	+2.6 (25.9)	−2.9 (27.4)	−2.8 (29.0)
Nausea/vomiting	−1.8 (20.8)	−1.2 (22.5)	−1.5 (19.3)	−2.5 (20.0)	−3.8 (16.9)
Pain	−0.8 (23.4)	+2.1 (21.6)	+2.8 (22.4)	+4.5 (29.0)	+4.9 (29.0)
Financial difficulty	+0.8 (29.6)	−1.7 (27.3)	+1.1 (26.8)	−1.2 (28.2)	−3.5 (35.6)

Footnotes: Positive values for functional scales and global health status represent improvement, whereas positive scores for symptom scales/items and financial impact represent increased symptomatology/financial impact. [a]A 10-point change from baseline for EORTC QLQ-C30 scores was predefined as the MID to designate a change as clinically meaningful (shown in bold)
Abbreviations: EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; MID: minimally important difference; SD: standard deviation
Source: Valle et al. (2021)[20]

Figure 2: EQ-5D-3L Dimensions Status change from baseline at Cycle 13



Abbreviations: EQ-5D-3L: EuroQol-5 Dimensions-3 Levels
Source: Goyal et al. (2023)[17]

Indirect treatment comparison (ITC)

A 15. Priority question. Four studies were found in the systematic literature review (SLR) that looked at pemigatinib. However, three were excluded from the ITC. The reasons given for the omission of these three studies do not seem particularly convincing. For FIGHT-101 and FIGHT-207, it appears that there were relevant sub-groups in the data, which could be utilised. Furthermore, the assumption that the study from China (NCT04256980) is not relevant because of the study's location is questionable, given that the company have already asserted in their sub-group analysis that race and nationality do not have a significant effect on outcome, and given that the futibatinib trial was multinational.

a) Please provide a table containing patient characteristics and outcome data for the 3 exclusions

The characteristics and outcomes from the FIGHT-101, FIGHT-207 and NCT04256980 clinical trials can be found in the Company Submission, Appendix D.2.1 and Appendix D.2.4. These are briefly summarised in Table 5 below. Health-related quality of life outcomes were not reported for the FIGHT-101, FIGHT-207 and NCT04256980 trials.

Table 5: Characteristics of the FIGHT-101, FIGHT-207 and NCT04256980 clinical trials, compared with FIGHT-202

Trial	Study design and patient population	Sample size	Availability of baseline patient characteristics data	Availability of OS KM data	Availability of PFS KM data	Median follow-up
FIGHT-202 (NCT02924376)[5, 16]	Phase II, open-label multicohort study in locally advanced/ metastatic or unresectable CCA harbouring FGF/FGFR alterations, translocations or no FGF/FGFR alterations (US only)	N=147 Cohort A: FGFR2 fusions or rearrangements (n=108)	Available for population of interest (Cohort A)	Available for population of interest (Cohort A)	Available for population of interest (Cohort A)	42.9 months
FIGHT-101 (NCT02393248)[21]	Phase I/II, open-label in pan-cancer patients with FGF/FGFR alterations and advanced disease	N=128	Not available for the subgroup of interest	No	No	NR
FIGHT-207 (NCT03822117)[22]	Phase II, single-arm, open-label, multiple cohort study in patients with locally advanced/metastatic or unresectable solid tumour malignancies harbouring FGFR1-3 gene mutations or translocations	N=107 Cohort A: FGFR 1-3 in-frame fusions or FGFR2 rearrangements (n=49)	Available for cohort A, which does not fully align with the population of interest (patients with FGFR2 fusions or rearrangements)	No	No	NR
NCT04256980[23]	Phase II, single-arm, open-label study in patients with advanced/metastatic CCA with FGFR2 fusions or rearrangements	Efficacy set: N=30 (preliminary DCO)	Available for population of interest	Available for population of interest, however most of the data only available for the preliminary DCO	Available for population of interest, however most of the data only available for the preliminary DCO	Preliminary DCO: 5.1 months Latest DCO: 25.6 months

Abbreviations: DCO: data cut-off; FGFR: fibroblast growth factor receptor; QD: once daily.

b) Please provide a more detailed rationale for these exclusions

A matching-adjusted indirect comparison (MAIC) is a pairwise analysis, meaning it is necessary to select one study to inform the comparator. Therefore, it is essential to select the study that is most relevant for the population of interest. Additionally, it is necessary for the trial to provide detailed baseline characteristics data for the population of relevance to this appraisal, and KM data for the outcomes of interest within this patient population, to allow for appropriate adjustment of the trials and to provide relevant efficacy inputs that can be used in the MAIC analysis and subsequently incorporated into an economic model.

In this submission, the FIGHT-202 study (n=108, Cohort A) was selected as the most relevant source of evidence for pemigatinib to inform the MAIC, since it provides evidence for pemigatinib in a population of patients directly of relevance to this appraisal.[5] The FIGHT-202 trial presents detailed baseline characteristics data, and PFS and OS KM curves that are directly relevant to the patient population of interest to this submission. The FIGHT-202 trial, Cohort A, was used to inform the efficacy of pemigatinib as part TA722, and was considered suitable for decision-making by the committee.[2, 15]

Rationale for excluding the FIGHT-101, FIGHT-207 and NCT04256980 trials is provided below:

- The FIGHT-101 trial was delivered in two parts – the first part did not restrict to patients with CCA, nor to patients with FGFR2 fusions or rearrangements and was not considered relevant for this submission, whereas the second part of the trial reported outcomes for patients with FGFR2 fusions or rearrangements. The FIGHT-101 trial was further set up as a dose escalation study (part 1, with different dose levels and dose intervals) and dose expansion study (part 2), where only part 2 applied the approved dosing schedule of pemigatinib. In part 2 of FIGHT-101, the FGFR2 CCA-patient population was much smaller (in total 20, treated with various dosing schemes of pemigatinib) than FIGHT-202, and KM data for OS or PFS of the CCA population were not separately reported. Due to the limitations of the small sample size and the paucity of KM data, it was not possible to conduct a MAIC analysis using the FIGHT-101 trial of the relevant patient population for this appraisal
- Similarly, the overall population in the FIGHT-207 trial is broader than the indication of relevance to this submission, since it did not restrict to patients with CCA only, nor to FGFR2 fusions or rearrangements.[22] The trial did report results for a smaller subgroup of patients with solid tumours and FGFR1–3 fusions (n=49), however, this indication is still broader than the population with CCA with a FGFR2 fusion or rearrangement as specified in the decision problem for this submission.[22] Additionally, the study did not report OS or PFS KM data for the overall population or the FGFR1–3 fusion population.[22] Consequently, due to the limited relevance of the patient population and lack of KM data, it was not possible to conduct a MAIC analysis versus FIGHT-207
- The NCT04256980 trial was conducted in a small sample of Chinese patients (n=31); the sample size is notably lower than in FIGHT-202 (n=108), which reduces the power of the study and limits its external and internal validity. Furthermore, the NCT04256980 trial was restricted to patients from China, and it is reasonable to assume that, compared to the FIGHT-202 study which included patients from the UK, the NCT04256980 trial population is less representative of the population anticipated to receive futibatinib in UK clinical practice. Additionally, the median follow-up for the final DCO was 25.6 months which is shorter than the final DCO of FIGHT-202 (42.9 months). For these reasons, while it would be theoretically feasible to conduct a MAIC versus NCT04256980, there would be extremely limited rationale to prefer the use of the NCT04256980 when compared to FIGHT-202, and any MAIC versus

NCT04256980 would be associated with substantial additional uncertainty, when compared to the MAIC versus FIGHT-202

For these reasons, FIGHT-202 was considered to be the most relevant study for pemigatinib with respect to the population of interest (patients with advanced CCA with an FGFR fusion or rearrangement) and consequently, was used to inform the ITC analysis and subsequently, the efficacy of pemigatinib in the economic model. This approach is consistent with TA722, where the FIGHT-202 trial was considered suitable to provide evidence for pemigatinib for the population of interest to this submission, i.e., patients with advanced cholangiocarcinoma with FGFR2 fusion or rearrangement.[2]

c) Please add any studies to the analysis whose exclusion cannot be justified. This should include the use of any formal ITC such as a MAIC.

The exclusion of the FIGHT-101, FIGHT-207 and NCT04256980 studies is deemed justifiable for the reasons described in Question A15b. Consequently, no further analyses have been conducted.

A 16. Priority question. The factors chosen for the sub-group analyses should also be relevant to the ITC Cox regression model, as these are all believed to be effect modifiers. However, race, region, FGFR2 status and prior (neo)adjuvant treatment (which were sub-group analysis factors) are not included in the Cox model. In addition, the potentially important variable of concomitant treatments was not included.

a) Please explain the reasons for the omission of these factors.

Firstly, it is important to note that clinical experts consulted as part of the May 2023 Advisory Board confirmed that the key prognostic factors and treatment effect modifiers were adjusted for in the ITC analysis. Furthermore, the clinical experts observed how the population characteristics were “remarkably similar” between the FIGHT-202 and FOENIX-CCA2 trials, with the Health Economist expert highlighting how this presents an advantage for the ITC analysis, since the populations are likely to be similar in unobservable characteristics.

As such, the exclusion of these additional factors is unlikely to have any meaningful impact on the results of the ITCs. Further details on the exclusion of each of these factors is provided below:

- The impact of race on OS and PFS has already been explored as sensitivity analyses in the MAIC; these analyses demonstrated that the addition of race as a covariate had minimal impact on the ITC results (see Tables 22–23, Document B). Similar to OS and PFS, race was considered in sensitivity analyses of ORR in the MAIC for the earlier DCO and was not considered to be a covariate that has a substantial impact on the results. Additionally, subgroup analyses for ORR revealed treatment effects were consistent across the four race groups investigated (see Section B.2.7.1 of Document B). Consequently, race was not considered to be a prognostic factor or treatment effect modifier and, to maximise the effective sample size, it was not adjusted for in the base case ITC analysis.

- There is no biologically plausible reason that region, as a standalone covariate, would represent a prognostic factor or treatment effect modifier. Instead, regional differences indirectly result in differences in outcomes – for example, due to differences in race or the treatment pathway in different countries. Therefore, as a standalone factor, it was not considered appropriate to adjust for region in the ITC analysis.
- FGFR2 status refers to the specific type of FGFR genetic aberration which was explored in the FOENIX-CCA2 trial – patients were categorised as having a "FGFR2 fusion" or "FGFR rearrangement". As part of the Advisory Board, clinical experts were consulted regarding the difference in treatment outcomes experienced by patients with FGFR2 fusions versus rearrangements.[7] Clinical experts confirmed that in reality, all patients with FGFR rearrangements have FGFR fusions and the difference in labelling is simply due to the accuracy of the test. As such, FGFR fusion versus rearrangement status would not have an effect on either disease prognosis or treatment effect and, therefore, FGFR2 status is not a prognostic factor or treatment effect modifier.[7] Based on this feedback, FGFR2 status was not adjusted for in the ITC analysis.
- The number of prior lines of therapy and prior surgery were adjusted for as part of the ITC meaning, overall, the impact of prior treatments was extensively explored as part of the MAIC. Prior (neo)adjuvant treatment was not directly adjusted for in the ITC analysis due to data limitations; these data were not reported in the primary or final publication for FIGHT-202 (Abou-Alfa et al. 2020; Vogel et al. 2022) and consequently, it was not possible to adjust for differences in prior neoadjuvant treatment between the FOENIX-CCA2 trial and the FIGHT-202 trial.[5, 16] Furthermore, clinical experts consulted as part of the Advisory Board identified that prior FGFR2 therapy is the only prior treatment, other than surgery, that would be anticipated to impact efficacy outcomes.[7] Since the FIGHT-202 and FOENIX-CCA2 trials excluded patients who had received prior FGFR2 therapy, and prior surgery was adjusted for in the ITC, it is deemed appropriate to not adjust for differences in the specific types of prior treatment that patients received.
- Concomitant treatments were not reported in the primary or final publication for FIGHT-202 (Abou-Alfa et al. 2020; Vogel et al. 2022) and consequently, it was not possible to adjust for any differences in concomitant treatments in the ITC analysis.[5, 16] Additionally, as described in the response to Question A13, most patients with advanced cholangiocarcinoma would be expected to receive concomitant treatments and it would not be statistically meaningful to conduct analyses based on this covariate.

b) If the omission of any of these cannot be justified, please perform a new MAIC with inclusion of any relevant factors

Race has been explored in sensitivity analyses and due to the minimal impact of including race on the overall ITC results, it is considered appropriate to exclude race from the base case ITC.

Rationale for excluding region, FGFR2 status and (neo)adjuvant treatment from the ITC are provided in response to clarification question A.16a) above and consequently, no further analyses have been conducted.

Overall, the results of the unadjusted, base case and sensitivity MAIC analyses are highly consistent – for example, the HRs for OS are 0.96, 0.95 and 0.96, respectively. This indicates that the inclusion of additional variables into the MAIC would be unlikely to have any notable impact on the results and observed conclusions of the analysis. Additionally, any differences observed would likely be the result of uncertainty introduced into the analysis, as a result of

reducing the effective sample size by including additional variables, rather than the result of the analysis producing a more accurately adjusted cohort for the study populations.

A 17. Priority question. As recommended in technical support document (TSD) 18: Methods for population-adjusted indirect comparisons in submissions to NICE, please provide evidence that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects, and present an estimate of the likely range of residual systematic error in the "adjusted" unanchored comparison.

Predicting absolute outcomes

In the absence of data for futibatinib and pemigatinib in UK clinical practice, there is no way of knowing whether 'absolute outcomes' for futibatinib and pemigatinib can be predicted with sufficient accuracy. However, given that the impact of the population adjustment in the MAIC is very minimal compared with the unadjusted results, this should not be considered to represent a source of uncertainty.

Range of residual systematic error

NICE TSD 18 recommends at least two common methods for quantifying the residual error from unobserved prognostic variables or effect modifiers in an unanchored ITC: the out-of-sample method and the in-sample method.

The out-of-sample method involves identifying a set of external studies with aggregate data on the relevant outcome in the target population, followed by a random effect pooling of absolute outcomes from each study arm. However, since the unanchored MAIC between futibatinib and pemigatinib relied on FOENIX-CCA2 and FIGHT-202 studies, and no further relevant studies involving pemigatinib were identified in the target population (as detailed in response to QA15), calculating the between study variance was not possible. In the absence of between-studies variation, quantification of residual error is not feasible.

On the other hand, the in-sample method compared with the out-of-sample method may underestimate the true amount of residual variation and may not be a suitable method for quantifying the residual heterogeneity. With small sample size, the performance metric could significantly fluctuate across different runs which could lead to potentially misleading conclusions about the model performance. Previous literature suggests serious deficiencies in using in-sample methods for the validation of time to event outcomes and no clear methods are available for cross validation of estimates from Kaplan-Meier curves.[24]

To better account for uncertainty from all sources in the treatment effect, we relied on bootstrapping, which is also a method noted in the NICE TSD 18 document.[25] The empirical distribution obtained from bootstrapping was used to estimate confidence intervals (CIs) for the treatment effect. These intervals inherently reflect the variability in the data due to sampling, as well as the uncertainty introduced by the matching and weighting process, and they were provided alongside the analysis results in the Submission document. In line with the reasoning above, this bootstrapping analysis was considered to be the most appropriate method of estimating uncertainty with the data available.

A 18. Priority question. The CS states: "*…both a MAIC and an STC were conducted…*" (p. 62). Although any form of population adjustment in an unanchored comparison is unreliable, this applies especially to MAICs: *"MAICs perform poorly in simulation studies, and in some scenarios perform worse than standard NMA with no population adjustment*" (p. 12).[26] Therefore, please present the details of the simulated treatment comparison (STC), including methods and results.

While an STC was not conducted as part of the Company submission, an STC was previously conducted to assess the efficacy of futibatinib against pemigatinib using data from an early data cut of both the FOENIX-CCA2 (October 2020) and FIGHT-202 (PFS; March 2019, OS: April 2020) trials.[16, 17] The MAIC presented in Document B utilised data from the final DCO of FOENIX-CCA2 (May 2021) and the most recently published data from the FIGHT-202 trial (Vogel et al., 2022[5]).

The results from the MAIC and STC analyses using the early DCOs, and a comparison with the results of the MAIC analysis using the later DCOs of both trials (as presented in Document B) are provided in Table 6.

Table 6. ITC results for the early and final DCOs

ITC	Model	HR for PFS	95% CI	HR for OS	95% CI
Early DCO					
N/A	Cox-naïve/unadjusted	0.812	0.579–1.138	0.897	0.595–1.352
MAIC	Base-case	0.827	0.584–1.170	0.881	0.580–1.338
	Sensitivity analysis	0.840	0.585–1.206	0.852	0.547–1.329
STC	Base-case	0.821	0.576–1.170	0.823	0.530–1.277
	Sensitivity analysis	0.831	0.574–1.201	0.823	0.511–1.324
Final DCO					
N/A	Cox-naïve/unadjusted	1.02	0.75–1.39	0.96	0.67–1.36
MAIC	Base-case	1.07	0.86–1.30	0.95	0.72–1.21
	Sensitivity analysis	1.11	0.89–1.36	0.96	0.71–1.25

Abbreviations: CI: confidence interval; DCO: data cut-off; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; N/A: not applicable; OS: overall survival; STC: stimulated indirect treatment comparison.

Overall, the results of the MAIC and STC analyses point towards futibatinib and pemigatinib having a very similar efficacy profile, with no statistically significant differences identified across any of the analyses.

Given the similarity between the MAIC and STC results at the time of the earlier DCOs, it was considered appropriate to only conduct MAICs for the final ITC (utilising the latest DCOs for FOENIX-CCA2 and FIGHT-202). It should be noted that the results of the STCs were more favourable than the MAICs with respect to both PFS and OS at the time of the earlier DCO, indicating that the use of MAICs for the final DCO could be considered conservative.

Health economic experts consulted as part of the May 2023 Advisory Board confirmed that MAIC is an appropriate methodology for the ITC since it aligns with the approach used in TA722,

whereby only a MAIC was conducted. The use of a MAIC was considered appropriate for decision-making as part of NICE TA722.[2]

Additionally, MAICs offer the advantage of producing marginal treatment effect estimates, since, by assigning differential weights to IPD for futibatinib, the aggregate measures on the modelled prognostic and treatment effect variables match (or as close as possible to) the values in the matched aggregate studies.[27] This weighting approach results in a marginal (population-level) treatment effect which consequently allows for a population-level ITC. In comparison, STCs only produce conditional (patient-level) treatment effects.[27]

As such, the use of the MAICs to inform the base case ITCs and economic analysis should not be considered to represent a source of uncertainty in this appraisal.

A 19. The CS states that a safety ITC was not performed because "*it was not considered feasible due to the differences in AE reporting definitions between FOENIX-CCA2 and FIGHT-202*". However, in Appendix D (table 16) the adverse event (AE) of hyperphosphataemia appears to be reported in both studies. As this is an AE of special interest, it appears feasible that this specific AE outcome could be used in an MAIC. Given the importance of AEs in the estimation of the relative benefits and harms of two treatments, please consider an adjusted MAIC for this outcome.

Since the PFS and OS outcomes were the key outcomes of interest to the submission and they informed the economic model, the MAICs were focused on these two outcomes. This aligns with the approach taken by the NICE evaluation of pemigatinib (TA722), which provided PFS and OS MAIC results only for the treatments of interest.

It should also be noted that AEs have a very limited impact on the economic model results, as demonstrated by the sensitivity analyses presented in Document B, Section B.3.11. Deterministic sensitivity analyses (DSA) were conducted for a variety of inputs, including AEs, by varying all parameters for which there were single input values in the model by ±20% of their mean value. The results of the DSA showed that the AEs input variation had a negligible effect on the model outcomes, measured in terms of incremental costs, QALYs and incremental net health benefit (INHB) (please refer to the Section B.3.11.2 in the submission document).

Notably, variation of the incidence of hyperphosphatemia was also included in the DSA, however it was not shown in the results in Section B.3.11.2 since it was not in the top ten variables that impacted the INHB outcome of the model. Varying the incidence of hyperphosphataemia for futibatinib by 20% changed the NHB by a negligible amount of ~0.0001. Further to this, the results of the PFS and OS MAICs demonstrated that population-adjustment had a very limited impact on the results. This potentially reflects the fact that, as highlighted by the UK clinical experts, the patient populations in the FOENIX-CCA2 and FIGHT-202 trials were similar.

Therefore, while in theory it would be feasible to conduct MAICs for specific safety outcomes, it would be expected to have a negligible impact on the economic model, as demonstrated by the DSA analyses. As such, the exclusion of MAICs for safety outcomes should not be considered to represent a source of uncertainty in this submission. This is aligned with the conclusions of the NICE committee as part of NICE TA722 for pemigatinib, where "The Committee concluded that

there was a lack of comparative safety evidence for pemigatinib and its comparators, but that this was unlikely to have much effect on the cost-effectiveness estimates."[2]

A 20. No justification is given for the omission of HRQoL or response rates from the MAIC analyses, apart from the implicit suggestion that they were not to be used for economic modelling. These outcomes have been requested by the NICE scope, and are therefore important aspects of the clinical evidence, which is important for clinical decision-making even if not carried through to economic modelling. They should therefore also be subjected to an MAIC, as without comparison to a reference treatment the meaning of the single arm results for these outcomes is questionable. [The EAG notes that the CS Appendices contain data comparing the FOENIX-CCA2 (Futibatinib) and FIGHT-202 (pemigatinib) trials for response rates (Table 15 in CS Appendices), HRQoL (Table 17 in CS Appendices) but these do not appear to be adjusted and so do not constitute MAICs.] Please consider performing MAICs for HRQoL and response rates.

ORR MAIC

A MAIC analysis for ORR was previously performed for the final DCO of the FOENIX-CCA2 trial versus a previous DCO of the FIGHT-202 trial. The ORR was evaluated as a binary outcome, in contrast to the methods used for PFS and OS MAICs, which evaluated PFS and OS as continuous variables. The results of this analysis are provided below.

The unadjusted ORR in FOENIX-CCA2 was 41.7% and from FIGHT-202 was 37.0% (Table 7).

Table 7: Unadjusted ORR for futibatinib and pemigatinib

Source	N	Median follow-up, months	ORR events, n (%)
FOENIX-CCA2, May 2021 DCO	102	25	43 (41.7)
FIGHT-202, April 2020 DCO	108	30.4	40 (37.0)

Abbreviations: ORR: objective response rate

There remained only a small reduction from the trial sample size after matching, suggesting good overlap in baseline characteristics between studies. No patient received a very large weighting, with the maximum rescaled weight being 1.78 (minimum 0.33).

The results from the unadjusted binomial model and covariate-adjusted MAIC analyses are shown in Table 8. Seven base-case prognostic factors were included in the base-case adjusted model (age, gender, ECOG status, prior lines, prior surgery, baseline hypoalbuminemia status, TP53 alteration status). In the base case, the OR estimate shows a non-statistically significant but numerically higher rate of ORR for futibatinib compared with pemigatinib (OR: 1.15; 95% CI: 0.66–2.02). This effect remained statistically non-significant in the sensitivity analysis.

Table 8: Unadjusted and adjusted ORR model results

Model	HR for ORR	95% CI; p value	Notes
Cox-naïve/ unadjusted	1.22	0.70–2.13; p=0.487	No covariate adjustment
Adjusted Cox MAIC model analyses			
Base-case covariates	1.15	0.66–2.02; p=0.618	Adjusted for age, gender, ECOG status, prior lines, prior surgery, baseline hypoalbuminemia status, TP53 alteration status
Sensitivity analysis	1.11	0.63–2.10; p=0.7195	Base-case + race

Abbreviations: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; MAIC: matching-adjusted indirect comparison; N/A: not applicable; OR: odds ratio; ORR: objective response rate; RMST: restricted mean survival time; TP53: tumour protein p53

Calculations have been made to provide a rough estimate of the sample size that might be required to differentiate ORR between futibatinib and pemigatinib, assuming that the probability of experiencing a response at the end of follow-up was as observed in the FOENIX-CCA2 (42%) and FIGHT-202 trial (37%) primary DCOs. These calculations suggested that approximately 3,000 patients would be required in total, which is 15 times greater than the current numbers enrolled in FOENIX-CCA2 and FIGHT-202.

DOR MAIC

A MAIC analysis for the latest DCO data of FOENIX-CCA2 and FIGHT-202 has been performed for the outcome of DOR, using the same methods reported for the PFS and OS MAICs in the Company submission, with the results provided below.

However, it is important to note that the DOR MAIC is associated with substantial limitations. In particular, only considering responders drastically reduces the sample size in both the futibatinib and pemigatinib arms, and results in fewer than [redacted] at risk patients for futibatinib and pemigatinib after 9 months of follow-up. Further, there are no patient characteristics data reported for the subgroup of responders in the FIGHT-202 trial. Consequently, the results of the DOR MAIC are associated with greater uncertainty compared with the PFS and OS MAICs and should be interpreted with caution.

The median DOR for the 43 responders from FOENIX-CCA2 was 9.46 months (95% CI: 7.62–10.30), compared with 9.1 months (95% CI: 6.0–14.5) for the 40 responders in FIGHT-202.

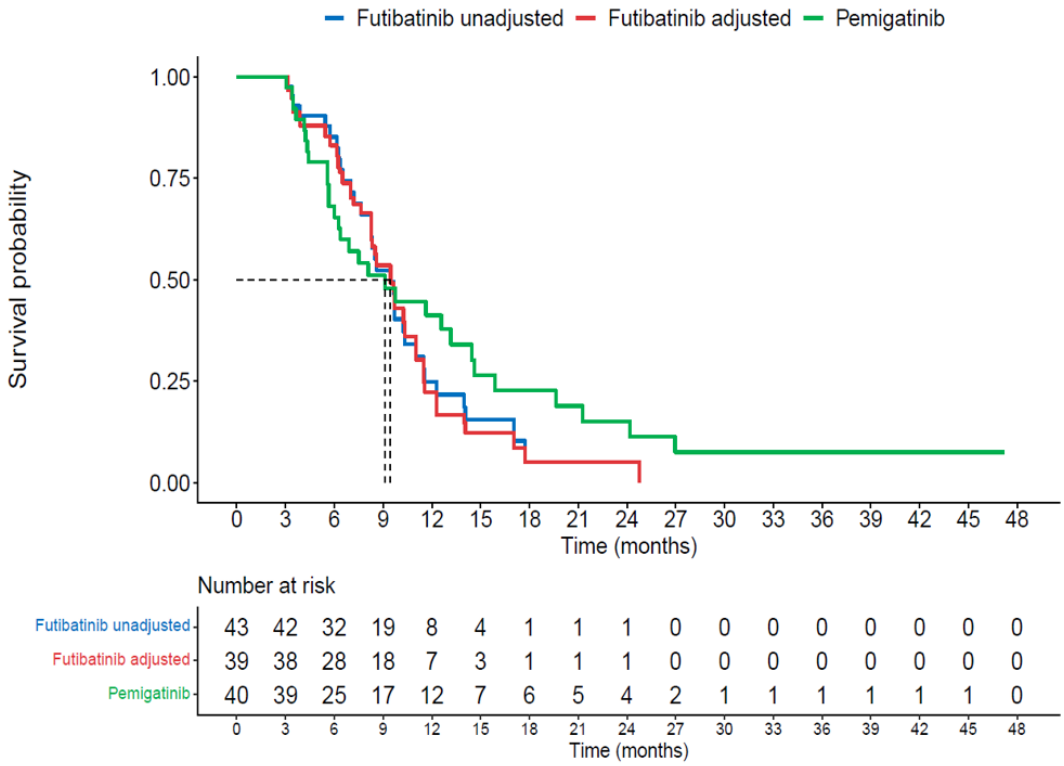
The estimated sample size (ESS) for the futibatinib group in the base-case was 36.0, which was a relatively small reduction from the sample size of responders (43 patients) and suggested good overlap in baseline characteristics between studies. No patient received a very large weighting, with the maximum rescaled weight being 2.31 (minimum 0.21). Figure 3 shows the unadjusted and weighted futibatinib DOR curves compared with the recreated pemigatinib DOR curve, and

Table 9 summarises the results from the unadjusted Cox model and covariate-adjusted MAIC analyses. The base-case MAIC analysis included all seven potential confounding factors previously detailed in Document B, Section B.2.9.

The results of the MAIC showed that DOR was comparable between futibatinib and pemigatinib patients (HR: 1.17; 95% CI: 0.69–1.97), with no statistically significant differences observed between the two treatments. Similarly, based on RMST calculation, futibatinib showed

comparable DOR to pemigatinib in both unadjusted and adjusted analysis at 24.77 months (Table 9).

Figure 3: Kaplan-Meier plot of unadjusted and MAIC-weighted DOR for futibatinib and pemigatinib



Abbreviations: DOR: duration of response; MAIC: matching-adjusted indirect comparison

Table 9: Unadjusted and adjusted DOR model results

Model	HR for DOR	95% CI; p value	RMST (months) for DOR at 24.77 months	RMST difference (months) for DOR	Notes
Cox-naïve/ unadjusted	1.23	0.74–2.06; p=0.420	Futibatinib unadjusted: 10.25 Pemigatinib: 11.50	-1.24 (-4.26, 1.77); p=0.419	No covariate adjustment
Adjusted Cox MAIC model analyses					
Base-case covariates	1.17	0.69–1.97; p=0.557	Futibatinib adjusted: 10.75	-0.75 (-2.22, 0.82); p=0.333	Adjusted for age, gender, ECOG status, prior lines, prior surgery, baseline hypoalbuminemia status, TP53 alteration status
Sensitivity analysis	1.30	0.73–2.32; p=0.375	N/A	N/A	Base-case + race

Abbreviations: CI: confidence interval; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; N/A: not applicable; RMST: restricted mean survival time; TP53: tumour protein p53

HRQoL MAIC

The HRQoL MAIC was considered for this submission, however it was decided that this MAIC would result in negligible impact on the economic model results due to futibatinib and pemigatinib resulting in similar efficacy and safety profiles (as discussed throughout this submission and confirmed by UK clinical experts), and due to the two treatments having the same mode of administration.

Consequently, it was considered that a HRQoL MAIC would not provide any new information compared with the PFS and OS MAICs which are presented in the Submission document.

Adverse events

A 21. The AEs section in Document B is brief, with no report of the individual AEs that were not deemed treatment emergent or of special interest. The reader is directed to Appendix F for more information, but Appendix F is empty apart from a note that AE data are available in document B. A fuller list of all AEs is required for a full assessment of benefit and harm. Please provide a table of individual AEs that were not deemed treatment emergent or of special interest.

A summary of adverse events is provided in Table 10 and a summary of treatment-related adverse events is provided in Table 11.

Table 10. Summary of AEs by worst CTC grade, by system organ class and preferred term (safety population)

System Organ Class, Preferred Term	Total (N %)	≥Grade 3 (N %)
Patients with at least one AE	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]
Atrioventricular block first degree	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]
Palpitations	[redacted]	[redacted]
Sinus arrhythmia	[redacted]	[redacted]
Sinus bradycardia	[redacted]	[redacted]
Sinus tachycardia	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]
External ear inflammation	[redacted]	[redacted]
Hypoacusis	[redacted]	[redacted]
Tinnitus	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]
Basedow's disease	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Inappropriate antidiuretic hormone secretion	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]
Arcus lipoides	[redacted]	[redacted]
Blepharitis	[redacted]	[redacted]
Blepharospasm	[redacted]	[redacted]
Cataract	[redacted]	[redacted]
Cataract cortical	[redacted]	[redacted]
Cataract nuclear	[redacted]	[redacted]
Chorioretinopathy	[redacted]	[redacted]
Conjunctival hyperaemia	[redacted]	[redacted]
Conjunctivitis allergic	[redacted]	[redacted]
Detachment of retinal pigment epithelium	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]
Ectropion	[redacted]	[redacted]
Eye allergy	[redacted]	[redacted]
Eye discharge	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]
Eyelash thickening	[redacted]	[redacted]
Floppy eyelid syndrome	[redacted]	[redacted]

Foreign body sensation in eyes	[redacted]	[redacted]
Growth of eyelashes	[redacted]	[redacted]
Keratitis	[redacted]	[redacted]
Lacrimation increased	[redacted]	[redacted]
Maculopathy	[redacted]	[redacted]
Ocular discomfort	[redacted]	[redacted]
Ocular hyperaemia	[redacted]	[redacted]
Photokeratitis	[redacted]	[redacted]
Photophobia	[redacted]	[redacted]
Punctate keratitis	[redacted]	[redacted]
Serous retinal detachment	[redacted]	[redacted]
Subretinal fluid	[redacted]	[redacted]
Swelling of eyelid	[redacted]	[redacted]
Trichiasis	[redacted]	[redacted]
Trichomegaly	[redacted]	[redacted]
Ulcerative keratitis	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]
Visual impairment	[redacted]	[redacted]
Vitreous haemorrhage	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Abdominal discomfort	[redacted]	[redacted]
Abdominal distension	[redacted]	[redacted]
Abdominal mass	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Anal haemorrhage	[redacted]	[redacted]
Angular cheilitis	[redacted]	[redacted]
Ascites	[redacted]	[redacted]
Colitis	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]
Enterovesical fistula	[redacted]	[redacted]
Erosive duodenitis	[redacted]	[redacted]
Faeces discoloured	[redacted]	[redacted]
Faeces hard	[redacted]	[redacted]
Flatulence	[redacted]	[redacted]
Gastritis	[redacted]	[redacted]
Gastritis erosive	[redacted]	[redacted]
Gastrointestinal haemorrhage	[redacted]	[redacted]
Gastrointestinal pain	[redacted]	[redacted]
Gastrooesophageal reflux disease	[redacted]	[redacted]
Gingival pain	[redacted]	[redacted]
Gingival recession	[redacted]	[redacted]

Glossitis	[redacted]	[redacted]
Glossodynia	[redacted]	[redacted]
Haematemesis	[redacted]	[redacted]
Haematochezia	[redacted]	[redacted]
Haemorrhoids	[redacted]	[redacted]
Hyperchlorhydria	[redacted]	[redacted]
Hypoaesthesia oral	[redacted]	[redacted]
Impaired gastric emptying	[redacted]	[redacted]
Intestinal obstruction	[redacted]	[redacted]
Intra-abdominal haematoma	[redacted]	[redacted]
Large intestinal obstruction	[redacted]	[redacted]
Lower gastrointestinal haemorrhage	[redacted]	[redacted]
Melaena	[redacted]	[redacted]
Mouth ulceration	[redacted]	[redacted]
Mucous stools	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Oesophageal varices haemorrhage	[redacted]	[redacted]
Oesophagitis	[redacted]	[redacted]
Oral dysaesthesia	[redacted]	[redacted]
Oral pain	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]
Paraesthesia oral	[redacted]	[redacted]
Periodontal disease	[redacted]	[redacted]
Proctalgia	[redacted]	[redacted]
Rectal haemorrhage	[redacted]	[redacted]
Small intestinal obstruction	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Tongue ulceration	[redacted]	[redacted]
Toothache	[redacted]	[redacted]
Umbilical hernia	[redacted]	[redacted]
Upper gastrointestinal haemorrhage	[redacted]	[redacted]
Varices oesophageal	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Chest discomfort	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]
Chills	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Facial pain	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Gait disturbance	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]
Malaise	[redacted]	[redacted]
Mucosal inflammation	[redacted]	[redacted]
Non-cardiac chest pain	[redacted]	[redacted]

Oedema peripheral	[redacted]	[redacted]
Pain	[redacted]	[redacted]
Peripheral swelling	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Bile duct obstruction	[redacted]	[redacted]
Cholangitis	[redacted]	[redacted]
Hepatic pain	[redacted]	[redacted]
Hepatomegaly	[redacted]	[redacted]
Hyperbilirubinaemia	[redacted]	[redacted]
Immune system disorders	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]
Seasonal allergy	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Appendicitis	[redacted]	[redacted]
Asymptomatic bacteriuria	[redacted]	[redacted]
Bacteraemia	[redacted]	[redacted]
Biliary tract infection	[redacted]	[redacted]
Candida infection	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Chlamydial infection	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]
Corona virus infection	[redacted]	[redacted]
Cystitis	[redacted]	[redacted]
Cytomegalovirus oesophagitis	[redacted]	[redacted]
Device related infection	[redacted]	[redacted]
Ear infection	[redacted]	[redacted]
Endocarditis	[redacted]	[redacted]
Fungal skin infection	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
Gingivitis	[redacted]	[redacted]
Infection	[redacted]	[redacted]
Lung infection	[redacted]	[redacted]
Nail infection	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Oesophageal candidiasis	[redacted]	[redacted]
Oesophageal infection	[redacted]	[redacted]
Onychomycosis	[redacted]	[redacted]
Oral candidiasis	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]
Otitis externa	[redacted]	[redacted]
Otitis media	[redacted]	[redacted]
Paronychia	[redacted]	[redacted]
Peritonitis	[redacted]	[redacted]
Peritonitis bacterial	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]

Pneumonia	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]
Skin infection	[redacted]	[redacted]
Splenic abscess	[redacted]	[redacted]
Staphylococcal bacteraemia	[redacted]	[redacted]
Tooth abscess	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Vaginal infection	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]
Vulvitis	[redacted]	[redacted]
Vulvovaginal mycotic infection	[redacted]	[redacted]
Wound infection	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Arthropod bite	[redacted]	[redacted]
Concussion	[redacted]	[redacted]
Contusion	[redacted]	[redacted]
Fall	[redacted]	[redacted]
Femur fracture	[redacted]	[redacted]
Humerus fracture	[redacted]	[redacted]
Incisional hernia	[redacted]	[redacted]
Muscle strain	[redacted]	[redacted]
Overdose	[redacted]	[redacted]
Procedural pain	[redacted]	[redacted]
Rib fracture	[redacted]	[redacted]
Road traffic accident	[redacted]	[redacted]
Skin abrasion	[redacted]	[redacted]
Tibia fracture	[redacted]	[redacted]
Wound	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Activated partial thromboplastin time prolonged	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]
Blood bilirubin increased	[redacted]	[redacted]
Blood calcium increased	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Blood phosphorus increased	[redacted]	[redacted]
Blood sodium decreased	[redacted]	[redacted]
Cardiac murmur	[redacted]	[redacted]
Creatinine renal clearance decreased	[redacted]	[redacted]
Culture urine positive	[redacted]	[redacted]
Electrocardiogram QT prolonged	[redacted]	[redacted]

Gamma-glutamyltransferase increased	[redacted]	[redacted]
International normalised ratio increased	[redacted]	[redacted]
Intraocular pressure increased	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Thyroid function test abnormal	[redacted]	[redacted]
Troponin I increased	[redacted]	[redacted]
Troponin T increased	[redacted]	[redacted]
Troponin increased	[redacted]	[redacted]
Urine analysis abnormal	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
White blood cell count increased	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]
Hypercalcaemia	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]
Hyperphosphataemia	[redacted]	[redacted]
Hypoalbuminaemia	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]
Hypoglycaemia	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]
Lactic acidosis	[redacted]	[redacted]
Metabolic acidosis	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Arthritis	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Bone infarction	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]
Flank pain	[redacted]	[redacted]
Joint stiffness	[redacted]	[redacted]
Joint swelling	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]
Muscle twitching	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]
Musculoskeletal chest pain	[redacted]	[redacted]
Musculoskeletal discomfort	[redacted]	[redacted]

Musculoskeletal pain	[redacted]	[redacted]
Musculoskeletal stiffness	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Pain in jaw	[redacted]	[redacted]
Pathological fracture	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	[redacted]	[redacted]
Basal cell carcinoma	[redacted]	[redacted]
Cancer pain	[redacted]	[redacted]
Malignant ascites	[redacted]	[redacted]
Malignant pleural effusion	[redacted]	[redacted]
Metastases to central nervous system	[redacted]	[redacted]
Oncologic complication	[redacted]	[redacted]
Oral haemangioma	[redacted]	[redacted]
Skin papilloma	[redacted]	[redacted]
Tumour associated fever	[redacted]	[redacted]
Tumour pain	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Ageusia	[redacted]	[redacted]
Amnesia	[redacted]	[redacted]
Aphasia	[redacted]	[redacted]
Brain oedema	[redacted]	[redacted]
Burning sensation	[redacted]	[redacted]
Cauda equina syndrome	[redacted]	[redacted]
Clonus	[redacted]	[redacted]
Cognitive disorder	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Dysarthria	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]
Extrapyramidal disorder	[redacted]	[redacted]
Focal dyscognitive seizures	[redacted]	[redacted]
Guillain-Barre syndrome	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Hepatic encephalopathy	[redacted]	[redacted]
Hyperaesthesia	[redacted]	[redacted]
Hypoaesthesia	[redacted]	[redacted]
Intention tremor	[redacted]	[redacted]
Memory impairment	[redacted]	[redacted]
Migraine	[redacted]	[redacted]
Neuralgia	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]
Syncope	[redacted]	[redacted]

Taste disorder	[redacted]	[redacted]
Transient ischaemic attack	[redacted]	[redacted]
Tremor	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Abnormal dreams	[redacted]	[redacted]
Agitation	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]
Delirium	[redacted]	[redacted]
Depression	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Mood altered	[redacted]	[redacted]
Psychomotor retardation	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]
Bladder disorder	[redacted]	[redacted]
Chromaturia	[redacted]	[redacted]
Crystalluria	[redacted]	[redacted]
Dysuria	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]
Micturition urgency	[redacted]	[redacted]
Nephrolithiasis	[redacted]	[redacted]
Pollakiuria	[redacted]	[redacted]
Proteinuria	[redacted]	[redacted]
Renal injury	[redacted]	[redacted]
Urethral stenosis	[redacted]	[redacted]
Urinary retention	[redacted]	[redacted]
Urinary tract pain	[redacted]	[redacted]
Urine abnormality	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]
Breast discolouration	[redacted]	[redacted]
Erectile dysfunction	[redacted]	[redacted]
Menorrhagia	[redacted]	[redacted]
Menstruation irregular	[redacted]	[redacted]
Nipple pain	[redacted]	[redacted]
Pelvic pain	[redacted]	[redacted]
Vaginal discharge	[redacted]	[redacted]
Vaginal haemorrhage	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Catarrh	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Dysphonia	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]
Hiccups	[redacted]	[redacted]
Nasal congestion	[redacted]	[redacted]

Nasal dryness	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]
Pharyngeal inflammation	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Pneumothorax	[redacted]	[redacted]
Rhinitis allergic	[redacted]	[redacted]
Upper-airway cough syndrome	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]
Blister	[redacted]	[redacted]
Dermatitis	[redacted]	[redacted]
Dermatitis acneiform	[redacted]	[redacted]
Dermatitis bullous	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]
Erythema	[redacted]	[redacted]
Hair disorder	[redacted]	[redacted]
Hair texture abnormal	[redacted]	[redacted]
Hidradenitis	[redacted]	[redacted]
Hirsutism	[redacted]	[redacted]
Hyperkeratosis	[redacted]	[redacted]
Hypertrichosis	[redacted]	[redacted]
Keratosis pilaris	[redacted]	[redacted]
Madarosis	[redacted]	[redacted]
Nail discolouration	[redacted]	[redacted]
Nail disorder	[redacted]	[redacted]
Nail dystrophy	[redacted]	[redacted]
Nail hypertrophy	[redacted]	[redacted]
Nail pigmentation	[redacted]	[redacted]
Nail toxicity	[redacted]	[redacted]
Onychalgia	[redacted]	[redacted]
Onychoclasis	[redacted]	[redacted]
Onycholysis	[redacted]	[redacted]
Onychomadesis	[redacted]	[redacted]
Pain of skin	[redacted]	[redacted]
Palmar-plantar erythrodysaesthesia syndrome	[redacted]	[redacted]
Petechiae	[redacted]	[redacted]
Photosensitivity reaction	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Rash macular	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]
Rash papular	[redacted]	[redacted]
Skin discolouration	[redacted]	[redacted]
Skin disorder	[redacted]	[redacted]
Skin exfoliation	[redacted]	[redacted]
Skin fissures	[redacted]	[redacted]

Skin induration	[redacted]	[redacted]
Skin ulcer	[redacted]	[redacted]
Telangiectasia	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Arteriosclerosis	[redacted]	[redacted]
Haematoma	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Orthostatic hypotension	[redacted]	[redacted]
Peripheral ischaemia	[redacted]	[redacted]
Varicose vein	[redacted]	[redacted]

Abbreviations: AE; adverse event; CTC: common terminology criteria.

Table 11. Summary of treatment-related adverse events by worst CTC grade, system organ class and preferred term (safety population)

System Organ Class Preferred Term	Total (N %)	>=Grade 3 (N %)
Patients with at least one AE	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Atrioventricular block first degree	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]
Palpitations	[redacted]	[redacted]
Sinus arrhythmia	[redacted]	[redacted]
Sinus bradycardia	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]
Tinnitus	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]
Basedow's disease	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]
Arcus lipoides	[redacted]	[redacted]
Blepharitis	[redacted]	[redacted]
Cataract	[redacted]	[redacted]
Cataract cortical	[redacted]	[redacted]
Cataract nuclear	[redacted]	[redacted]
Chorioretinopathy	[redacted]	[redacted]
Conjunctival hyperaemia	[redacted]	[redacted]
Detachment of retinal pigment epithelium	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]
Eye discharge	[redacted]	[redacted]

Eye pain	[redacted]	[redacted]
Eyelash thickening	[redacted]	[redacted]
Foreign body sensation in eyes	[redacted]	[redacted]
Growth of eyelashes	[redacted]	[redacted]
Keratitis	[redacted]	[redacted]
Lacrimation increased	[redacted]	[redacted]
Maculopathy	[redacted]	[redacted]
Ocular discomfort	[redacted]	[redacted]
Ocular hyperaemia	[redacted]	[redacted]
Photokeratitis	[redacted]	[redacted]
Photophobia	[redacted]	[redacted]
Punctate keratitis	[redacted]	[redacted]
Serous retinal detachment	[redacted]	[redacted]
Subretinal fluid	[redacted]	[redacted]
Swelling of eyelid	[redacted]	[redacted]
Trichiasis	[redacted]	[redacted]
Trichomegaly	[redacted]	[redacted]
Ulcerative keratitis	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]
Visual impairment	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Abdominal distension	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Anal haemorrhage	[redacted]	[redacted]
Angular cheilitis	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Enterovesical fistula	[redacted]	[redacted]
Gastritis	[redacted]	[redacted]
Gastrointestinal pain	[redacted]	[redacted]
Gastrooesophageal reflux disease	[redacted]	[redacted]
Gingival recession	[redacted]	[redacted]
Glossitis	[redacted]	[redacted]
Haemorrhoids	[redacted]	[redacted]
Hypoaesthesia oral	[redacted]	[redacted]
Mouth ulceration	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Oesophagitis	[redacted]	[redacted]
Oral dysaesthesia	[redacted]	[redacted]
Oral pain	[redacted]	[redacted]
Paraesthesia oral	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]
Tongue ulceration	[redacted]	[redacted]

Upper gastrointestinal haemorrhage	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Chills	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Malaise	[redacted]	[redacted]
Mucosal inflammation	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Pain	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Cholangitis	[redacted]	[redacted]
Hyperbilirubinaemia	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Candida infection	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]
Infection	[redacted]	[redacted]
Oesophageal candidiasis	[redacted]	[redacted]
Onychomycosis	[redacted]	[redacted]
Otitis externa	[redacted]	[redacted]
Paronychia	[redacted]	[redacted]
Skin infection	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Skin abrasion	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Activated partial thromboplastin time prolonged	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]
Blood bilirubin increased	[redacted]	[redacted]
Blood creatine phosphokinase increased	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]
Blood phosphorus increased	[redacted]	[redacted]
Creatinine renal clearance decreased	[redacted]	[redacted]
Electrocardiogram QT prolonged	[redacted]	[redacted]
International normalised ratio increased	[redacted]	[redacted]
Intraocular pressure increased	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Thyroid function test abnormal	[redacted]	[redacted]
Troponin I increased	[redacted]	[redacted]

Troponin T increased	[redacted]	[redacted]
Troponin increased	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]
Hypercalcaemia	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]
Hyperphosphataemia	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]
Metabolic acidosis	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Arthritis	[redacted]	[redacted]
Bone infarction	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]
Musculoskeletal stiffness	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	[redacted]	[redacted]
Oral haemangioma	[redacted]	[redacted]
Skin papilloma	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Ageusia	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Hypoaesthesia	[redacted]	[redacted]
Memory impairment	[redacted]	[redacted]
Migraine	[redacted]	[redacted]
Neuralgia	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]
Peripheral sensory neuropathy	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]
Syncope	[redacted]	[redacted]
Taste disorder	[redacted]	[redacted]
Transient ischaemic attack	[redacted]	[redacted]

Tremor	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]
Depression	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Chromaturia	[redacted]	[redacted]
Crystalluria	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]
Nephrolithiasis	[redacted]	[redacted]
Urinary tract pain	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]
Erectile dysfunction	[redacted]	[redacted]
Menstruation irregular	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]
Nasal dryness	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]
Pharyngeal inflammation	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]
Blister	[redacted]	[redacted]
Dermatitis	[redacted]	[redacted]
Dermatitis acneiform	[redacted]	[redacted]
Dermatitis bullous	[redacted]	[redacted]
Dry skin	[redacted]	[redacted]
Hair disorder	[redacted]	[redacted]
Hair texture abnormal	[redacted]	[redacted]
Hyperkeratosis	[redacted]	[redacted]
Hypertrichosis	[redacted]	[redacted]
Keratosis pilaris	[redacted]	[redacted]
Madarosis	[redacted]	[redacted]
Nail discolouration	[redacted]	[redacted]
Nail disorder	[redacted]	[redacted]
Nail dystrophy	[redacted]	[redacted]
Nail hypertrophy	[redacted]	[redacted]
Nail pigmentation	[redacted]	[redacted]
Nail toxicity	[redacted]	[redacted]
Onychalgia	[redacted]	[redacted]
Onychoclasis	[redacted]	[redacted]
Onycholysis	[redacted]	[redacted]
Onychomadesis	[redacted]	[redacted]
Pain of skin	[redacted]	[redacted]
Palmar-plantar erythrodysaesthesia syndrome	[redacted]	[redacted]

Pruritus	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Skin disorder	[redacted]	[redacted]
Skin exfoliation	[redacted]	[redacted]
Skin fissures	[redacted]	[redacted]
Skin induration	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Orthostatic hypotension	[redacted]	[redacted]

Abbreviations: AE; adverse event; CTC: common terminology criteria.

A 22. The [redacted] deaths reported in the AEs section (p. 65 of the CS) are described as non-treatment related. However, no further information is given. Please provide more details of these deaths, including their assumed cause.

Of the [redacted] deaths due to AEs:

- [redacted]
- [redacted]

B: Clarification on cost-effectiveness data

Model structure

B.1. In the CS it is mentioned that the model submitted is in line with the model developed for TA722. However, according to Table 26 of the CS, the model in TA722 has five health states, whereas the current model has three. Please explain the main differences between the two models, the rationale for the changes and whether these are expected to have any impact on the cost effectiveness results.

The Company's model is a partitioned survival model (PSM) which considers health states based on PFS and OS outcomes, with patients moving between progression-free (PF), progressed disease (PD) and death states. The model in TA722 is also a PSM but incorporates time-on-treatment (ToT) outcomes in addition to PFS and OS, and therefore has two additional health states to account for patients being on- and off- treatment. In the original Company base case, ToT for futibatinib and pemigatinib was assumed to be equal to PFS, and thus these additional health states were not required. This assumption was required to ensure a fair comparison in the absence of publicly available Kaplan–Meier data for ToT for pemigatinib.

However, it should be noted that, whilst ToT was modelled independently of PFS in TA722, a structural restriction was included in the company model that ensured ToT could not exceed PFS for any modelled treatment arm, such that all patients discontinued treatment prior to or at the point of disease progression.[2] This was considered to be in line with UK clinical practice as well as the licence for pemigatinib. As such, these modelling approaches are functionally very similar.

The Company have added functionality permitting modelling of ToT independently of PFS as part of the response to Question B4, and therefore the two model structures are now functionally equivalent.

Clinical effectiveness parameters

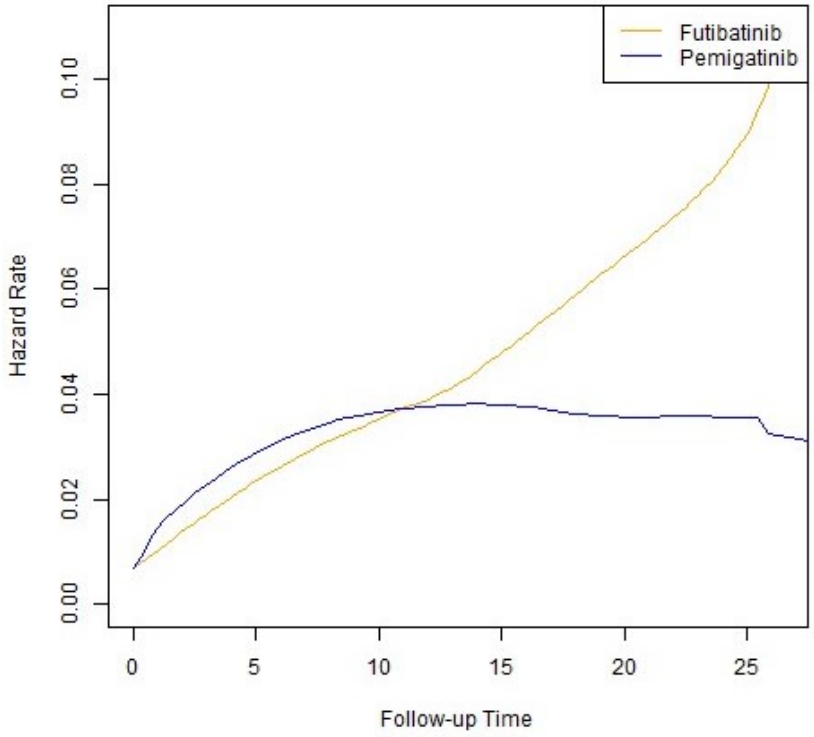
B.2. Priority question. Please answer the following questions regarding the proportional hazard (PH) assumption:

a) Please provide a plot of the hazard functions (over time) for both futibatinib and pemigatinib, and for both progression-free survival (PFS) and overall survival (OS).

The plots of the hazard functions (over time) for futibatinib and pemigatinib (observed data) for both progression-free survival (PFS) and overall survival (OS) observed data are provided below. Smoothed plots of the hazard function for futibatinib were generated using individual patient data from the FOENIX-CCA2 trial (29 May 2021 DCO). For pemigatinib, smoothed plots of the hazard function were created using pseudo-IPD generated from digitised Kaplan-Meier plot of pemigatinib observed PFS and OS. The default settings of the muhaz function from the muhaz R package were used to generate these plots. These plots demonstrate that hazard rates for futibatinib and pemigatinib were similar up to ~10 months of follow-up; the tail ends of both curves should be interpreted with caution, given the low numbers of patients at risk at later timepoints.

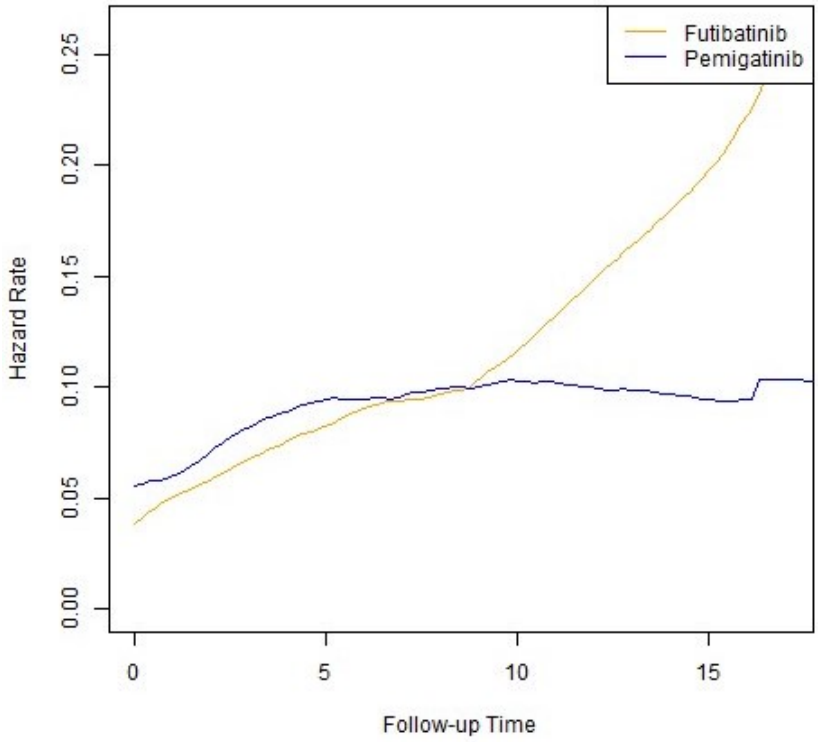
In addition, the cost-effectiveness model has been updated to include plots displaying the instantaneous hazard rates corresponding to the selected extrapolation for both futibatinib and pemigatinib PFS and OS. The hazard rates associated with selected extrapolations match well to the hazard functions for the observed data, particularly up to ~10 months of follow-up. Whilst there is some deviation between the smoothed hazards for futibatinib observed data and extrapolated data in the long term, this is not unexpected; as discussed in Section B.3.3.2 and B.3.3.3 of the Company submission, the Lognormal models were selected as the base case extrapolation for both OS and PFS despite marginally poorer statistical fit (differences between AIC and BIC values were not substantial), given these curves were ranked highest in terms of clinically plausibility by clinical experts.

Figure 4: Instantaneous hazard over time of futibatinib and pemigatinib observed OS



Abbreviations: OS: overall survival.

Figure 5: Instantaneous hazard over time of futibatinib and pemigatinib observed PFS



Abbreviations: PFS: progress-free survival.

b) Based on the hazard functions, please provide a plot of the hazard ratio (over time) for both PFS and OS.

The Company have updated the cost-effectiveness model has been updated to present a plot displaying the hazard ratio (HR) over time for both PFS and OS based on the selected extrapolations on the 'Survival' tab. Given the different trial follow-up periods between the two arms, the Company find it more appropriate to present the HR over time based on selected extrapolations, as opposed to generating a HR over time from IPD/pseudo IPD.

As expected, in the original Company base case these plots display a constant HR over time, given PFS and OS for pemigatinib were derived by applying the inverse of the PFS and OS HRs for futibatinib versus pemigatinib in the base-case MAIC to the futibatinib extrapolations.

c) Please clarify how the log-cumulative hazards (e.g., Figure 18) were estimated i.e., were they based on individual participant data (IPD) or pseudo-IPD data, or was it based on a Cox model (which assumes PH) as in the MAIC?

The analyses were based on the IPD from FOENIX-CCA2 (for futibatinib) and reconstructed pseudo-IPD from FIGHT-202 (for pemigatinib) using the Guyot et al. method, in line with the MAIC methods described in the Submission document.

d) Despite the Schoenfeld tests reporting non-significant p-values, the log-cumulative hazard plots cross at several time points. This would suggest a violation of the PH assumption, which might also be supported by the plot of

the HR over time requested above. In any case, please include in the model the option of modelling PFS and OS for both futibatinib and pemigatinib *independently*, as an alternative to the current approach which assumes PH and uses a HR to estimate the survival curves for pemigatinib.

The use of HRs to estimate survival curves for pemigatinib is considered appropriate, given the Schoenfeld residual plot showed no evidence of the PH assumption being violated and the Schoenfield test reported a non-significant p-values for both PFS and OS. The log-cumulative hazard plots for PFS and OS showed that the futibatinib and pemigatinib curves largely ran parallel to each other, with one instance of crossing at 30 months for PFS. As mentioned in the submission this must be interpreted with caution given the low numbers of patients at risk at this time point.

However, for completeness, the option to model PFS and OS for pemigatinib independently using unadjusted data from the FIGHT-202 trial has been included in the model. This can be implemented by selecting 'Independent parameterisations' from the drop-down in cell E56 of the 'Settings' tab. When this option is selected, PFS and OS for pemigatinib in the model are informed by parametric models based on pseudo-IPD derived from digitised FIGHT-202 trial Kaplan–Meier data.

In line with the approach described in the Company submission for futibatinib, the selection of the most appropriate extrapolation for pemigatinib PFS and OS was informed by the recommendations of NICE DSU TSD 14.[28] Specifically, goodness-of-fit statistics were calculated and assessed to understand which parametric form had the best statistical fit to the Kaplan Meier data, assessment of visual fit was conducted, and clinical expert opinion was sought regarding the plausibility of the long-term extrapolations of each function.[7] The explored extrapolations included log-logistic, lognormal, exponential, Weibull, Gompertz and generalised gamma.

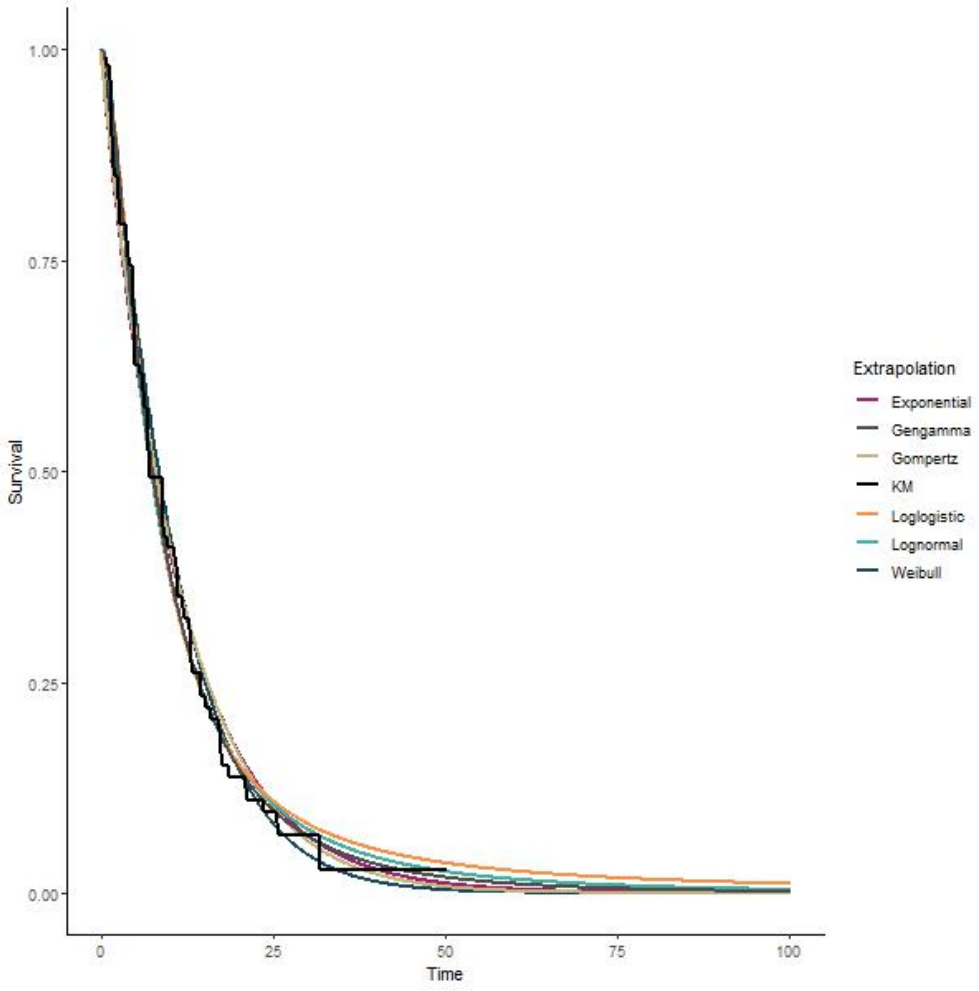
The Generalised gamma and Log-logistic models were selected as the preferred models for PFS and OS, respectively, given they were considered the most plausible by clinical experts, and showed good statistical and visual fit to the Kaplan–Meier data.

Table 12: Model fit statistics for PFS parametric survival functions for pemigatinib

Function	PFS			
	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	602.78	5	605.46	4
Weibull	601.07	4	606.44	5
Gompertz	604.59	6	609.96	6
Lognormal	594.95	1	600.31	1
Log-logistic	597.95	3	603.32	2
Generalised gamma	596.62	2	604.67	3

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

Figure 6: Pemigatinib PFS parametric survival function extrapolations



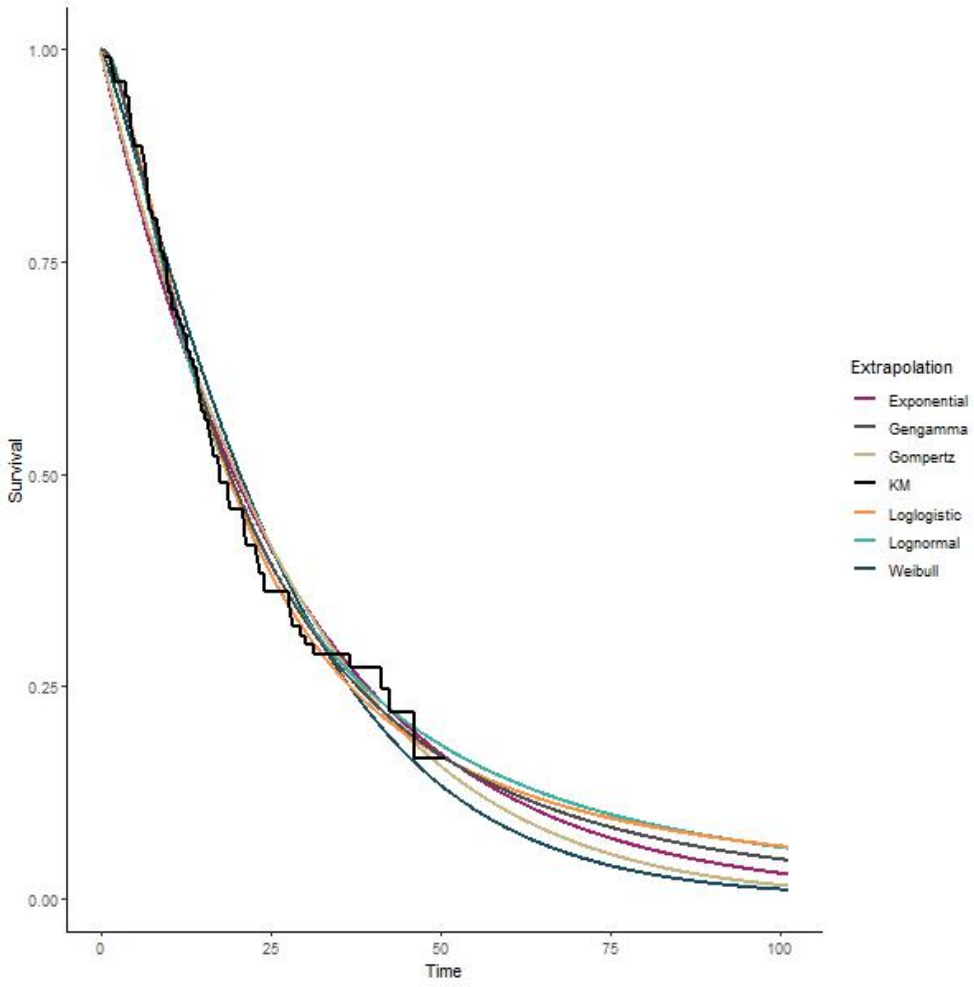
Abbreviations: KM: Kaplan-Meier; PFS: progression-free survival.

Table 13: Model fit statistics for OS parametric survival functions for pemigatinib

Function	OS			
	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	652.98	5	655.66	3
Weibull	651.72	4	657.09	5
Gompertz	654.77	6	660.14	6
Lognormal	647.15	2	652.51	2
Log-logistic	646.10	1	651.47	1
Generalised gamma	648.81	3	656.85	4

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Figure 7: Pemigatinib OS parametric survival function extrapolations



Abbreviations: KM: Kaplan-Meier; OS: overall-free survival

A scenario analysis exploring independent extrapolations for futibatinib and pemigatinib has been explored (see Appendix B).

To ensure a fair comparison, in this scenario, futibatinib PFS and OS are based on MAIC-adjusted FOENIX-CCA2 data (matched to the FIGHT-202 trial), as per the response to Question C2. This scenario has limited impact on cost-effectiveness results, with futibatinib remaining dominant at list price.

B.3. Regarding the parametric models for PFS and OS, clinical experts also provided feedback on the survival extrapolation predictions of the pemigatinib data and ranking of the extrapolation curves, based on report of the UK HTA advisory board meeting (held on 22nd May 2023). Please explain if and how the clinical feedback on pemigatinib extrapolations was considered when selecting the most appropriate model fit for both curves, or

if it was only based on futibatinib feedback as it is currently unclear in sections B.3.3.2 and B.3.3.3 of the CS.

Selection of the survival extrapolation curves was performed solely based on the clinical feedback for futibatinib. This was considered appropriate due to the model approach of applying HRs to the futibatinib parametric extrapolations to obtain PFS and OS predictions for pemigatinib and the consistent feedback from clinicians stated that the survival profile for the two treatments would be very similar.

Treatment discontinuation and effect waning

B.4. Priority question. In the base case analysis, the company assumed that time on treatment (ToT) is equal to PFS for both treatments. However, there seems to be no option in the model to use ToT data. Please include this option in the model. This should be at least possible for futibatinib. Please provide also a comparison of PFS and ToT curves (plot and area under the curve).

In the original Company base case, ToT for futibatinib and pemigatinib was assumed to be equal to PFS. This assumption was required to ensure a fair comparison in the absence of publicly available Kaplan–Meier data for ToT for pemigatinib. As described in Section B.3.3.4 of the Company submission, this assumption is aligned with the data from the FOENIX-CCA2 trial, where the median PFS for futibatinib was 8.9 months, compared to a median duration of treatment of 9.07 months. Similarly, the median PFS for pemigatinib for the DCO reported in TA722 (6.9 months) was aligned with the median duration of treatment in the safety population of 7.2 months (219 days) reported in TA722. Furthermore, the assumption that ToT is equal to the PFS was validated by UK clinical experts in CCA.

However, it should be noted that, whilst ToT was modelled independently of PFS in TA722, a structural restriction was included in the company model that ensured ToT could not exceed PFS for any modelled treatment arm, such that all patients discontinued treatment prior to or at the point of disease progression.[2] This was considered to be in line with UK clinical practice as well as the licence for pemigatinib. As such, these modelling approaches are functionally very similar.

However, for completeness, the Company have added functionality permitting modelling of ToT independently of PFS. In line with the approach described in the Company submission for OS and PFS, futibatinib ToT was modelled via extrapolation of the unadjusted individual patient data from the FOENIX-CCA2 trial (29 May 2021 DCO). The selection of the most appropriate extrapolation for futibatinib ToT was informed by the recommendations of NICE DSU TSD 14.[28] The explored extrapolations included log-logistic, lognormal, exponential, Weibull, Gompertz and generalised gamma. The Weibull model was selected for the base case, given it had the best fit according to both AIC and BIC, and good visual fit to the observed Kaplan–Meier data.

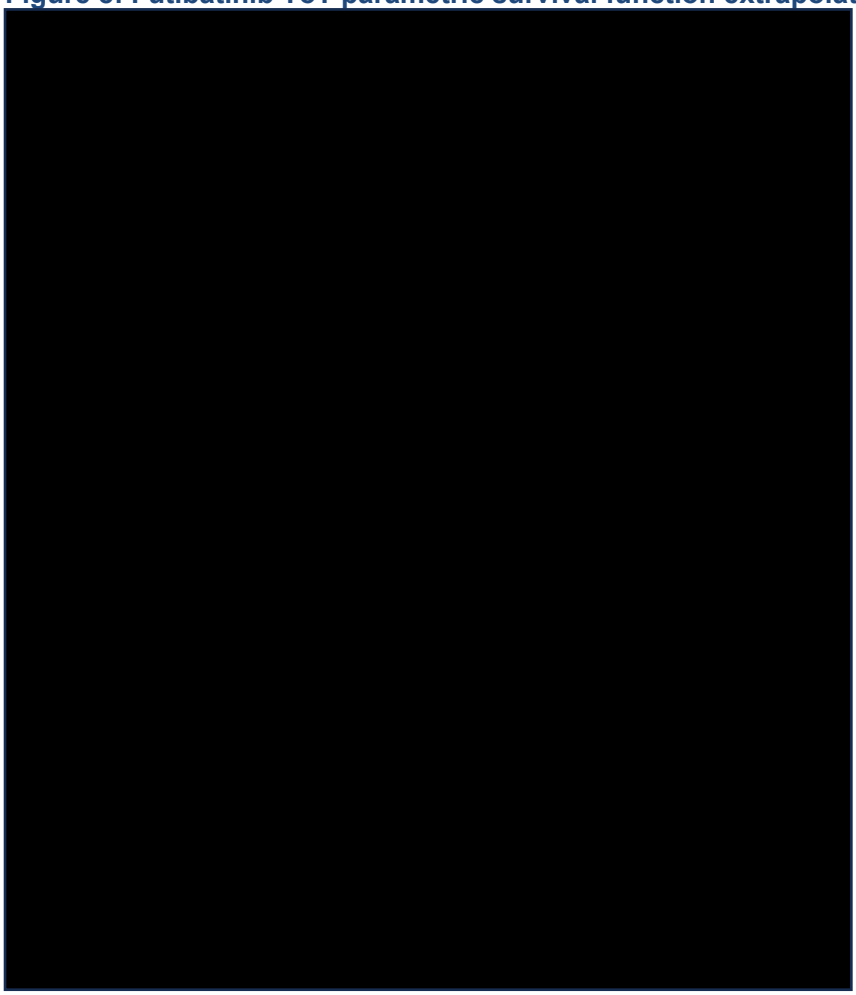
Table 14: Model fit statistics for ToT parametric survival functions for futibatinib

Function	ToT			
	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	695.32	6	697.96	6
Weibull	669.85	1	675.11	1

Gompertz	669.97	2	675.24	2
Lognormal	691.98	5	697.25	5
Log-logistic	689.10	4	694.37	4
Generalised gamma	670.35	3	678.25	3

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

Figure 8: Futibatinib ToT parametric survival function extrapolations



Abbreviations: KM: Kaplan-Meier; ToT: time on treatment.

Kaplan–Meier data for pemigatinib ToT are not publicly available, and thus an assumption is required to inform pemigatinib ToT when modelling independently of PFS. Pemigatinib ToT was modelled by applying the inverse of the base-case MAIC PFS HR (1.07) for futibatinib versus pemigatinib – i.e. a HR of 0.93 – to the futibatinib ToT extrapolation to derive a corresponding ToT extrapolation for pemigatinib. This was considered reasonable, given that any delays between disease progression and time to treatment discontinuation due to practical reasons would apply to both futibatinib and pemigatinib equally.

The results of the scenario analyses exploring modelling ToT for futibatinib and pemigatinib independently of PFS are presented in Appendix B, both excluding and including restrictions to ensure ToT could not exceed PFS (in line with the approach taken in TA722). Both scenarios have limited impact on cost-effectiveness results, with futibatinib remaining dominant at list price.

B.5. Priority question. Please present the results of a scenario in which when ToT = 0 (i.e., all patients have progressed or stopped due to toxicity, or died) there is no more treatment effect on OS. The current approach of assuming an HR for OS implies that there is still a benefit being modelled beyond the point where no more patients receive treatment. Please conduct other scenario analyses that are considered relevant to test the assumption of treatment effect waning.

The Company agree that no benefit between futibatinib and pemigatinib is expected beyond the point where no more patients are receiving treatment. Therefore, the model has been updated such that the hazard rates for OS and PFS for pemigatinib are set equal to those of futibitinib after a selected timepoint.

In the revised base case, this timepoint is set to 24 months, at which only ~11% and ~12% of patients on futibatinib and pemigatinib, respectively, were on-treatment (based on the PFS curve, which informs ToT in the base case). The introduction of this change has limited impact on cost-effectiveness results, as reported in Appendix B, with futibatinib remaining dominant at list price.

Adverse events

B.6. Besides the AEs reported in this submission, the TA722 submission also reported the following AEs: alanine aminotransferase increased, anaemia, anorexia, biliary event, cholangitis, decreased serum albumin level, palmar-plantar erythrodysesthesia syndrome and thromboembolic events (Table 45, page 107 of the committee papers dated May 5, 2021). Please clarify the discrepancy in AEs between the current submission and TA722.

Adverse events (AEs) were only included in the economic model if they were Grade 3 or above and occurred in >5% of patients in either the FOENIX-CCA2 trial or the FIGHT-202 trial, since these are the adverse events that are likely to be associated with meaningful decrements in health-related quality of life (HRQoL) or additional costs. AE incidences reported in Vogel et al. (2022) were used for pemigatinib, as this is the latest data cut from the FIGHT-202 trial (May 2021). Grade 2+ hyperphosphataemia was additionally included, given the high proportion of patients experiencing hyperphosphataemia in the FOENIX-CCA2 trial. Hypophosphataemia was listed in the model, however the incidence was set to 0% for futibatinib and pemigatinib, as this adverse event was not reported in the latest data cut of FIGHT-202 (Vogel et al. [2022]) or the FOENIX-CCA2 trial.

The adverse events listed above and included in TA722 did not meet the necessary criteria for either the FOENIX-CCA2 trial or the FIGHT-202 trial or were not reported in the latest data cut for FIGHT-202 (Vogel et al., [2022]) and as such were not included in the model. It should be noted that by using incidences reported in Vogel et al. (2022), some relevant adverse events for pemigatinib may have been excluded. For example, Abou-Alfa et al. (2020), which reports data from the October 2020 data cut of FIGHT-202 reported that grade 3 hypophosphatemia occurred in 6.8% of patients. However, to avoid using different data cuts to inform AE incidences, only

those reported in Vogel et al. (2022) have been included. This is considered a conservative assumption, as relevant adverse events associated with pemigatinib have potentially been excluded.

Health-related quality of life

B.7. Priority question. On page 91 of the CS, it is mentioned that EQ-5D-3L outcomes were collected in the FOENIX-CCA2 trial, and therefore no mapping was required. However, it is not mentioned if the utilities used in the model were derived using the UK tariff. Please clarify that this was the case; otherwise please adjust the utilities in the model using the UK tariff.

The company can confirm that the utility values from the FOENIX-CCA2 trial were derived using the UK tariff.[29]

B.8. Please discuss the (face) validity of the EQ-5D values presented in Table 37 (e.g., compare the values presented in this submission with other sources of utilities for this or similar diseases – e.g., studies retrieved by the SLR, and with the utility values for the general population). Regarding the progressive disease (PD) utility value in Table 37 of the CS, it is mentioned that, based on clinical feedback, the PD utility value derived from FOENIX-CCA2 was slightly higher than expected. It was further noted that to address this uncertainty, this was explored as part of scenario analyses (page 93). Please clarify what scenario analysis was included to address the uncertainty around this parameter.

The Company apologise for this typographical error. The Company maintain that the utility values derived from the EQ-5D-3L data from the FOENIX-CCA2 trial are the most appropriate, given this trial is the most relevant source of information for the population of interest to this submission. Alternative utilities values were not explored in the scenario analyses given the paucity of suitable alternative utilities in the published literature.

The utility values from FIGHT-202 used in TA722 are redacted, and the only study reporting utility values for patients with CCA identified in the HRQoL SLR was Lamarca *et al.* (2022).[30] This publication, which did not specifically include a population of patients with FGFR2 fusions or rearrangements, reported utility values for patients receiving either mFOLFOX or ASC at either Baseline or Month 4. As utility values reported at single timepoints, these are not suitable to inform the economic model, while more broadly, based on the patient population and treatments received, this study is poorly generalisable to the decision problem of relevance to this appraisal. Therefore, this is no rationale to explore the use of the utility values from Lamarca et al. (2022) in the economic model in place of the directly relevant utility values from FOENIX-CCA2.

The model considers a patient population with a starting age of 55.7 years. Male and female patients 56 years of age in the general population report utility values of 0.8394 and 0.8627,

respectively, according to the HSE 2014 dataset. Therefore, the progression-free health state utility value of [redacted] derived from FOENIX-CCA2 appears to be clinically plausible compared to these – and UK clinical experts confirmed that this PF health state utility appeared clinically plausible.

UK clinical experts did explain that the PD utility value from FOENIX-CCA2 was slightly higher than expected – hypothesising that this may be the result of most assessments of HRQoL being completed early following disease progression, with highly symptomatic patients not completing the questionnaire regularly following disease progression. Indeed, this is a common limitation of clinical trials in oncology, whereby patients may regularly complete HRQoL questionnaires whilst on treatment, but patients receive more limited follow-up and do not regularly complete HRQoL questionnaires following disease progression and treatment discontinuation.

However, in this submission, the PD utility value is associated with minimal uncertainty, because, as previously detailed, both PFS and OS are extremely similar between futibatinib and pemigatinib, with no statistically significant differences between the two treatments. Therefore, the time spent in both the PFS and PD health states is extremely similar regardless of the initial treatment received, and therefore the specific utility value applied to each health state is associated with a limited amount of uncertainty, as the same utility value is applied to both treatments.

To explore any uncertainty surrounding the utility values used in the base case economic analysis, the deterministic sensitivity analysis (DSA), where all parameters for which there were single input values were varied in the model by ±20% of their mean value, has been updated to include the PF utility and PD utility decrement. As shown in Appendix B, the DSA shows that the utility values have very limited influence on cost-effectiveness results.

Varying the PF and PD utilities by ±20% results in a change to the INHB of [redacted] and [redacted], respectively.

Resource use and costs

B.9. Priority question. Please use ToT instead of PFS to estimate total drug acquisition costs for both treatment arms in the model. In TA722, the company considered PFS with or without treatment as separate health states, using ToT data to estimate acquisition costs. We know that in that case, PFS ≥ ToT. Therefore, using PFS to inform ToT could overestimate pemigatinib acquisition costs, which could have a major impact on the model results.

In the original Company base case, ToT for futibatinib and pemigatinib was assumed to be equal to PFS. This assumption was required to ensure a fair comparison in the absence of publicly available Kaplan–Meier data for ToT for pemigatinib. As discussed in response to question B4, for completeness, the Company have added functionality permitting modelling of ToT independently of PFS.

Scenario analyses exploring modelling ToT for futibatinib and pemigatinib independently of PFS have been explored (see Appendix B), whereby ToT informed acquisition costs, and have limited impact on cost-effectiveness results with futibatinib remaining dominant at list price.

B.10.Priority question. In the base-case analysis, drug wastage was included by assuming that half a pack of futibatinib or pemigatinib is wasted per patient. This was justified on the assumption that, on average, patients discontinue treatment halfway through a pack, which was validated by UK clinical experts. Please explain why patients would discontinue treatment halfway through a pack. Would this be attributed to toxicity or disease progression? Please provide more details on how this has been implemented in the model (e.g. is it assumed for every cycle?). In the economic model, when excluding the drug wastage from the computations, the total acquisition costs for both futibatinib and pemigatinib increase, which seems counterintuitive. Please explain if this a modelling error. Alternatively, please provide an explanation for these results. Please also explain the implications of assuming patients would discontinue treatment halfway through a pack while at the same time ToT was assumed to be equal to PFS.

The model assumes that patients may discontinue treatment upon either toxicity or disease progression at any point during a model cycle, and so may not incur costs for a full treatment cycle (note, 3 packs are required per treatment cycle). In the economic model, it is therefore assumed that patients would on average discontinue treatment halfway through a treatment cycle (3 weeks), which was validated by UK clinical experts.[7] This is assumed for every cycle in the model.

As discussed in response to question B4, the Company have added functionality permitting modelling of ToT independently of PFS; the assumption of drug wastage is independent of the selected outcome used to inform ToT.

In the economic model, the counterintuitive results for treatment costs were the result of the wastage options being incorrectly switched. The Company apologises for this error and this has now been corrected in the provided economic model, with updated base-case results provided in Appendix B.

B.11.Please add the codes used to inform the unit costs in Table 40 of the CS.

The codes used to inform the resource use unit costs are detailed in Table 15.

Table 15: Resource use unit costs

Resource	Unit cost, £	Source
Clinical examination	221.48	NHS reference costs 2021/22: WF01A, Consultant led, medical oncology, non-admitted face-to-face attendance, follow-up

CT scan	181.82	NHS reference costs 2021/22: RD22Z, Outpatient Imaging; Computerized Tomography Scan of One Area, with Pre- and Post-Contrast
OCT (retinal scan)	158.18	NHS reference costs 2021/22: BZ88A, Outpatient procedures, Retinal Tomography 19 years and over
Blood test	2.96	NHS reference costs 2021/22: DAPS05, Haematology
Pain medication	0.46	eMIT, 2022/23 (30mg/1ml solution for injection, pack of 10). Dose: BNF, 2023 (30mg dose daily for opioid-naïve patients in palliative care)

Abbreviations: BNF: British National Formulary; CT: computed tomography; eMIT: electronic market information tool; NHS: National Health Service; OCT: optical coherence tomography.

Cost-effectiveness results

B.12. Priority question. On page 106 of the CS, it is stated that the probability of futibatinib being cost-effective to be [redacted]% and [redacted]% at a willingness-to-pay (WTP) threshold of £20,000 and £30,000 per quality-adjusted life year (QALY), respectively. However, these results do not match with the results presented neither in Figure 27 (i.e. cost effectiveness (CE) plane in which it is clear that at a WTP of £30,000 per QALY not [redacted]% of the simulations would remain below the threshold) nor with the results presented in Figure 28. As these results are derived from the economic model, please correct any potential errors and update the results accordingly.

The Company apologies for this error in the economic model; the formulae in columns AY and AZ of the 'PSA iterations tab' have been updated such that the of probability of futibatinib being cost-effective is based on INHB, and the results in the model now show that futibatinib is cost-effective in [redacted]% of simulations at a WTP threshold of £20,000 and [redacted]% of simulations at a WTP threshold of £30,000 (based on the revised base case).

B.13. Please provide a plot of the Markov traces obtained in the base-case and discuss their validity.

The updated economic model includes plots of health state membership over time in the 'Results' tab. The external validity of PFS and OS extrapolations for futibatinib and pemigatinib, which inform health state occupancy, has been discussed previously in detail in Sections B.3.3.2 and B.3.3.3 in the Company submission.

B.14. Please clarify why scenario analysis 1 (cost comparison) is not equivalent to the scenario analysis where the HR = 1 for both PFS and OS (see Table 51 in the CS – note there is a typo in the number of scenarios; after 11 it goes to 8 again).

In the cost comparison scenario the rate of adverse events is set equal for both treatments, in addition to the PFS and OS being equivalent (i.e. HR=1). The aim of this scenario is to ensure that there are no differences in health benefits between futibatinib and pemigatinib, and that only differences in costs are considered. In the scenario where the HR is set to 1 for PFS and OS, the rate of adverse events is different between the two treatments, and as such the disutilities applied for each treatment are different.

Validation

B.15.Priority question. Please provide details about what validation efforts were performed in Section B.3.14 of the company submission and the results of these validation efforts (currently details about input data and model outcomes validation seem to be missing). This could be presented for example (but not necessarily) with the help of the validation tool AdViSHE (https://advishe.wordpress.com/author/advishe/). Regarding validation of the model outcomes, please present a comparison between the results of the pemigatinib arm and those in TA722 and the other studies presented in Table 26 of the CS, wherever possible. Black-box tests to detect modelling errors were conducted using the TECH-VER tool, as mentioned on page 112 of the CS. Please provide the results of these tests.

A comparison of the total QALYs and life years reported for pemigatinib in TA722 and other studies presented in the original company submission are presented in Table 16. This shows that the pemigatinib results from the model are closely aligned to those reported in TA722 and the previous CADTH submission, providing validation of the model outcomes. The lower total QALY and LY results reported by Chen et al (2023) is assumed to be due to the model using a shorter 5-year time horizon.

Table 16. Total QALY and LY results for pemigatinib from TA722 and previous studies

Source	Total QALY	Total LYG
Company submission	[redacted]	2.25
TA722[2]	NR	2.44
Chen, 2023[23]	1.15	1.61
CADTH, 2022[31]	1.65	2.56

Abbreviations: LYG: life-year gained; QALY: quality-adjusted life years

As reported in Section B.3.14.1 of the Company submission, the correct functioning of the sensitivity and scenario analyses was also reviewed, and two checklists (for technical and stress test checks), based on the published TECH-VER checklist,[32] were completed to ensure that the model generated accurate results which were consistent with input data and robust to extreme values. The results of these checklists are reported in Table 17 below.

Table 17. Results of internal validation checklist

Test	Expected effect	Observed effect
Set initial number of patients to 0.	Costs and QALYs across all treatments should be 0.	As expected
Set initial number of patients to 1.	ICER should not change.	As expected
Set both treatment and comparator to same intervention.	Costs and QALYs across all treatments should be equal.	As expected
Set all efficacy data equal across treatments, and set disutility associated with adverse events to 0.	QALYs across all treatments should be equal.	As expected
Set mortality rate to 0% at all ages (and any other mortality in the model)	There are no deaths in the model.	As expected
Set mortality rate to 100% at all ages	All patients are dead in the first cycle.	As expected
Increase mortality rate	Costs are reduced.	As expected
Set the health state utilities the same for all states (if applicable, set AE disutilities to 0)	Life years to QALY ratio should be the same across all treatments.	As expected
Set disutility of adverse events to 0 (remove AE disutilities)	Overall QALYs should increase. QALYs of adverse events = 0. QALYs of health states should not change. Costs should not change.	As expected
Set the utilities for all health states to 0 and adverse events to 0	All QALYS = 0. Costs should not change.	As expected
Set the utilities for all health states to 1 and adverse events to 0	No difference between LYs and QALYs for each treatment arm. Costs should not change.	As expected
Halve all utilities and disutilities	ICERs should double.	As expected
Set the cost and utility consequences for adverse events and discontinuation to 0, then undo these changes and set all adverse event rates to 0	Results in both cases are the same. Costs and QALYs associated with AEs are 0.	As expected
Set adverse event and discontinuation rates to 0, then undo these changes and set adverse and discontinuation rates to a high level	The first scenario should result in lower costs (AE costs = 0) and greater QALYs (AE disutilities = 0) than the second. Other disaggregated results should not change.	As expected
Set (per-cycle) treatment discontinuation to 0%, then set to 100%	The first scenario should result in no patients staying on treatment after the first cycle, the second scenario should result in all patients remaining on treatment for the entire time horizon.	As expected

Decrease the utilities for all health states simultaneously whilst keeping event-based utility decrements constant	QALYs of health states are reduced. LYs and costs should not change.	As expected
Set all health state utilities <0 (i.e. negative)	QALYs decrease over time.	As expected
Set equal the effectiveness, utility and safety-related model inputs for all treatment options	No difference between LYs and QALYs for each treatment arm, at any given time.	As expected
Set the costs of treatments to 0	All treatments costs = 0. LYs, QALYs and other disaggregated cost results (excepted for subsequent treatment costs) should not change. Subsequent treatment costs should be lower.	As expected
Double the costs of treatments	Treatment costs doubled. LYs, QALYs and other disaggregated cost results (excepted for subsequent treatment costs) should not change. Subsequent treatment costs should be higher.	As expected
Set relative dose intensity of treatments to 0	Drug acquisition costs should be 0.	As expected
Set all administration costs to 0	All administration costs = 0. LYs, QALYs and other disaggregated cost results (except for subsequent treatment costs) should not change. Subsequent treatment costs should be lower.	As expected
Double all administration costs	Administration costs doubled. LYs, QALYs and other disaggregated cost results (except for subsequent treatment costs) should not change. Subsequent treatment costs should be higher.	As expected
Set all end of life costs to 0	End of life costs = 0. Other disaggregated cost results, LYs and QALYs should not change.	As expected
Double all end of life costs.	End of life costs doubled. Other disaggregated cost results, LYs and QALYs should not change.	As expected
Alter the time horizon	Total costs and QALYS increase/decrease in accordance with longer/shorter horizons.	As expected
Increase average patient age	LYs and QALYs decrease	As expected
Increase the OR/RR/HR baseline probabilities.	The probabilities of events derived from OR/RR/HR baselines probabilities should increase.	As expected
Set discount rates to 100%	Costs and QALYs reduce significantly.	As expected
Increase inflation rates	Any cost inputs relying on inflation should increase.	As expected
Run the DSA/OWSA and check all input parameters affect results when values are changed	Any input parameters should affect the incremental QALYS, costs or both (unless it has an exactly equal effect on all arms in the model). Investigate parameters that do not change the ICER (or incremental costs/QALYs) from baseline. Cost	As expected

	parameters should only impact incremental costs. Utility parameters should only impact incremental QALYs. Efficacy parameters likely impact costs and QALYs.	
Open model base case, check results. Reset input base case, check results	Results should not change after resetting inputs.	As expected
Record base case results. Change any inputs from default values, then reset inputs	Inputs should be reset to default values and results should restore to original value.	As expected
Check plots of OS/PFS extrapolations and KM curves (only relevant for PSMs)	All extrapolation curves (of both intervention and comparators) should be presented in plots. Extrapolations should be smooth curves.	As expected
Change the curve choice selected for OS/PFS for each treatment (only relevant for PSMs)	The graph which shows the selected extrapolation should change when curve choice changes.	As expected
Change OS curve choice for each treatment (only relevant for PSMs)	LYs and QALYs should change, but only for the “PD” health state and Total. Only results for the respective treatment should change unless HRs are used to derive other treatments (in which case those results should also change).	As expected
Change PFS curve choice for each treatment (only relevant for PSMs)	Total LYs should not change (but distribution between the PF and PD health state should change). Overall and disaggregated QALYs can change. Only results for the respective treatment should change unless HRs are used to derive other treatments (in which case those results should also change).	As expected
Compare survival curves and the respective results of the treatments	Treatments with higher OS curves on the OS graph should have more LYs and likely more QALYs, and vice versa.	As expected

Abbreviations: AE: adverse events; DSA: deterministic sensitivity analysis; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; LY: life years; OR: odds ratio; OS: overall survival; OWSA: one-way sensitivity analysis; PFS: progression-free survival; PSM: partitioned survival models; QALY: quality-adjusted life year; RR: relative risk; ToT: time on treatment

B.16.Priority question. Despite the validation efforts conducted, the External Assessment Group (EAG) has found several errors in the model. These can be found under "Economic model" below. Please correct them and provide an updated version of the model. If correcting these errors (or any other errors identified by the company) led to changes on the cost-effectiveness results, please report these too (together with a full list of amendments made to the model).

The Company has addressed the errors as per the responses to questions B10 and B18 in the updated economic model. The corrections as per question B18 have resulted in no changes to the economic model base-case. Updates to the model base-case as per the correction of the error in question B10 is reported in Appendix B, and have no material impact on cost-effectiveness results, with futibatinib remaining dominant at list price.

B.17.The expert rankings of futibatinib PFS survival curves in Table 31 and OS in Table 33 do not seem to be in line with the presented evidence. For example, even if the numbers at risk are low after months 15 for PFS, which could indicate uncertainty around the long-term extrapolations, the experts have selected as preferred extrapolations those providing the highest long-term survival probabilities. However, these choices are hard to justify based on goodness of fit to the data. Please clarify why the experts have chosen extrapolations which seem to poorly fit the observed data. Please also provide objective evidence to confirm model predictions.

As outlined in NICE TSD 14, statistical fit to the observed KM data is one of a number of factors which should be used to inform the selection of the most appropriate extrapolations to include in a cost-effectiveness model. Indeed, NICE TSD 14 states that:

"Statistical tests can be used to compare alternative models and their relative fit to the observed trial data. This is important, particularly when there is only a small amount of censoring in the dataset and thus the extrapolation required is minimal. ***However it is of even greater importance to justify the plausibility of the extrapolated portion of the survival model chosen, as this is likely to have a very large influence on the estimated mean survival. This is difficult, but may be achieved through the use of external data sources, biological plausbility, or clinical expert opinion****."*[33]

In the absence of long-term follow-up data relating to the use of FGFR2 inhibitors for patients in UK clinical practice, it is impossible to provide objective evidence to confirm the predictions of the model. Instead, the long-term clinical plausibility of the extrapolations was informed by UK clinical expert opinion, and as the best available evidence, this formed a key component in the choice of the base case PFS and OS extrapolations.

The selection of the base case PFS and OS extrapolations for futibatinib is briefly re-capped below – as detailed, the visual and statistical fit of most of the extrapolations to the observed KM data was similar. Therefore, as guided by NICE TSD 14, the selection of the most appropriate extrapolations was guided by long-term clinical plausibility, based on the opinion from UK clinical experts:

OS

- The experts selected the lognormal (Rank 2 + 1) and log-logistic (Rank: 1 + 3) as the two most appropriate OS extrapolations, based on a combination of visual fit to the observed KM data as well as long-term clinical plausibility
- With the exception of the exponential, all of the curves provided a similar visual fit to the observed KM data (CS, Figure 24)
- The log-normal curve falls within 2 AIC points and 1 BIC point of the best statistically fitting Weibull extrapolation, indicating that both models provide an equally good statistical fit to the observed data (CS, Table 32)
- Therefore, the only meaningful difference between the curves is their long-term clinical plausibility – and based on this, the lognormal was selected as the most appropriate extrapolation in line with UK clinical expert feedback

PFS

- The experts selected the lognormal (Rank 1 + 2) and the log-logistic (Rank 3 + 1) as the two most appropriate PFS extrapolations
- With the exception of the exponential, all of the curves appeared to fit broadly well to the visual data – as the EAG note, the log-logistic and lognormal do deviate slightly from the observed data from approximately Month 16 onwards, there are very few patients at risk from these timepoints (N=7 patients at risk from Month 18), meaning that the observed data beyond those timepoints is associated with uncertainty (CS, Figure 20)
- The base case log-normal curve falls within 4 AIC points and 4 BIC points of the best fitting Weibull extrapolation. This indicates that there are no differences between the two models with respect to BIC, but potentially supports a difference between the two models with respect to AIC (CS, Table 30)
- However, as with OS, this means that the only meaningful difference between the curves is the long-term clinical plausibility – therefore, similar to OS, the lognormal extrapolation was selected as the most appropriate extrapolation, in line with UK clinical expert feedback

Economic model

B.18.Priority question. Please correct the following errors in the model:

a) Survival tab the [Restore sheet] option gives an error. Run-time error 1004. "Method "range" of object '_worksheet" failed.

The Company has addressed this error in the updated economic model.

b) Sensitivity analysis sheet, cell F70, shows the probability of being cost effective based on the information in 'PSA iterations'!AZ14. However, in the PSA iteration sheet, column AZ the formula has a typo. Please check carefully the CEAC calculations.

The Company has addressed this error in the updated economic model, as per the response to question B12.

c) Datastore: cell C89 is not linked to any cost calculations.

The Company has addressed this error in the updated economic model, and cell O37 in the 'Costs' sheet is now linked to cell C89 in the datastore.

B.19. On the sheet "survival" of the economic model there is the option to select a naïve comparison for the survival modelling approach. Please explain how this option has been specified and if it has been presented in the CS.

The 'naïve' modelling approach (which has been replaced with a switch in cell E56 of the Settings tab to 'independent parameterisation') gives the option to model PFS and OS for futibatinib and pemigatinib independently, using data from the FOENIX-CCA2 and FIGHT-202 trials, respectively.

In this approach a HR is not used to obtain survival curves for pemigatinib and instead independent survival extrapolation curves are used to model PFS and OS for futibatinib and pemigatinib.

This scenario was not presented in the submission as the use of HRs from the MAIC was considered the most suitable approach, due to the reasons listed in response to clarification question B.2d).

As per the response to B.2d) a scenario exploring independent extrapolations for pemigatinib based on the unadjusted data from FIGHT-202, versus independent extrapolations for futibatinib based on the MAIC-adjusted data from FOENIX-CCA2 (to ensure a fair comparison) has been provided as part of the clarification question response (see Appendix B).

B.20. Please add to the figure of the survival curves presented in the results sheet the OS of the general population.

As requested, the corresponding survival curve for OS for the general population has been added to the figure in the model.

C: Textual clarification and additional points

C1. On pages 80 and 81 of the CS, the company mentioned unadjusted KM data and MAIC PFS hazard ratio (HR) equal to 1.07. However, in Table 21 and page 58, this HR is referred to as the Adjusted Cox MAIC model analyses. On page 83, the unadjusted MAIC PFS HR is equal to 1.02. Please clarify which HRs are adjusted, which ones are unadjusted and correct this in the CS.

The Company can confirm that, as detailed in Table 21, Page 59 of the Company submission, the unadjusted MAIC PFS HR is equal to 1.02, and the adjusted MAIC PFS HR is equal to 1.07.

The text on Pages 80-81 of the Company submission does not specify that the adjusted MAIC PFS HR is equal to 1.07. Instead, the text on Page 80-81 of the CS highlights that, in the base case economic analysis:

- Extrapolations for futibatinib are fitted to the unadjusted PFS KM data from FOENIX-CCA2
- Subsequently, the inverse of the adjusted MAIC PFS HR of 1.07 (i.e. 0.93) is applied to the chosen futibatinib PFS extrapolation, in order to derive a corresponding PFS extrapolation for pemigatinib

No corrections to the CS are required.

C2. On page 80 of the CS, it is mentioned that "futibatinib was modelled via extrapolation of the unadjusted Kaplan-Meier data obtained from the FOENIX-CCA2 trial, and pemigatinib was modelled via applying the inverse of the MAIC PFS HR (1.07) for futibatinib versus pemigatinib in the base-case MAIC". Please explain what the unadjusted Kaplan-Meier data in this sentence are. Please confirm if this means that the company used the Kaplan-Meier data from the FOENIX-CCA2 and not the Kaplan-Meier data from the MAIC analysis. Please explain the reasoning behind this analysis. If that is the case, please re-run the analysis using the MAIC analysis and survival data.

As discussed in Section B.3.3.2 of the Company submission, the base case analysis used unadjusted KM data from the FOENIX-CCA2, rather than the adjusted KM data derived from the MAIC.

Pemigatinib was modelled by applying the inverse of the adjusted MAIC PFS and OS HRs for futibatinib versus pemigatinib to the futibatinib extrapolation to derive a corresponding PFS and OS extrapolation for pemigatinib. This approach permitted the use of the adjusted base case MAIC results, which represent the least biased estimates of the relative effects between futibatinib and pemigatinib. It also allowed the futibatinib extrapolations to be based on the maximum sample size; avoiding the reduction in effective sample size that would be associated

with extrapolation of the MAIC-adjusted FOENIX-CCA2 data. Clinical validation of the most plausible survival curves for futibatinib was also performed based on curves generated using unadjusted FOENIX-CCA2 data.

However, for completeness, functionality has been added to the model to permit modelling of PFS and OS for futibatinib based on the MAIC-adjusted FOENIX-CCA2 data.

This can be implemented by selecting 'MAIC-adjusted' from the drop-down in cell E58 of the 'Settings' tab. A scenario analysis has been explored where the MAIC-adjusted FOENIX-CCA2 data are used; for consistency with the base case and given similar long-term survival predictions, no changes were made to the selected parametric extrapolations for PFS and OS (i.e. the Lognormal model was selected in both cases). As per the base case approach, pemigatinib OS and PFS were derived by applying the inverse of the MAIC PFS and OS HRs for futibatinib versus pemigatinib MAIC to the revised futibatinib extrapolations. This scenario has limited impact on cost-effectiveness results (see Appendix B), with futibatinib remaining dominant at list price.

C3. Table 51: Please report incremental QALYs with four decimals.

The model has been updated to report all QALY results to four decimal places.

Appendix A: STC Methods and Results

STC methods

The stimulated treatment comparison (STC) applied a regression equation to adjust the FOENIX-CCA2 trial population. Following the NICE DSU TSD 18, an outcome model was fitted using the individual patient-level data (IPD) in the comparator trial:[34]

g(μt(comp)(X)) = β0 + β_1^TX + β_2^TXEMI(t=comp)

where comp = comparator treatment, β_0 is an intercept term, β1 is a vector of coefficients for prognostic variables, β2 is a vector of coefficients for effect modifiers XEM (a sub vector of the full covariate vector X), and μt(comp)(X) is the expected outcome of an individual assigned treatment T with covariate values X, which is transformed onto a chosen linear predictor scale with link function g(.).

In the Cox proportional hazards regression framework, a log link function was employed between the hazard function and the linear predictor component of the model. The validity of the proportional hazards assumption between treatments within each of the studies was tested by a visual inspection of the log-cumulative hazard plots, as well as the Schoenfeld global test of proportionality.

IPD for PFS and OS from the FIGHT-202 trial were estimated by extracting data from KM curves, using standard software (Engauge Digitizer [version 12.1]). The extracted curve data presented the survival probability over time and number of events and numbers at risk. To generate pseudo-IPD from this data, the well-established Guyot algorithm and accompanying R-code were used.[35] The pseudo-IPD from each study/outcome were then compared with the corresponding data from FOENIX-CCA2.

Progression-free survival results

Table 18 presents the results from the unadjusted Cox model used to calculate HRs for the relative effect of futibatinib versus pemigatinib, and the covariate-adjusted MAIC and STC analyses for PFS. The MAIC analysis resulted in an adjusted PFS HR of 0.827 (95% CI: 0.584–1.170) and the STC analysis resulted in a PFS HR of 0.821 (95% CI: 0.576–1.170), with both results having no statistically significant differences between the two treatment groups.

A sensitivity analysis was also conducted, with the race covariate added to the base-case analysis covariates. The results of this analysis were similar to those in the base case (Table 18).

Overall, the results demonstrate there is no statistically significant difference in PFS between pemigatinib and futibatinib.

Table 18. Unadjusted and adjusted PFS model results

Model	HR for PFS	95% CI; p value	Notes
Unadjusted analyses			
Cox-naïve/unadjusted	0.812	0.579–1.138	No covariate adjustment
Adjusted Cox MAIC model analyses			

Base-case	0.827	0.584–1.170	Adjusted for age, gender, ECOG status, prior lines, prior surgery, baseline hypoalbuminemia status, TP53 alteration status
Sensitivity analysis	0.840	0.585–1.206	Base-case covariates + race
Adjusted Cox STC model analyses			
Base-case	0.821	0.576–1.170	Adjusted for age, gender, ECOG status, prior lines, prior surgery, baseline hypoalbuminemia status, TP53 alteration status
Sensitivity analysis	0.831	0.574–1.201	Base-case covariates + race

Abbreviations: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; PFS: progression-free survival; STC: stimulated indirect treatment comparison.

Appendix B: Revised company base case

Updated deterministic cost-effectiveness results are presented in Table 19 (at futibatinib list price, without the severity modifier applied), demonstrating the impact of each correction to the model independently. The combined impact of these changes is also presented as the revised company base case, which has been used as the basis of additional scenarios. In all explored scenarios, INHB was positive for futibatinib, demonstrating the base-case results to be robust to uncertainties in inputs and assumptions.

Table 19. Updated deterministic base-case and key scenario results (futibatinib list price, excluding severity modifier)

#	Description	Pemigatinib				
		Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	NHB at 20K (QALYs)	NHB at 30K (QALYs)
Original company base case		[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Model corrections and revised base case						
1	QB10: Correction of wastage implementation	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
2	QB5: Hazard rates for OS and PFS set equal between futibatinib and pemigatinib when all patients have discontinued (24 months)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
3	**Revised base case (1 + 2)**	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Additional scenarios						
3a	QB1, B4 and B9: ToT modelled independently of PFS (no restriction)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
3b	QB1, B4 and B9: ToT modelled independently of PFS (ToT restricted by PFS, as per TA722)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
3c	QC2: Futibatinib PFS and OS based on MAIC-adjusted FOENIX-CCA2 data	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
3d	3c[a] + QB2d: Independent extrapolations for pemigatinib OS (Loglogistic) and PFS (Generalised Gamma)	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

[a]To ensure a fair comparison, futibatinib PFS and OS are based on MAIC-adjusted FOENIX-CCA2 data (matched to the FIGHT-202 trial) in the scenario where pemigatinib survival is based on independent extrapolations of the unadjusted FIGHT-202 data.

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc.: incremental; MAIC: matching-adjusted indirect comparison; INHB: incremental net health benefit; PFS: progression-free survival; QALY: quality-adjusted life years; OS: overall survival; ToT: time on treatment.

Appendix C: Revised DSA tornado plot

Figure 9: Revised DSA tornado diagram for futibatinib and pemigatinib (INHB)

Abbreviations: DSA: deterministic sensitivity analysis; HR: hazard ratio; INHB: incremental net health benefit; OS: overall survival; PD: progressed disease; PF: progression-free; PFS: progression-free survival.

References:

1. Khan SA, Davidson BR, Goldin RD, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. Gut 2012;61:1657-69.
2. National Institute for Health and Care Excellence. TA722: Pemigatinib for treating relapsed or refractory advanced CCA with FGFR2 fusion or rearrangement. Available at: https://www.nice.org.uk/guidance/ta722 [Last accessed: 02 November 2023]. 2021.
3. Lamarca A, Palmer, D. H., Wasan, H. S., Ross, P. J., Ma, Y. T., Arora, A., Falk, S., Gillmore, R., Wadsley, J., Patel, K., Anthoney, A., Maraveyas, A., Iveson, T., Waters, J. S., Hobbs, C., Barber, S., Ryder, W. D., Ramage, J., Davies, L. M., Bridgewater, J. A, Valle, J.W. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol. 2021;22:690–701.
4. Vogel A, Bridgewater J, Edeline J, et al. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2023;34:127-140.
5. Vogel A, Sahai, V., Hollebecque, A., Vaccaro, G., Melisi, D., Al-Rajabi, R., Paulson, S., Borad, M., Gallinson, D., Murphy, A., Oh, D., Dotan, E., Catenacci, D., Van Cutsem, E., Lihou, C., Zhen, H., Veronese, L. and Abou-Alfa, G. O-2 Pemigatinib for previously treated locally advanced or metastatic cholangiocarcinoma: Final results from FIGHT-202. Ann Oncol 2022;33:S379.
6. Rushbrook SM, Kendall TJ, Zen Y, et al. British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma. Gut 2023.
7. Taiho Oncology. Data on File. FOENIX-CCA2 Advisory Board Report. 22 May 2023.
8. Daniele P, Mamolo C, Cappelleri JC, et al. Overall and complete response rates as potential surrogates for overall survival in relapsed/refractory multiple myeloma. Future Oncol. 2023;19:463–471.
9. Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. Contemp Clin Trials 2008;29:456-65.
10. TA948: National Institute for Health and Care Excellence. Ivosidenib for treating advanced cholangiocarcinoma with an IDH1 R132 mutation after 1 or more systemic treatments. Technology appraisal guidance. Available at: https://www.nice.org.uk/guidance/ta948 [Accessed 7th March 2024].
11. National Institute for Health and Care Excellence. Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template. 2022. Available at: https://www.nice.org.uk/process/pmg24/chapter/clinical-effectiveness#critical-appraisal-of-the-relevant-clinical-effectiveness-evidence. Last Accessed: March 2024.
12. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination, University of York, 2008.
13. Genus T, Tataru D, Morement H, et al. (late submission poster) Incidence and mortality rates of cholangiocarcinoma in England. Annals of Oncology 2019;30:iv155.
14. Genus T, Tataru D, Morement H, et al. THU508 - Cholangiocarcinoma in England - a national study examining changes in incidence, diagnostic routes and overall survival. Journal of Hepatology 2020;73:S393-S394.
15. National Institute for Health and Care Excellence. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement. Technology appraisal guidance. Final Appraisal Determination. Available at: https://www.nice.org.uk/guidance/ta722/documents/final-appraisal-determination-document-2. [Accessed 07 March 2024].
16. Abou-Alfa GK, Sahai, V., Hollebecque, A., Vaccaro, G., Melisi, D., Al-Rajabi, R., Paulson, A. S., Borad, M. J., Gallinson, D., Murphy, A. G., Oh, D. Y., Dotan, E.,

Catenacci, D. V., Van Cutsem, E., Ji, T., Lihou, C. F., Zhen, H., Féliz, L., Vogel, A. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol. 2020;21:671–684.
17. Goyal L, Meric-Bernstam F, Hollebecque A, et al. Futibatinib for FGFR2-Rearranged Intrahepatic Cholangiocarcinoma. N Engl J Med 2023;388:228-239.
18. Sedgwick P. Pitfalls of statistical hypothesis testing: type I and type II errors. Bmj 2014;349.
19. Barraclough H, Govindan R. Biostatistics primer: what a clinician ought to know: subgroup analyses. Journal of Thoracic Oncology 2010;5:741-746.
20. Valle JW, Hollebecque A, Furuse J, et al. FOENIX-CCA2 quality of life data for futibatinib-treated intrahepatic cholangiocarcinoma (iCCA) patients with FGFR2 fusions/rearrangements. Journal of Clinical Oncology 2021;39:4097-4097.
21. Subbiah V, Iannotti NO, Gutierrez M, et al. FIGHT-101, a first-in-human study of potent and selective FGFR 1-3 inhibitor pemigatinib in pan-cancer patients with FGF/FGFR alterations and advanced malignancies. Ann Oncol 2022;33:522-533.
22. Rodon J DS, Furqan M, Garcia-Donas J, Imai H, Italiano A, Spanggaard I, Ueno M, Yokota T, Veronese L, Oliveira N, Li X, Gilmartin A, Goyal L. Abstract CT016: Clinical and translational findings of pemigatinib in previously treated solid tumors with activating FGFR1-3 alterations in the FIGHT-207 study. Cancer Res 2023;82:CT016.
23. Shi GM, Huang XY, Wen TF, et al. Pemigatinib in previously treated Chinese patients with locally advanced or metastatic cholangiocarcinoma carrying FGFR2 fusions or rearrangements: A phase II study. Cancer Med 2023;12:4137-4146.
24. Simon RM, Subramanian J, Li MC, et al. Using cross-validation to evaluate predictive accuracy of survival risk classifiers based on high-dimensional data. Brief Bioinform 2011;12:203-14.
25. Efron B. Bootstrap Methods: Another Look at the Jackknife. In: Kotz S, Johnson NL, eds. Breakthroughs in Statistics: Methodology and Distribution. New York, NY: Springer New York, 1992:569-593.
26. Welton NJ, Phillippo DM, Owen R, et al. NICE DSU Report. CHTE2020 sources and synthesis of evidence; update to evidence synthesis methods. Sheffield: Decision Support Unit, ScHARR, 2020:98.
27. National Institute for Health and Care Excellence. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency [ID3802]. Technology appraisal guidance [TA779]. Available at: https://www.nice.org.uk/guidance/ta779/documents/committee-papers [Accessed 04 March 2024].
28. University of Sheffield. NICE Decision Support Unit. Full list of technical support documents. Available at: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list [Accessed 16 August 2023].
29. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095-108.
30. Lamarca A, Palmer D, Wasan HS, et al. Quality of life (QoL) and value of health (V-He) in advanced biliary cancers (ABC) treated with second-line active-symptom-control (ASC) alone or ASC with oxaliplatin/5-FU chemotherapy (ASC+FOLFOX) in the randomised phase III, multi-centre, open-label ABC-06 trial. Ann Oncol. 2022;33:S564–S565.
31. CADTH Reimbursement Recommendation. Pemigatinib (Pemazyre). Available at: https://www.cadth.ca/sites/default/files/DRR/2022/PC0252%20Pemazyre%20-%20CADTH%20Final%20Rec.pdf. [Accessed 07 March 2024]. 2022.
32. Büyükkaramikli NC, Rutten-van Mölken M, Severens JL, et al. TECH-VER: A Verification Checklist to Reduce Errors in Models and Improve Their Credibility. Pharmacoeconomics 2019;37:1391-1408.

33. NICE DSU TECHNICAL SUPPORT DOCUMENT 14: SURVIVAL ANALYSIS FOR ECONOMIC EVALUATIONS ALONGSIDE CLINICAL TRIALS - EXTRAPOLATION WITH PATIENT-LEVEL DATA
34. Phillippo D, T. Ades, S. Dias, S. Palmer, K. R. Abrams and N. Welton. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. (Technical Support Documents). Volume 2022, 2016.
35. Guyot P, Ades AE, Ouwens MJNM, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Medical Research Methodology 2012;12:9.

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Single Technology Appraisal

Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [ID6302]

Patient Organisation Submission

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].

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- Your response should not be longer than 10 pages.

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About you

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 – The Cholangiocarcinoma Charity is a CIO, registered with the Charity Commission for England and Wales, registration no 1198095. It is the UK's only charity dedicated solely to cholangiocarcinoma. **Please note**: AMMF recently completed a change of status process which involved re-registration with the Charity Commission. AMMF is now a Charitable Incorporated Organisation (CIO), registration no 1198095. *(The charity was originally registered in 2002 with the name, The Alan Morement Memorial Fund, using the working title, AMMF, under the registration number 1091915. This version of the charity remains in existence and can be seen on the Charity Commission website. However, the main business of the charity is now carried out under the CIO, registration no 1198095.*) Funding is received via donations from members of the public, and some industry funding is received as sponsorship to support AMMF's various projects. The charity does not have members.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in	In the last 12 months AMMF has received the following sponsorship from Taiho Oncology: **£10,000** received March 2024 to help support AMMF's Cholangiocarcinoma Patient Pathway Mapping project - ongoing. **£10,000** received March 2024 to help support the translation of AMMF's Cholangiocarcinoma Patient Organisation Education project documents into European languages (documents prepared to provide educational information on cholangiocarcinoma for pan-cancer organisations and advocacy groups across Europe) – ongoing.

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	**£10,000** received April 2024 to help support AMMF's Cholangiocarcinoma Patient Education Webinars project – ongoing. **£25,000** received April 2024 to help support AMMF's 2024 Hybrid European Cholangiocarcinoma Conference (held 08-10 May 2024).
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 patient round tables, and on the Patient & Carer Day at AMMF's annual conference. AMMF also has very active private online discussion forums (for Patient & Carers, and for Patients Only) and discussions on treatments and trials are conducted there. 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. For carers, too, understanding the diagnosis and its implications can be as difficult for them as for the patient. Many struggle to comprehend the situation - that there is really is no curative treatment for their loved one. Currently a resection is the only potentially curative treatment for CCA, so inoperable patients are left with very limited options. The standard first line treatment for those with inoperable CCA has recently changed and, for the first time in over a decade, an improved combination is now recommended – durvalumab (an immunotherapy) with the chemotherapy combination, Gemcitabine and Cisplatin. However, this is not curative, and although it may well extend life, this may well come with a number of very difficult side effects. 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 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 by many to be a cancer affecting older people, at AMMF we hear from those in their 20s, 30s, 40s with this diagnosis. AMMF's data project now confirms the number of younger adults diagnosed with this cancer – and this work has been published[1]. 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: "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."

	"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." [1] *Cholangiocarcinoma across England: Temporal changes in incidence, survival and routes to diagnosis by region and level of socioeconomic deprivation.* https://www.jhep-reports.eu/article/S2589-5559(23)00314-2/fulltext

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients see a number of therapies, for example targeted therapies, immunotherapies, SIRT (selective internal radiation therapy) and HAI (hepatic arterial infusion) with FUDR (floxuridine) and others, available to CCA patients in other countries, and they find it very difficult to understand why these effective treatments – albeit not curative but life extending, and in some cases leading to downstaging meaning surgery becomes possible - are not available to cholangiocarcinoma patients within the NHS. Many will search for treatments they can access 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[2], with many younger adults being diagnosed. Currently resection is the only potentially curative treatment, but few are eligible for this. Standard of care 1st line treatment for inoperable CCA patients has recently changed and offers improved survival, but is not curative. More approved targeted therapies are needed as we learn more about the mutations and fusions in CCA. New and more effective treatments for CCA are desperately needed. <u>Specialist MDTs and Centres of Expertise for CCA patients are needed</u> There seems to be no set pathway/guidance for the care of cholangiocarcinoma patients, leading to many never being seen by those with specialist knowledge, and therefore many are not considered for surgery nor for clinical trials. AMMF strongly believes that all CCA patients should have confirmation of their diagnosis (operable/inoperable), and their treatment pathway endorsed by an HPB multidisciplinary team experienced and knowledgeable in CCA. And that this and their care should be undertaken in 'centres of expertise'. <u>Molecular profiling is needed for all CCA patients</u> Following NICE approval of the first target therapy for CCA, molecular profiling should now be available for all those diagnosed with CCA. Where offered, currently this is only at 2nd line. However, with the advent of targeted therapies it should be available at diagnosis or during 1st line treatment - essential so that all those eligible for such treatments can be considered in a timely manner. Currently, although molecular profiling under the NHS should now be available to those diagnosed with CCA, it seems it is still offered to only very few CCA patients, with many having to seek this privately.

	[2] *Cholangiocarcinoma across England: Temporal changes in incidence, survival and routes to diagnosis by region and level of socioeconomic deprivation.* https://www.jhep-reports.eu/article/S2589-5559(23)00314-2/fulltext

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	For those with CCA, treatment in the second line is standard chemotherapies – which may or may not be helpful - and/or best supportive care. For those with certain mutations there are now targeted therapies: for those with an IDH1 mutation, ivosidenib, for those with an FGFR2 fusion, pemigatinib. However, futibatinib is a further treatment offered in a second line setting to those CCA patients with the FGFR2 fusion. This offers an opportunity for those with this particular fusion to have a further treatment should they experience resistance to a first targeted therapy. It also offers healthcare professionals a choice of therapy for their patients. A recently published case report has noted "… prolonged clinical benefit using FGFR inhibitors sequentially …" Further that toxicity was mild and easily manageable and, because the therapy was well tolerated, good quality of life was maintained[3]. Because futibatinib is a targeted therapy, those with an FGFR2 cholangiocarcinoma and who are eligible for this therapy, will know from the outset that this should work for them - and this brings with it the hope of extending survival over the more standard chemotherapies and/or best supportive care that might be otherwise be offered following a first line treatment. Plus, as an oral therapy, futibatinib has certain quality of life advantages over an intravenous therapy, including spending less time in hospital receiving treatment. [3] https://www.dovepress.com/prolonged-clinical-benefit-with-futibatinib-in-a-patient-with-fgfr-inh-peer-reviewed-fulltext-article-OTT

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients and carers see new technologies heralding new hope – the only disadvantages expressed by patients and carers that AMMF is aware of is that clinical trials are available to so few, and similarly that new technology and therapies are not adopted in a timely and uniform manner.

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.	All those patients with CCA, who have an FGFR2 fusion and who fit the eligibility criteria should benefit from futibatinib.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that AMMF is aware of.

Other issues

13. Are there any other issues that you would like the committee to consider?	CCA patients and carers see that this therapy has already been approved in other countries, and so those in this country who should be eligible to receive it find it very difficult to understand why it is not available to them under the NHS.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• CCA is a cancer with increasing incidence, and a mortality that parallels that incidence. • Many younger adults now receive a diagnosis of CCA, often at a late stage when treatment options are limited. • Surgery remains the only potentially curative option but, mainly because of late diagnosis, this is available to few. • For those with targetable fusions or mutations, targeted therapies now provide realistic further treatment options, offering the opportunity to extend life with tolerable side effects. • Futibatinib is a life extending targeted therapy, which is well tolerated and offers an additional treatment to those eligible CCA patients with an FGFR2 fusion.

Thank you for your time.

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Single Technology Appraisal

Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [ID6302]

Professional organisation submission

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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Cholangiocarcinoma UK
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes
5a. Brief description of the organisation (including who funds it).	Cholangiocarcinoma UK is a branch of the British Association for Study of the Liver (BASL) and is a group of scientists and physicians specialising in the diagnosis and treatment of cholangiocarcinoma.
5b. 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.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prolong survival in advanced incurable disease.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A reduction of the tumour by 50% in one dimension, a prolongation the progression free survival by 6 months or overall survival by 3 months.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, the median survival for patients on chemotherapy alone is approximately 12 months.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	1st line treatment is cisplatin and gemcitabine chemotherapy (the addition of durvalumab has been recently approved by NICE but yet to be implemented). 2nd line therapy is FOLFOX chemotherapy but the benefit of this is modest. Pemigatinib is NICE approved for FGFR2 fusion +ve patients and has a very similar profile.
9a. Are any clinical guidelines used in the	ESMO (European Society of Medical Oncology) [1], BSG (British Society of Gastroenterology) [2] and NCCN (btc.pdf (nccn.org)) guidelines recommend the use of FGFR2 inhibitors for FGFR fusion +ve cholangiocarcinoma.

treatment of the condition, and if so, which?	
9b. 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.)	1st and 2nd line chemotherapy well established although only 50% of patients get active treatment. [3] Durvalumab recently approved and will be introduced into 1st line treatment. Testing (as defined by National Directory) patchy and a minority of patients currently getting tested.
9c. What impact would the technology have on the current pathway of care?	2nd and subsequent line option FGFR2 fusion patients.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Oral medication introduced as new treatment in outpatient clinic.
10a. How does healthcare resource use differ between the technology and current care?	This would be in addition to current care.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Centres of Expertise familiar with targeted therapies in cholangiocarcinoma. [2]
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Centres of Expertise familiar with targeted therapies in cholangiocarcinoma. [2]

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, improved progression free and overall survival with maintained QoL.
11a. Do you expect the technology to increase length of life more than current care?	Yes as above.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes as above
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	FGFR2 fusion patients ONLY

The use of the technology

13. 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 treatments needed, additional clinical requirements, factors	Experience of FGFR2 inhibitors and management of toxicities currently limited to academic centres in which studies previously run. BSG guideline recommendation for patients to be initially reviewed in centre of expertise[2] to be considered for ongoing FGFR2 studies. Recommended that use outside of experienced centres be limited until greater understanding of testing and novel toxicities established.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	FGFR2 fusion must be demonstrated either on NGS, RNA sequencing or fISH. The first 2 are on the national directory and run at the referring genomic laboratory hub. The latter may be run locally in addition.
15. 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?	No
16. 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?	Likely to result in improvement in survival of 2 or more years with modest toxicity. [4]
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any	Likely to result in improvement in survival of 2 or more years with modest toxicity. This is a significant improvement on the current median survival of 13 months.

particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Primary side effects hyperphosphataemia, hand-foot syndrome, nail loss and mucositis. All toxicities manageable and aart from asymptomatic hyperphosphataemia, rarely more than grade 2. Grade 3 hyperphosphataemia asymptomatic.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free survival and overall survival.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA722?	No
21. How do data on real-world experience compare with the trial data?	Equivalent

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A

Topic-specific questions

23 What proportion of eligible patients with FGFR2 fusion or rearrangement are treated with a targeted treatment (e.g. pemigatinib) vs combination chemotherapy, following failure of first-line chemotherapy.	No data but likely approaching 100%.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Step change in therapy with respect to improved survival • Manageable toxicities • Convenient oral therapy • Established pathways for testing • Recommended centre of expertise supervision

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1. Vogel A, Bridgewater J, Edeline J, et al. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023; **34**(2): 127-40.
2. Rushbrook SM, Kendall TJ, Zen Y, et al. British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma. *Gut* 2023: gutjnl-2023-330029.
3. Zalin-Miller A, Jose S, Knott C, et al. Regional variation in routes to diagnosis of cholangiocarcinoma in England from 2006 to 2017. *World J Gastroenterol* 2023; **29**(24): 3825-42.
4. Goyal L, Meric-Bernstam F, Hollebecque A, et al. Futibatinib for FGFR2-Rearranged Intrahepatic Cholangiocarcinoma. *New England Journal of Medicine* 2023; **388**(3): 228-39.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [ID6302]

Professional organisation submission

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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	The Royal College of Pathologists
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathologists is a professional membership organisation with charitable status concerned with all matters relating to the science and practice of pathology. It is a body of its Fellows, Diplomates, Affiliates and trainees, supported by the staff who are based at the College's London offices. The College is a charity with over 11,500 members worldwide. The majority of members are doctors and scientists working in hospitals and universities in the UK. The College oversees the training of pathologists and scientists working in 17 different specialties, which include cellular pathology, haematology, clinical biochemistry and medical microbiology.
5b. 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.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	no
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

The aim of treatment for this condition

6. 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 submission concerns the use of Futibatinib for the treatment of patients with previously treated advanced cholangiocarcinoma where the tumour has an FGFR2 fusion or rearrangement. The aim of treatment is to improve symptoms and quality of life, slow tumour progression, and increase overall survival.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant treatment response would include a reduction in tumour size by at least 30% (partial response defined by RECIST guidelines v1.1).
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Cholangiocarcinoma is a rare tumour albeit with rising incidence. Surgery is the only cure but the disease is usually too advanced at presentation to allow this. 10-20% of patients with intrahepatic cholangiocarcinoma have tumours with an FGFR2 fusion or rearrangement. The prognosis for patients with cholangiocarcinoma who cannot have curative surgery and are treated with standard-of-care chemotherapy is poor. There is a significant unmet need to increase the quality of life and overall survival of patients in this situation.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Patients with cholangiocarcinoma who have progressed to first line chemotherapy are treated with active symptom control and, if fit enough, second line oxaliplatin and fluorouracil (FOLFOX). Patients whose tumours bear an FGFR2 fusion may be treated with the FGFR2 inhibitor pemigatinib. Molecular testing of a sample of

	tumour (by FISH or sequencing) is required to identify FGFR2 fusions/rearrangements that define treatment eligibility.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	ESMO guidelines for treatment of biliary tract cancer were updated in 2023 (Ann Oncol. 2023;34(2):127-140), and the BSG guidelines were also updated in 2023 (Gut 2024;73:16-46).
9b. 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 pathway of care is well-defined in the UK. I work in Scotland but participate in UK-wide management guideline development. FGFR2 fusion testing of tumours is undertaken at the request of the oncologist, the MDT, or the reporting pathologist.
9c. What impact would the technology have on the current pathway of care?	Futibatinib would be used for patients with advanced disease whose tumour have an FGFR2 fusion. This is the same indication as pemigatinib, and both have shown similar benefits compared with standard chemotherapy although futibatinib may have greater activity and also have activity against some of the resistance mutations that can develop following treatment with pemigatinib. No additional molecular testing would be required as FGFR2 fusion testing should already be undertaken.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Futibatinib would be prescribed by the oncologist as an alternative to pemigatinib or in cases where resistance on pemigatinib treatment has developed.
10a. How does healthcare resource use differ between the technology and current care?	Futibatinib will be used as an alternative to pemigatinib.
10b. In what clinical setting should the technology be used? (For example,	Futibatinib would be used in oncology departments in secondary care.

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional molecular testing is required as testing to identify those tumours with FGFR2 fusions should already standard of care.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Futibatinib will provide significant benefits above FOLFOX treatment in patients with an FGFR2 rearranged tumour.
11a. Do you expect the technology to increase length of life more than current care?	See 11.
11b. Do you expect the technology to increase health-related quality of life more than current care?	See 11.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Futibatinib is only effective for the treatment of patients whose tumours have FGFR2 fusions.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or	Futibatinib will be as easy to use as pemigatinib.

healthcare professionals than current care? Are there any 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.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will only be started after the identification of FGFR2 fusions by molecular testing.
15. 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?	No
16. 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	Futibatinib will provide significant benefits above FOLFOX treatment in patients with an FGFR2 rearranged tumour.

way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	Futibatinib would be an alternative to pemigatinib but its effectiveness where resistance to pemigatinib has developed would be unique.
16b. Does the use of the technology address any particular unmet need of the patient population?	See 16a.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The most common grade 3 treatment-related adverse event was hyperphosphatemia (in 30% of the patients). None of the patients discontinued treatment because of hyperphosphatemia. Serious treatment-related adverse events were reported in 10 patients (10%). The side effect profile is equivalent to that seen in other FGFR inhibitors.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the trial population reflects the UK population, and several UK centres participated in the FOENIX-CCA2 trial.
18a. If not, how could the results be extrapolated to the UK setting?	NA
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	42% of treated patients had a response (v 36% for pemigatinib, 5% of FOLFOX), including one complete response, and 83% had disease control. The median progression-free survival was 9.0 months (v 7 months for pemigatinib, 4 months for FOLFOX), 12-month progression-free survival of 40% (30% for

	pemigatinib, 6% for FOLFOX). The median overall survival was 21.7 months (21.1 months for pemigatinib, 6.2 months for FOLFOX). The 12-month overall survival rate was 72%.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Clinical outcomes measured, no surrogates used.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA722?	An indirect comparison of futibatinib with pemigatinib was undertaken for 2022 ASCO GI (Journal of Clinical Oncology Volume 40, Number 4_suppl, #440), suggesting possible numerical advantages for futibatinib.
21. How do data on real-world experience compare with the trial data?	No real-world data for the use of futibatinib is available.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	NA

Topic-specific questions

23 What proportion of eligible patients with FGFR2 fusion or rearrangement are treated with a targeted treatment (e.g. pemigatinib) vs combination chemotherapy, following failure of first-line chemotherapy.	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Futibatinib increases survival in patients with FGFR2 rearranged cholangiocarcinoma above FOLFOX. • Futibatinib is an alternative to pemigatinib with data suggesting possible greater efficacy. • No additional molecular testing is needed on tissue samples to use futibatinib as FGFR2 testing is already standard to guide personalised treatment. • •

Thank you for your time.

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

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [ID6302]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

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

Information on completing this form

In part 1 we are asking you about living with this condition or caring for a patient with the condition. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

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.

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. Please type information directly into the form.

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. 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.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **31 May 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, 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 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.

Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement or caring for a patient with previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement

Table 1 About you, the condition, current treatments and equality

1. Your name	Andrew Clay
2. Are you (please tick all that apply)	☒ A patient with this condition? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with this condition? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	AMMF
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when 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

Patient expert statement

	☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: Active member of self-help groups in the UK & US
6. What is your experience of living with this condition? **If you are a carer (for someone with this condition) please share your experience of caring for them**	I was diagnosed in Jan 2018, had Whipple Surgery in Jun 2018 and subsequently received two regimens of chemotherapy, first Capecitabine followed by Gem/Cis. In Nov 2019 I enrolled in a drug trial for M7824 at UCLH. Due to impact on my kidneys, so stopped in Mar 2020. I have not required treatment since. I am also a moderator on a Cholangiocarcinoma self-help group for a number of years with about 2,000 members.
7a. What do you think of the current treatments and care available for this condition on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	From the experiences I have heard from other patients, there is a lack of awareness of Cholangiocarcinoma and its possible treatments outside of the large NHS facilities. Many patients have to request for second opinions from specialist centres to access the proper treatments. There are a broader range of treatments available in the US which are visible to patients in the UK but are not able to access them here. Molecular profiling should be a standard test for all Cholangiocarcinoma patients under the NHS. Our views are broadly consistent as our experiences are similar.
8. If there are disadvantages for patients of current NHS treatments for this condition (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Pemigatinib is approved by NICE in July 2021. I am not a medical expert but I understand Futibatnib works differently from Pemigatinib and offers another life extending option to the patients who become resistant to Pemigatinib.
9a. If there are advantages of futibatinib over current treatments on the NHS please describe these. For example, the effect 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?**	Futibatinib is an inhibitor for the FGFR mutation and has been demonstrated to be an effective treatment for Cholangiocarcinoma patients with this mutation in the US. In Dr Lipika words "the molecule Futibatinib is unique in that it's a covalently binding inhibitor and its irreversibly binding". This is different from Pemigatinib. I do not have first-hand experience, possible serious side effects impacting eyes and hyperphosphatemia are present in both. The alternative is generic Folfox which comes with unpleasant side effects and inconvenience of drug administration. If I have to suffer side effects, I will go for the treatment that offers a specific target.

9c. Does futibatinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	It is irreversible binding making it more durable compared to other FGFR inhibitors making their activity limited by acquired drug resistance. Therefore Futibatinib can be a viable second option when the first failed.
10. If there are disadvantages of futibatinib over current treatments on the NHS please describe these. For example, are there any risks with futibatinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Not that I am aware of. The serious side effects appear to be similar, however nail disorder is common with Futibatinib , this can be psychologically disturbing.
11. Are there any groups of patients who might benefit more from futibatinib 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	Patients with the FGFR mutation will benefit more from Futibatinib than those without the mutation as it is a targeted therapy.
12. Are there any potential equality issues that should be taken into account when considering this condition and futibatinib? Please explain if you think any groups of people with this condition are particularly disadvantage 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	Not that I am aware of.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	Cholangiocarcinoma is difficult to detect early and very aggressive, so once diagnosed, the patient often has a short amount of time to receive treatment. As many treatment options as possible are needed to extend and/or save lives for these patients.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [ID6302]

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

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Date completed 18 April 2024

Source of funding: This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number STA 13/62/69.

Declared competing interests of the authors None.

Acknowledgements: We gratefully acknowledge the expert clinical advice input from Prof Hendrik Tobias Arkenau (HCA Healthcare UK, UCL Cancer Institute and Ellipses Pharma).

Rider on responsibility for report

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

This report should be referenced as follows:

Perry M, Corro Ramos I, Qendri V, Krijkamp E, McDermott K, Armstrong N, Stirk L, Tian X, Al M, and Wolff R. Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [ID6302]: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2024.

Contributions of authors

Mark Perry acted as joint project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence, critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, and contributed to the writing of the report. Isaac Corro Ramos acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Venetia Qendri, Eline Krijkamp and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Xiaoyu Tian acted as a hybrid systematic reviewer/health economist, critiqued the clinical effectiveness methods/evidence and economic evaluation and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Maiwenn Al acted as health economist on this assessment and conducted the technical validation of the company's model. Robert Wolff acted as joint project lead, supervised meetings and the running of the project, and contributed to the writing of the report.

Abbreviations

5-FU	Fluorouracil
AdViSHE	Assessment of the Validation Status of Health-Economic decision models
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike Information Criterion
ALT	Alanine transaminase
ASC	Active symptom control
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BIC	Bayesian Information Criterion
BNF	British National Formulary
BOR	Best overall response
BSC	Best supportive care
BSG	British Society of Gastroenterology
CADTH	Canadian Agency for Drugs and Technologies in Health
CCA	Cholangiocarcinoma
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
COVID-19	Coronavirus disease 2019
cPAS	Comparator Patient Access Scheme
CR	Complete response
CR0	Complete response
CRD	Centre for Reviews and Dissemination
CRF	Case report form
CS	Company submission
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DARE	Database of Abstracts of Reviews of Effects
DCO	Data cut-off
DCR	Disease control rate
DOR	Duration of response
DoT	Duration of treatment
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ VAS	EuroQoL visual analogue scale
EQ-5D-3L	Euro-QoL-5 dimensions-3 levels
ESHPM	Erasmus School of Health Policy and Management
ESMO	European Society of Medical Oncology
ESS	Effective sample size
EU	European Union

EU-CTR	European Union – Clinical Trials Register
EUR	Erasmus University Rotterdam
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
FE	Fixing errors
FGF	Fibroblast growth factor
FGFR	Fusion growth factor receptor
FGFR2	Fusion growth factor receptor 2
FISH	fluorescent in situ hybridisation
FMI	Foundation Medicine, Inc.
FOLFOX	Folinic acid, fluorouracil and oxaliplatin
FV	Fixing violations
GnRH	Gonadotropin-releasing hormone
GP	General population
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
iDBC	Disease burden calculator
iMTA	Institute for Medical Technology Assessment
Inc.	Incremental
INHB	Incremental net health benefit
IPD	Individual Participant Data
IRC	Independent Review Committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISRCTN	International Standard Randomised Controlled Trial Number Registry
ITC	Indirect treatment comparison
Kg	Kilogram
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews Ltd
LH-RH	Luteinising hormone-releasing hormone
LYG	Life years gained
m^2	Metres squared
MAIC	Matching-adjusted indirect comparison
mFOLFOX	Modified folinic acid, fluorouracil and oxaliplatin
MHRA	Medicines and Healthcare Products Regulatory Agency
MID	Minimally important difference
MJ	Matters of judgement
MMRM	Mixed model for repeated measures
N/A	Not applicable
NCI	National Cancer Institute
NE	Not estimable
NHB	Net health benefit
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NL	Netherlands
NMA	Network meta-analysis
NR	Not reported
OCT	Optical coherence tomography
ORR	Objective response rate
OS	Overall survival

PAS	Patient Access Scheme
PD	Progressive disease
PF	Progression free
PFS	Progression-free survival
PH	Proportional hazard
PPE	Palmar–plantar erythrodysesthesia
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRO	Patient-reported outcomes
PS	Performance Status
PSA	Probabilistic sensitivity analyses
PSM	Partitioned survival model
PSS	Personal Social Services
PSW	Propensity score weighting
QALY	Quality-adjusted life year
QD	Once daily
QLQ	Quality of life questionnaire
QoL	Quality of life
QT	Interval between the start of the Q wave (ECG) to the end of the T wave
QTcF	Fridericia's corrected QT interval
RCT	Randomised controlled trial
RDI	Recommended dosing intensity
RECIST	Response Evaluation Criteria in Solid Tumours
RMST	Restricted mean survival time
R.O.C.	Republic of China
SAE	Serious adverse event
SF-36	Short Form-36
SD	Stable disease
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
STC	Simulated treatment comparison
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
ToT	Time on treatment
TP53	Tumour protein p53
TRAE	Treatment-related adverse event
TSD	Technical Support Document
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WTP	Willingness-to-pay

Table of Contents

Table of Tables

Table of Figures

1. Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 relates to the clinical effectiveness, and Section 1.5 is related to the cost effectiveness (CE). A summary is presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (CE) for more details.

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

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report Sections
1	Further rationale needs to be given for the absence of the modified FOLFOX regimen.	2.3
2	Clinical expert guidance is used to assert that the trial and target populations are comparable. Clinical expert guidance may be insufficient because the similarity between trial and target populations in England and Wales is highly important, having implications for the relevance of the trial results to the target populations.	3.2.3
3.	The company implies that the sub-group analyses suggest no effect modification from the chosen variables. However, this is not necessarily the case, with some evidence of effect modification.	3.2.5.4
4	Only 10/11 of the pre-planned sub-group analyses are reported. The omitted analysis was defined by 'patients with solid tissue sample and report'. Also, 'concomitant treatments', a potentially important covariate that could have a large impact on effect size, is not a sub-grouping variable.	3.2.5.4
5	The ITC Cox regression model did not include the potentially important variable of concomitant treatments.	3.4
6	Need for evidence that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects, and present an estimate of the likely range of residual systematic error in the "adjusted" unanchored comparison	3.4
7	Need for an additional STC given the lack of reliability of any form of population adjustment in an unanchored comparison.	3.4
8	Inadequate justification is given for the omission of HRQoL from the MAIC analyses.	3.4
9	The EAG disagrees with the company's approach of modelling OS and PFS assuming PH.	4.2.6
10	The EAG disagrees with the company's approach of assuming ToT equal to PFS.	4.2.6

ID1457	Summary of issue	Report Sections
11	The EAG is uncertain about the number of remaining errors in the company's economic model.	4, 5 and 6

FOLFOX = folinic acid, fluorouracil and oxaliplatin; HRQoL = health-related quality of life; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; PHs = proportional hazards; STC = simulated treatment comparison; ToT = time on treatment; UK = United Kingdom

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the following:

- As detailed in Section 4.2.6, independent modelling of overall survival (OS) (Weibull) and progression-free survival (PFS) (log-normal) curves (EAG) instead of assuming a proportional hazards (PHs) model for both OS and PFS (company).
- The assumption that hazard rates for OS and PFS are equal between futibatinib and pemigatinib when all patients have discontinued treatment (company) does not apply under independent modelling.
- OS and PFS extrapolations should be based on (matching-adjusted indirect comparison (MAIC)) adjusted data (EAG), instead of unadjusted futibatinib data (company).
- Time on treatment (ToT) should be modelled independently of PFS (EAG) instead of assuming they are equal (company).
- The company omitted costs of genetic testing for fusion growth factor receptor 2 (FGFR2) in their base-case. The EAG considered appropriate to add these costs in the EAG base-case analysis following expert opinion and TA722 committee preferred assumptions.

1.2 Overview of key model outcomes

NICE Technology Appraisals (TAs) compare how much a new technology improves length (OS) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, based on the company's base-case results, the new technology is modelled to affect QALYs by:

- Decreasing the number of QALYs in PFS, and increasing the number of QALYs in PD, resulting in an overall increase in QALYs.
- Slightly reducing the QALYs lost due to experiencing adverse events (AEs).

Overall, based on the company's base-case results, the technology is modelled to affect costs by:

- Its lower unit price compared to pemigatinib.
- Slightly decreasing costs associated to AEs and end of life.
- A minor increase in costs due to monitoring.

The modelling assumptions that have the greatest effect on the ICER are:

- Assuming PHs or independent modelling of survival data.
- The changes in hazard ratios (HRs) for OS and PFS, when a PHs model is assumed for survival data extrapolation. However, the EAG does not consider PHs plausible.

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there were discrepancies between the comparators requested in the NICE final scope and those adopted in the decision problem (Table 1.2).

Table 1.2: Key issue 1: Omission of scope comparators

Report Section	2.3
Description of issue and why the EAG has identified it as important	The case made by the company for omitting mFOLFOX from the decision problem is based on one analysis carried out as part of TA722, which has shown that pemigatinib may be more effective than mFOLFOX and symptom control. The conclusion is therefore that it is unnecessary to include mFOLFOX because if pemigatinib is superior to mFOLFOX, then any superiority of futibatinib over pemigatinib would automatically imply superiority of futibatinib over mFOLFOX as well. However, comments by the EAG in TA722 explain that the result of this pemigatinib versus mFOLFOX analysis is uncertain because it was not based on a direct comparison. In the TA722 committee papers it is further reported that the EAG had reservations about the methodology of this unanchored indirect comparison, particularly in terms of the limited adjustment for possible effect modifiers and prognostic variables. Therefore, it appears that the evidence base for excluding mFOLFOX as a comparator is ambiguous. The company suggested that omission of mFOLFOX is also supported by guideline positions and expert clinical opinion, but these guidelines recommend pemigatinib as an option, and mFOLFOX continues to be recommended. Therefore, the EAG does not regard these sources as a substitute for objective data on clinical practice in England and Wales.
What alternative approach has the EAG suggested?	To include mFOLFOX as a comparator.
What is the expected effect on the CE estimates?	Unclear. If futibatinib is less effective and less costly than pemigatinib, as in the EAG base case, then the ICER of futibatinib versus mFOLFOX would need to be estimated in a full incremental analysis.
What additional evidence or analyses might help to resolve this key issue?	If mFOLFOX is a relevant comparator, then the ICER of futibatinib versus pemigatinib and mFOLFOX would need to be estimated in a full incremental analysis. However, if futibatinib and pemigatinib were equally effective and futibatinib less costly then there would be no point in the analysis given that pemigatinib was found to be cost effective compared to mFOLFOX.
CE = cost effectiveness; CS = company submission; EAG = External Assessment Group; FOLFOX = folinic acid, fluorouracil and oxaliplatin; ITC = indirect treatment comparison; mFOLFOX = modified FOLFOX; SLR = systematic literature review; TA = Technology Appraisal	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified several major concerns with the evidence presented on the clinical effectiveness, namely the lack of evidence of similarity between trial and target population (Table 1.3), the incorrect assertion that there are no effect modifiers (Table 1.4), the need for further sub-group analyses (Table 1.5), potentially insufficient covariates in the MAIC model (Table 1.6), a need for

evidence that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects (Table 1.7), need for an additional simulated treatment comparison (STC; Table 1.8) and need for an additional MAIC on health-related quality of life (HRQoL; Table 1.9).

Table 1.3: Key issue 2: No evidence of similarity between trial and target population

Report Section	**3.2.3**
Description of issue and why the EAG has identified it as important	Clinical expert guidance is used to assert that the trial and target populations are comparable. Clinical expert guidance, though useful, may not be sufficient for such an important issue as the similarity between trial and target populations in England and Wales. If characteristics of the target population are different to those in the trial, then the trial results may not represent the results that might be expected in clinical practice in England and Wales. Furthermore, if the characteristics that differ are those that are amongst those included as variables in the pre-specified sub-group analyses, then it may be possible to infer how outcomes in clinical practice will be affected by these differences. Therefore, knowledge of any differences is potentially very useful. The company have stated that they do not know of any quantitative data describing target population characteristics, but it is unclear if this is based on a systematic search. Whilst reliance on expert clinical opinion is unavoidable in the presence of no objective data, the lack of objective data means that the basis for assuming the trial results are generalisable to the target population in England and Wales is questionable.
What alternative approach has the EAG suggested?	The company should attempt a systematic search for the characteristics of the target population in England and Wales, with special reference to the characteristics used for sub-group analyses.
What is the expected effect on the CE estimates?	Unclear. However, if there are differences between populations then the trial/ITC results may not be suitable for a CE analysis that is relevant to the target population.
What additional evidence or analyses might help to resolve this key issue?	The company should attempt a systematic search for the characteristics of the target population in England and Wales, with special reference to the characteristics used for sub-group analyses.
CE = cost effectiveness; EAG = External Assessment Group; ITC = indirect treatment comparison	

Table 1.4: Key issue 3: Incorrect assertion that there are no effect modifiers

Report Section	**3.2.5.4**
Description of issue and why the EAG has identified it as important	The company implies that the sub-group analyses suggest no effect modification from the chosen variables. However, this is not necessarily the case. The sub-group analyses show a trend for age to be an effect modifier, with older age being associated with a more robust response to treatment. For 'prior systemic therapy' there was an apparent dose-response effect, which supports the possibility that efficacy may increase with increased prior systemic therapy. The 95% CI for the strata in all sub-grouping analyses overlap, but this does not necessarily mean that the differences are 'non-significant', as it is quite possible for overlapping 95% CIs to be consistent with significant difference at an alpha of 0.05.

Report Section	3.2.5.4
	In any event, the sub-group analysis is probably underpowered: the groups may be so small that detection of 'significant' differences will be difficult. This implies that any significant results are to be taken seriously, because they will probably require a large effect size to be so detected. On the other hand, there may be a high risk of type II errors if the statistical analyses show a marginally 'non-significant' result, and therefore it would make sense to pay attention to strong but non-significant trends in the data. The EAG suggested that a statistical analysis of the sub-grouping analysis should therefore be presented. In the response to clarification, the company stated that statistical analysis was not carried out because of underpowering. The EAG are not satisfied with this response because it fails to consider the points made in the clarification question – that the likely underpowering of the analysis means that any significant effects would represent a large magnitude of effect, and that any non-significant trends would indicate variables requiring consideration (given the greater need to avoid type II errors than type I errors in this particular context).
What alternative approach has the EAG suggested?	The company should carry out a statistical analysis on the sub-group analyses. Given the underpowering of the analysis, any strong trends should be identified and discussed.
What is the expected effect on the CE estimates?	Unclear. However, if there are probable effect modifiers that differ in magnitude between populations, then the trial/ITC results may not be suitable for a CE analysis that is relevant to the target population in England and Wales.
What additional evidence or analyses might help to resolve this key issue?	The company should carry out a statistical analysis on the sub-group analyses. Given the underpowering of the analysis, any strong trends should be identified and discussed.
CE = cost effectiveness; CI = confidence interval; EAG = External Assessment Group; ITC = indirect treatment comparison	

Table 1.5: Key issue 4: Need for further sub-group analyses

Report Section	3.2.5.4
Description of issue and why the EAG has identified it as important	Only 10/11 of the pre-planned sub-group analyses are reported. The omitted analysis was defined by 'patients with solid tissue sample and report'. The company stated that this was omitted because of a very small sample size (n=4) in one sub-group. The EAG would note that for the sub-group analysis of 'prior neo-adjuvant treatment' there are also only four patients in one sub-group. The EAG is therefore unclear why the rationale for exclusion of one variable (the omitted variable) would not apply to another ('prior neo-adjuvant treatment'). Also, 'concomitant treatments', a potentially important covariate that could have a large impact on effect size, is not a sub-grouping variable. The company did not analyse this as they approached it as a yes/no variable – that is, because everyone had concomitant treatments then there would be no independent variable contrast. However, the EAG's response to this is that consideration of concomitant treatments could have been made by categorising the given concomitant treatments into three or four bins, based on type. This is viewed as important, given that concomitant

Report Section	3.2.5.4
	treatments may influence outcomes and it is plausible that concomitant treatment choice may differ in the target population in England and Wales to that in the trial.
What alternative approach has the EAG suggested?	The company should provide the sub-group analysis for these outcomes if appropriate.
What is the expected effect on the CE estimates?	Unclear (see key issue 4).
What additional evidence or analyses might help to resolve this key issue?	The company should provide the sub-group analysis for these outcomes if appropriate.
CE = cost effectiveness; EAG = External Assessment Group	

Table 1.6: Key issue 5: Covariates in MAIC model

Report Section	3.4
Description of issue and why the EAG has identified it as important	The ITC Cox regression model did not include the potentially important variable of different types of concomitant treatments. It was not possible for the company to include this variable, given that it was not available for the comparator, but some uncertainty in outcome may have arisen as a result.
What alternative approach has the EAG suggested?	Consideration of the uncertainty the omission of this variable may have on results.
What is the expected effect on the CE estimates?	Unclear, but potential for increase or decrease.
What additional evidence or analyses might help to resolve this key issue?	Consideration of the uncertainty the omission of this variable may have on results.
CE = cost effectiveness; EAG = External Assessment Group; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison	

Table 1.7: Key issue 6: Need for evidence that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects

Report Section	3.4
Description of issue and why the EAG has identified it as important	As recommended in TSD18, it is important for the company to provide evidence that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects and present an estimate of the likely range of residual systematic error in the "adjusted" unanchored comparison.
What alternative approach has the EAG suggested?	To provide evidence that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects and present an estimate of the likely range of residual systematic error in the "adjusted" unanchored comparison.
What is the expected effect on the CE estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	See above.
CE = cost effectiveness; EAG = External Assessment Group; TSD = Technical Support Document	

Table 1.8: Key issue 7: Need to present the additional STC

Report Section	3.4
Description of issue and why the EAG has identified it as important	There is a need to present the details of the STC given the lack of reliability of any form of population adjustment in an unanchored comparison.
What alternative approach has the EAG suggested?	See above.
What is the expected effect on the CE estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	See above.
CE = cost effectiveness; EAG = External Assessment Group; STC = simulated treatment comparison	

Table 1.9: Key issue 8: Omission of HRQoL from the MAIC analyses

Report Section	3.4
Description of issue and why the EAG has identified it as important	No justification is given for the omission of HRQoL from the MAIC analyses, apart from the implicit suggestion that it was not to be used for economic modelling. The company assumes that HRQoL for futibatinib and pemigatinib will be similar because of similar efficacy and safety profiles, alongside a similar mode of administration. This appears to be based on a simplistic model of how efficacy outcomes and AEs may interact in real-world patients. This outcome has been requested by the NICE final scope and is therefore an important aspect of the clinical evidence, which is important for clinical decision-making even if not carried through to economic modelling. It should therefore also be subjected to an MAIC, as without comparison to a reference treatment the meaning of the single arm results for this outcome is questionable.
What alternative approach has the EAG suggested?	Perform ITCs for HRQoL.
What is the expected effect on the CE estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Perform ITCs for HRQoL.
AEs = adverse events; CE = cost effectiveness; EAG = External Assessment Group; HRQoL = health-related quality of life; ITCs = indirect treatment comparisons; MAIC = matching-adjusted indirect comparison; NICE = National Institute of Health and Care Excellence	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

A full summary of the cost effectiveness (CE) evidence review conclusions can be found in Section 6.4 of this report. The company's CE results are presented in Section 5, the EAG's summary and detailed critique are in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The key issues in the CE evidence are discussed in Tables 1.10, 1.11 and 1.12.

Table 1.10: Key issue 9: The EAG disagrees with the company's approach of modelling OS and PFS assuming PH

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The company assumed: • PHs to model OS and PFS treatment effect between futibatinib and pemigatinib. • Extrapolation model selection was based on unadjusted data for futibatinib and MAIC (adjusted) for pemigatinib. • OS curve selection: futibatinib log-normal, pemigatinib HR. • PFS curve selection: futibatinib log-normal, pemigatinib HR.
What alternative approach has the EAG suggested?	The EAG prefers: • Independent modelling, as it considers the PH assumption is likely to be invalid. • Extrapolation model selection should be based on MAIC-adjusted data for both futibatinib and pemigatinib. • OS curve selection: Weibull. • PFS curve selection: log-normal. • OS benefit modelled as long as patients are on treatment.
What is the expected effect on the CE estimates?	Decrease in both incremental costs and incremental QALYs, but the magnitude depends on the selection of the curves. Because survival and hazard curves for futibatinib and pemigatinib cross after some time [redacted].
What additional evidence or analyses might help to resolve this key issue?	None.
CE = cost effectiveness; EAG = External Assessment Group; HR = hazard ratio; ICER = incremental cost effectiveness ratio; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; PH = proportional hazard; QALYs = quality-adjusted life years	

Table 1.11: Key issue 10: The EAG disagrees with the company's approach of assuming ToT equal to PFS

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The company assumed ToT to be equal to PFS.
What alternative approach has the EAG suggested?	The EAG prefers: • Modelling ToT and PFS independently, as ToT is smaller than or equal to PFS. • Extrapolation model selection for ToT should be based on adjusted data for both futibatinib and pemigatinib. However, ToT data for pemigatinib are not available. • ToT curve selection for futibatinib: Weibull. • ToT curve selection for pemigatinib: same PFS HR estimated from the MAIC.

Report Section	4.2.6
What is the expected effect on the CE estimates?	Likely decrease in incremental costs, but uncertain.
What additional evidence or analyses might help to resolve this key issue?	Comparison of ToT and PFS data for both futibatinib and pemigatinib.
CE = cost effectiveness; EAG = External Assessment Group; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; PFS = progression-free survival; ToT = time on treatment	

Table 1.12: Key issue 11: The EAG is uncertain about the number of remaining errors in the company's model

Report Section	4, 5 and 6
Description of issue and why the EAG has identified it as important	The EAG identified several errors in the updated model received after clarification. Triggered by this, the EAG noticed that, while most of the errors found in the updated model were related to the changes made by the company in response to the EAG clarification requests, some of them were already present in the original model. The EAG would like to express its concerns regarding the numerous errors identified in the company's model, and because of this, the EAG is concerned that additional errors may still exist in the model.
What alternative approach has the EAG suggested?	Given the lack of data and time, the EAG did not correct all the identified errors in the company's original model. Most of these errors were related to the implementation of the PSA and, therefore, these did not impact the company's base-case results. However, the EAG also noticed that the implementation of the half-cycle correction was incorrect in both the original and updated models. Since this error did impact the model results, it was corrected by the EAG. For the EAG base-case and PSA results, which are based on the model received after clarification, the EAG corrected as many errors as possible.
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	A new model where extensive technical verification has been conducted, preferably by an external party.
CE = cost effectiveness; EAG = External Assessment Group; PSA = probabilistic sensitivity analysis	

1.6 Summary of the EAG's view

The decision problem differed from the NICE scope in its restriction of comparators to pemigatinib alone. Although the omission of best supportive care was justified, the company were unable to give a strong rationale for the omission of modified folinic acid, fluorouracil and oxaliplatin (mFOLFOX) as a comparator. For mFOLFOX to be justifiably omitted, it would need to be shown to be inferior to pemigatinib in the same population, but this was not achieved. This was a concern because it meant that any demonstration of superiority for futibatinib over pemigatinib would not necessarily indicate futibatinib was better than mFOLFOX.

The single-study trial data of 103 patients in the specified population demonstrated futibatinib was associated with an OS at 12 months of 73.1%, a PFS of 35.4% at 12 months, complete response (CR) in 1% and partial response (PR) in 42% at the final data cut-off (DCO) (median follow-up 25 months), and a mean improvement of EuroQoL visual analogue scale (EQ VAS) of 4.76 points at 9 months. Because of the single arm data, it was not possible to eliminate extraneous effects and attribute these findings solely to treatment effects. It was unclear how representative these trial results were to the target population as no characteristics of the target population were available for comparison with the trial baseline characteristics. Despite the company's confidence in expert clinical opinion, it was not possible to exclude population differences in age and prior systemic therapy, which had shown trends in the sub-group analysis for outcome modification. It was also not possible to exclude population differences in concomitant medication types or population differences in patients with solid tissue samples, which had not been included in the sub-group analysis but were plausible effect modifiers. The company's rationale for omitting these from the sub-group analysis was insufficiently strong, according to the opinion of the EAG. It is possible therefore that the trial results might not precisely apply to the target population, although the EAG accepts that any effect of population differences in these variables on outcomes is likely to be small.

AEs from futibatinib were generally manageable, with 11 serious treatment related adverse events (TRAEs) in 103 patients, and no deaths. It is unclear how these would compare to those for pemigatinib.

As the trial results did not involve a comparator, an MAIC was used to facilitate comparison of futibatinib with pemigatinib. The single arm trial used for the pemigatinib data was appropriate, and although the covariates used for adjustment of the data were appropriately chosen, 'types of concomitant therapy', which is a plausible effect modifier, was not included in the MAIC model. The MAIC results demonstrated that the treatments were similar in terms of OS and PFS. Given the methodology used by the company, and the company's clear responses to clarification questions, the EAG has reasonable confidence that the MAIC results reflect the equipoise of futibatinib and pemigatinib. However, the EAG have concerns that the submission did not exclude the fact that mFOLFOX may have been superior to pemigatinib and therefore also superior futibatinib. The EAG also have concerns about the external validity of the results to the target population, though this is of lesser magnitude.

The step-by-step changes made by the EAG to derive its base-case, using the CS base-case and the model submitted after clarification as starting point, can be seen in Table 6.8. The change with the largest impact on the results was the independent modelling of OS and PFS combined with removing the restriction on equal OS and PFS hazard rates after 24 months. Changing to independent modelling alone may result in invalid survival curves for pemigatinib. Therefore, independent modelling has to be used in combination without restricting the hazard rates after 24 months. This change led to a decrease in the incremental costs and to negative incremental QALYs. Independent modelling of ToT had also a substantial impact on the incremental costs, by reducing the difference between futibatinib and pemigatinib treatments. The impact of the other changes made by the EAG was minor.

Table 1.13: Summary of EAG's preferred assumptions and ICERs

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CS base-case					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	140,130	[redacted]			
CS base-case after the clarification					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	142,163	[redacted]			
Correction of the half-cycle correction implementation					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	135,191	[redacted]			
Independent modelling of OS (Weibull) and PFS (log-normal)*					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	117,775	[redacted]			
Remove restriction on equal OS and PFS hazard rates after 24 months					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	143,638	[redacted]			
Independent modelling of OS (Weibull) and PFS (log-normal) & remove restriction on equal OS and PFS hazard rates after 24 months					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	336,212**
Pemigatinib	136,821	[redacted]			
OS and PFS extrapolations based on (MAIC) adjusted data					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	138,497	[redacted]			
ToT modelled independent of PFS					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	124,703	[redacted]			

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ToT modelled independent of PFS and restricted by PFS					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	116,671	[redacted]			
Include costs of genetic testing					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	142,503	[redacted]			
EAG's base-case					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	352,788**
Pemigatinib	128,216	[redacted]			

Based on the model submitted following the clarification phase.[1]

* This change (independent modelling) may result in invalid survival curves for pemigatinib since it has to be used together with the assumption "Remove restriction on equal OS and PFS hazard rates after 24 months". Therefore, looking at this change alone can be misleading.

** ICER in SW quadrant of the CE-plane.

CE = cost effectiveness; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; Inc. = incremental; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; ToT = time on treatment

2. Critique of company's definition of decision problem

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG Comment
Population	Adults with locally advanced or metastatic CCA with FGFR2 fusion or rearrangement that has progressed after at least one prior systemic therapy	Adult patients with locally advanced or metastatic CCA with FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy	N/A	N/A
Intervention	Futibatinib	Futibatinib	N/A	N/A
Comparator(s)	• Pemigatinib • mFOLFOX regimen • BSC	Pemigatinib	Pemigatinib is the only targeted treatment recommended by NICE for the target population in the UK. UK clinical experts highlighted that patients known to have an FGFR2 fusion or rearrangement would receive pemigatinib in clinical practice, given the magnitude of the survival benefit for pemigatinib versus chemotherapy. As such, chemotherapy or BSC are not considered to be relevant comparators to futibatinib in this appraisal	Further rationale needs to be given for the absence of the modified FOLFOX regimen. The case made for omitting mFOLFOX from the decision problem is that one study has shown that pemigatinib may be more effective than mFOLFOX and symptom control, and therefore it is unnecessary to include mFOLFOX. However, TA722[2-4] explains that the pemigatinib versus mFOLFOX result is uncertain because it was not a direct comparison. In the TA722 committee papers it is reported that the EAG had reservations about the methodology of this

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG Comment
				unanchored indirect comparison, particularly in terms of the limited adjustment for possible effect modifiers and prognostic variables. Therefore, it appears that the evidence base for excluding mFOLFOX as a comparator is ambiguous

Outcomes	The outcome measures to be considered include:
	• OS
	• PFS
	• Response rates
	• Adverse effects of treatment
	• HRQoL
		• Efficacy data
		  • ORR
		  • DOR
		  • PFS
		  • OS
		  • DCR
		• HRQoL data
		  • EORTC QLQ-C30
		  • EQ-5D-3L
		  • EQ VAS
		• AE data
			N/A	The decision problem includes all outcomes in the NICE final scope.
				DOR and DCR are outside the NICE final scope.

Economic analysis	The reference case stipulates that the CE of treatments should be expressed in terms of incremental cost per QALY. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published	As per the NICE reference case, CE is expressed in terms of incremental cost per QALY, and costs considered from the perspective of the NHS and PSS, with a lifetime horizon	N/A	The economic analyses are in line with the NICE reference case.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG Comment
	NICE TA guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and CE 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 PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.			
Subgroups to be considered	None reported			The company did not report the use of any sub-grouping strategies in the decision problem. However, in the trial, several sub-grouping variables were chosen. These were formulated pre-hoc and appear appropriate.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG Comment
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	N/A

Based on Table 1 of the CS[5]

BSC = best supportive care; CCA = cholangiocarcinoma; CE = cost effectiveness; CS = company submission; DCR = disease control rate; DOR = duration of response; EAG = External Assessment Group; EORTC QLQ C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L = Euro-QoL-5 dimensions-3 levels; EQ VAS = EuroQol visual analogue scale; FGFR2 = fusion growth factor receptor 2; FOLFOX = folinic acid, fluorouracil and oxaliplatin; HRQoL = health-related quality of life; mFOLFOX = modified FOLFOX; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PSS = Personal Social Services; QALY = quality-adjusted life years; UK = United Kingdom

2.1 Population

The National Institute for Health and Care Excellence (NICE) final scope describes the populations as adults with locally advanced or metastatic cholangiocarcinoma (CCA) with fusion growth factor receptor 2 (FGFR2) fusion or rearrangement that has progressed after at least one prior systemic therapy. The decision problem has exactly the same definition.

2.2 Intervention

The NICE final scope describes the intervention as futibatinib, which concurs exactly with the decision problem.

2.3 Comparators

The NICE final scope describes the comparators as:

- Pemigatinib
- Modified folinic acid, fluorouracil and oxaliplatin (mFOLFOX) regimen
- Best supportive care (BSC)

The decision problem only includes pemigatinib, and does not include the mFOLFOX regime, nor BSC. The company justify these omissions in the company submission (CS)[5] by stating that, "*Pemigatinib is the only targeted treatment recommended by NICE for the target population in the UK. UK clinical experts highlighted that patients known to have an FGFR2 fusion or rearrangement would receive pemigatinib in clinical practice, given the magnitude of the survival benefit for pemigatinib versus chemotherapy. As such, chemotherapy or BSC are not considered to be relevant comparators to futibatinib in this appraisal"*. It is further stated that, *"For patients who experience disease progression on first-line therapy, current treatment options in the UK are dependent on the patients' genetic profiles, including FGFR mutation status. Historically, second-line treatment has consisted of modified folinic acid, fluorouracil and oxaliplatin (mFOLFOX) in combination with active symptom control (ASC). However, since TA722, UK clinical experts confirmed almost all patients with an FGFR2 fusion or rearrangement would receive targeted treatment with pemigatinib. The use of FGFR2-targeted treatments in eligible populations is supported by the ESMO 2022 and BSG 2023 guidelines"*.

EAG comment:

- Further rationale needs to be given for the absence of the mFOLFOX regimen. The case made by the company for omitting mFOLFOX from the decision problem is based on one analysis carried out as part of Technology Appraisal 722 (TA722),[2-4] which has shown that pemigatinib may be more effective than mFOLFOX and symptom control. The conclusion is therefore that it is unnecessary to include mFOLFOX because if pemigatinib is superior to mFOLFOX, then any superiority of futibatinib over pemigatinib would automatically imply superiority of futibatinib over mFOLFOX as well. However, comments by the EAG in TA722[2-4] explain that the result of this pemigatinib versus mFOLFOX analysis is uncertain because it was not based on a direct comparison. In the TA722 committee papers it is further reported that the EAG had reservations about the methodology of this unanchored indirect comparison, particularly in terms of the limited adjustment for possible effect modifiers and prognostic variables. Therefore, it appears that the

evidence base for excluding mFOLFOX as a comparator is ambiguous. A request for further justification of the comparator omissions was put to the company in the clarification letter.[6]

- The company responded to the request for further clarification by stating that, *"At the time of the NICE appraisal of pemigatinib, the most recent British Society of Gastroenterology (BSG) guidelines for the management of CCA (which, at the time, were published in 2012), recommended combination chemotherapy in patients with adequate performance status following failure of first-line chemotherapy. .....However, the introduction of targeted therapies, including pemigatinib, has changed the treatment landscape for advanced CCA with FGFR2 fusions or rearrangements, due to these treatments offering apparent substantial survival benefits compared with second-line chemotherapy. In the ABC-06 study which evaluated FOLFOX plus ASC versus ASC alone in patients with locally advanced or metastatic biliary tract cancer, FOLFOX plus ASC resulted in a median overall survival (OS) of 6.2 months (95% CI: 5.4–7.6) versus 5.3 months (4.1–5.8) in the ASC alone arm. In comparison, in the FIGHT-202 trial, patients with CCA with FGFR fusions or rearrangements with disease progression following at least one previous treatment receiving pemigatinib had a median OS of 17.5 months (95% CI: 14.4, 22.9). These substantial survival gains resulted in a positive recommendation of pemigatinib from NICE in adult patients with locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement that has progressed after systemic therapy".*[7]
- The External Assessment Group (EAG) do not think that the above section of the response offers an improved rationale, as it merely restates the data from the unanchored and improperly adjusted matching-adjusted indirect comparison (MAIC) used in TA722 to claim superiority of pemigatinib over mFOLFOX. There is no presentation of new evidence that would suggest that mFOLFOX is inferior to pemigatinib and therefore should not be included as a comparator.
- The company also stated that, *"These developments are reflected in the most recent guidelines for the treatment of CCA. The European Society of Medical Oncology (ESMO) guidelines (2022) position FOLFOX as a second-line therapy for patients without targetable genetic aberrations only, and recommend the exclusive use of FGFR inhibitors in eligible patients with FGFR2 fusions or rearrangements. This aligns with the updated BSG (2023) guidelines: although, unlike the ESMO guidelines, they do not present a specific treatment pathway, these guidelines do however strongly recommend that CCA should be subjected to molecular profiling at the earliest opportunity, and that treatment options should be reviewed by clinicians with appropriate expertise".*[7]
- The EAG do not regard the above guideline positions as strengthening the rationale, as the evidence upon which the guideline decisions are based is not made clear.
- The company go on to state that, *"The exclusive use of pemigatinib in UK clinical practice in eligible patients with FGFR2 fusions or rearrangements was also supported by expert clinical opinion. As part of an Advisory Board, UK clinical experts in CCA highlighted that owing to the significant survival benefits associated with targeted treatment for patients with recognisable oncogenic mutations, in UK clinical practice, following one prior therapy, patients with CCA with FGFR2 fusions or rearrangements receive targeted treatment with pemigatinib (an FGFR2 inhibitor). The experts additionally highlighted that response rates to treatment in patients with CCA with FGFR2 fusions or rearrangements increased from ~5% in patients receiving non-targeted chemotherapy to ~40% in patients receiving pemigatinib, an 8-fold increase. Due to these substantial differences in both response rates and survival, FOLFOX is not used in UK clinical practice in patients with FGFR2 fusions or rearrangements. Clinical expert feedback and most recent guidelines therefore align in that mFOLFOX does not represent a relevant comparator to futibatinib in the indication of relevance to this submission.".*[7]

- With regard to the above response, whilst the EAG always respect clinical opinion, it cannot be regarded as equivalent to objective data on actual use in clinical practice. Therefore, again, the EAG remain unconvinced. The omission of mFOLFOX as a comparator is thus a key issue.
- Finally, the company state that, *"It is however acknowledged that there may be patients in UK clinical practice who are not fit enough to receive treatment with pemigatinib and who may therefore receive only ASC or BSC. However, as futibatinib is associated with a comparable safety profile to pemigatinib, it is reasonable to assume that patients who are not fit enough to receive pemigatinib, would also be unable to receive futibatinib. As such, patients with FGFR2 fusions or rearrangements receiving ASC or BSC in UK clinical practice represent a distinct subgroup of patients that is not relevant to this submission. Neither ASC nor BSC therefore represent a relevant comparator to futibatinib in this indication."*[7]
- The EAG agree that BSC is therefore an inappropriate comparator.

2.4 Outcomes

The NICE final scope lists the following outcome measures:

- overall survival (OS)
- progression-free survival (PFS)
- response rates
- adverse effects of treatment
- health-related quality of life

The decision problem included OS and PFS. One outcome covering response rates is also present in the decision problem – objective response rate (ORR). Three quality of life (QoL) measures are included in the decision problem – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), Euro-QoL-5 dimensions-3 levels (EQ-5D-3L), and EuroQoL visual analogue scale (EQ VAS). Adverse data are also included.

EAG comment:

- There are no omissions: all outcomes requested by the NICE final scope[8] have been appropriately covered.
- The decision problem includes duration of response (DOR) and disease control rate (DCR), which are not in the NICE final scope.[8] The company were asked in the clarification letter[6] why these two outcomes have been included.
- The company responded by stating that, *"The NICE scope specifies that response rate outcomes should be included in the evaluation. Disease control rate (DCR), based on confirmed CR, PR and stable disease (SD), was therefore included in the submission in addition to objective response rate (ORR) which is based on confirmed complete response (CR) and partial response (PR), to provide additional response rate data on futibatinib. The duration of response (DOR) outcome, in addition to providing further evidence related to patient responses, is considered to be an established and clinically important outcome in the field of oncology. As a result, both DCR and DOR were considered to be relevant outcomes for inclusion in the submission, alongside the main efficacy outcomes of overall survival (OS), progression-free survival (PFS) and ORR. The relevance of these outcomes in this indication is supported by the fact that both outcomes were included in the two most recent appraisals in CCA submitted to NICE."*[7] The EAG agrees that DCR relates to the CR, PR and SD response rate outcomes. However, these are already reported separately in the results, and inclusion of DCR would constitute double-counting. Therefore, DCR results are not

included in the EAG report. DOR is not a measure of response rate and so is not relevant to the outcomes listed by the NICE final scope.[8] Therefore, this outcome has also not been included in the EAG report.

2.5 Other relevant factors

The CS[5] states that *"Futibatinib is licenced by the Medicines and Healthcare products Regulatory Agency (MHRA) for treatment of adult patients with locally advanced or metastatic cholangiocarcinoma (CCA) with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy."*

The CS[5] states that, *"There are no known equality issues relating to the use of futibatinib in patients with previously treated, unresectable, locally advanced, or metastatic CCA with FGFR2 fusions/rearrangements."*

The Food and Drug Administration (FDA) granted accelerated approval to futibatinib (Lytgobi, Taiho Oncology, Inc.) for adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic CCA harbouring FGFR2 gene fusions or other rearrangements on 30 September 2022.

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.[5, 9] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[10, 11] The EAG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS[5] details the systematic literature review (SLR) conducted to identify relevant clinical evidence on the efficacy and safety of futibatinib and pemigatinib for the treatment of adult patients with locally advanced or metastatic CCA with FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy.[9] The searches were conducted in September-October 2023. A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	1974-4.9.23	4.9.23
MEDLINE (inc. In Process & Other Non-Indexed Citations and Daily)	Ovid	1946-4.9.23	4.9.23
CENTRAL	Cochrane Library	To Issue 7/12 July 2023	4.9.23
CDSR	Cochrane Library	To Issue 8/12 August 2023	4.9.23
DARE	CRD website	2015-4.9.23	4.9.23
Conferences			
• ASCO • ESMO • ESMO World Congress on Gastrointestinal Cancer • ISPOR Annual Meetings	Internet	2021-2023	6.9.23
Trials registries			
• www.ClinicalTrials.gov • EU-CTR • ISRCTN	Internet	2015+	11.9.23

ASCO = American Society of Clinical Oncology; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CRD = Centre for Reviews and Dissemination; DARE = Database of Abstracts of Reviews of Effects; ESMO = European Society of Medical Oncology; EU = European Union; EU-CTR = EU Clinical Trials Register; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; ISRCTN = International Standard Randomised Controlled Trial Number Registry

EAG comment:

- Searches were undertaken in September-October 2023 to identify clinical evidence on the efficacy and safety of futibatinib and pemigatinib for the treatment of adult patients with locally advanced or metastatic CCA with FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy. The CS, Appendix D and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[5, 7, 9]
- A good range of bibliographic databases, conferences and trials registers were searched. Reference checking was conducted. Searches were well structured, transparent and reproducible.
- The database searches for the clinical effectiveness SLR combined facets for CCA AND neoplasm metastasis AND FGFR2. In the Embase and MEDLINE searches, this was then combined with a study design filter for clinical trials. Animal-only studies were excluded.
- Database searches were limited to studies from 2015-date. No language limit was applied to the searches.
- Conference proceedings were handsearched for four key international conferences between 2021 and 2023. The rationale for this was that:
  'Abstracts from congresses prior to 2021 were excluded, under the assumption that the majority of conference abstracts are usually published in a journal article within 2 years.'
  Embase however, which also contains conference proceedings, was limited to conferences proceedings from 2022-2023, rather than 2021-2023 (Appendix D, Table 2; Lines 33-34[9]). The EAG feels that more extensive conferences proceedings searches could have been conducted on Embase, and that this might have retrieved additional useful records.
- The clinical effectiveness searches were very narrow in focus, retrieving small numbers of references. A number of approaches could have helped increase the sensitivity of the searches, thus reducing the risk of missing potentially useful references without a large increase in the numbers of records to be screened:
  - Additional synonyms could have been added to all facets to make them more sensitive, including *'late stage'* in the neoplasm metastasis facet, *'bek protein tyrosine kinase'*, *'cd332 antigen'* and the truncation of *'2*'* in the FGFR2 facet, and additional free-text terms such as *'(bile or biliary) and (tract or duct) and (neoplas* or carcinoma* or tum?r* or malignan*)'* in the CCA facet.
  - A more cautious approach might have been to not include the 'neoplasm metastasis' facet. The EAG notes that this would not have greatly increased the yield of the searches and would have resulted in a more sensitive search.
  - Given the focus of the searches to a very narrow population, and the low numbers of records retrieved by the searches, the EAG does not believe it was necessary to include a study design filter. However comprehensive a filter is, it will always run the risk of removing potentially relevant records. The MEDLINE search, for example, retrieved only 230 records before the clinical trials filter was applied, and the Embase search retrieved only 587 records.

  The EAG re-ran the MEDLINE searches, incorporating the above changes, and found an additional 228 records from this database alone. Screening of the title/abstract of those records by the EAG identified some potentially relevant papers, however the EAG is unable to assess their final inclusion in the SLR after full-text screening, and any subsequent effect this might have had on the overall conclusions.

3.1.2 Inclusion criteria

The CS[5] states that a SLR was conducted in September–October 2023 to identify clinical evidence on the efficacy and safety of futibatinib and pemigatinib for the treatment of adult patients with locally advanced or metastatic CCA with FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy. Sixteen publications derived from five studies were identified. The process for the identification and appraisal of the evidence base in this submission is summarised in this Section.

The eligibility criteria used in the search strategy as described in Appendix D of the CS[9] to identify relevant evidence is detailed in Table 3.2.

Table 3.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Inclusion	Exclusion
Population	Patients ≥18 years with histologically confirmed, unresectable CCA that is locally advanced, metastatic, or recurrent and harbours FGFR2 gene rearrangements or fusions	• Patients <18 years with other types of solid tumours • Patients who have not received any prior pharmacological intervention for the treatment of metastatic CCA • Studies conducted in animals or in vitro
Interventions	The following interventions will be eligible for inclusion in any line of therapy, as monotherapy: • Futibatinib • Pemigatinib	• Trials that refer to interventions by drug class (e.g. FGFR2 inhibitors), but do not report outcomes for individual drugs • Interventions other than those listed
Comparator	N/A	N/A
Outcomes	Studies reporting clinical outcomes including: • RECIST defined outcomes (PFS, DOR, ORR, DCR, EFS) • OS • Safety outcomes, including overall rates of AEs including rates of SAEs; TRAEs; TEAEs • Rates of individual AEs: hyperphosphatemia, retinal disorders, hepatotoxicity, nail disorders, plantar erythrodysesthesia syndrome and rash • HRQoL outcomes including EORTC QLQ-C30, EQ-5D (3L or 5L), SF-36 (and variations) and FACT measures	N/A

	Inclusion	Exclusion
Study design	Phase II onwards clinical trials including: • RCTs • Non-randomised comparative trials • Single-arm trials • Post-hoc analyses of eligible clinical trials will be included if they report eligible outcomes	• Pooled data from relevant trials • SLRs and NMAs • Other study designs e.g., observational studies and real-world studies, retrospective or prospective registry studies, surveys, case series, or case reports and economic studies • Phase I trials or Phase I portion of Phase I/Phase II trials
Language restrictions	Publications with an abstract/full-text in the English language	Publications not written in the English language
Date limit	• Full-text articles published in peer-reviewed journals between 2015 and 2023 • Conference abstracts published from 2021 onwards, if they report data for relevant clinical trials that are not yet published in a peer-reviewed journal, or if they report additional data for relevant clinical trials	• Full-text articles published before 2015 • Conference abstracts published before 2021
Publication type	• Full-text articles published in peer-reviewed journals or clinical trial registries • Conference abstracts	Comments, letters or editorials

Based on Table 5, Appendix D of CS[9]

[a] Patients were also eligible if they meet the above criteria and were part of a wider population of patients with solid tumours; outcomes had to be reported independently for the eligible CCA population.

[b] Subpopulations of interest included FGFR subtypes and CCA subtypes.

[c] Publications were assessed for additional individual trial data.

[d] Relevant SLRs/(N)MAs were included at the title/abstract stage to be handsearched but were excluded at the full-text review stage unless they present primary research.

AE = adverse event; CCA = cholangiocarcinoma; CS = company submission; DCR = disease control rate; DOR = duration of response; EFS = event-free survival; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D = EuroQol 5 Dimension; FACT = Functional Assessment of Cancer Therapy; FDA = Food and Drug Administration; FGFR2 = fusion growth factor receptor; HRQoL = health-related quality of life; N/A = not applicable NMA = network meta-analysis; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; QLQ = quality of life questionnaire; RCT = randomised controlled trial; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = serious adverse event; SF-36 = Short Form-36; SLR = systematic literature review; TEAEs = treatment-emergent adverse events; TRAEs = treatment-related adverse events; UK = United Kingdom

EAG comment: The protocol above was detailed and comprehensive in terms of the inclusion and exclusion criteria, but did not outline how data would be analysed or synthesised. This would have allowed scope for analysis/synthesis decisions to be made post-hoc, increasing the risk of bias.

3.1.3 Critique of data extraction

Title and abstracts were screened by two independent reviewers with any uncertainties of an articles status, being marked as an 'include'. Any disagreements were resolved by discussion until consensus was reached. In the event that consensus could not be reached, a third independent reviewer would make final decision. As conducted with titles and abstracts, full papers were also screened by two independent reviewers and any disagreements were resolved by consensus. Where necessary, a third independent reviewer made the final decision in the event that consensus could not be reached. Where the publication did not give enough information to be sure that it meets the inclusion criteria, the publication was excluded to ensure that only relevant publications are ultimately included in the SLR.

EAG comment:

- The CS[5] does not supply adequate information to determine the methods by which data extraction was conducted. While some brief information is provided in the appendices of the CS[5] to list data of interest, no mention is made on the manner of its extraction. The EAG emphasises the need for clarity in describing processes for the identification and analysis of evidence. To determine the manner by which data extraction occurred, we asked the company in the clarification letter to provide more detail.[6]
- In their response to clarification, the company state that, "*For each included study, key information was extracted into a pre-specified data extraction grid in Microsoft Word – the variables to be extracted were pre-specified, to avoid data dredging. A single reviewer extracted data from each of the included studies. Each extraction was checked by an independent reviewer who verified the accuracy and completeness of the data extracted. Any discrepancies were discussed by the two reviewers until a consensus was reached or were referred to and resolved by a third independent reviewer not involved in the data collection process. In total, three independent reviewers were involved in data extraction."*[7]
- The EAG thanks the company for their clarification.

3.1.4 Quality assessment

The CS[5] describes the approach to quality assessment by stating that *"The FOENIX-CCA2 trial was assessed for risk of bias and generalisability using the quality assessment tool developed by the York University CRD in line with NICE requirements".*

EAG comment:

- While this statement is referenced to the Centre for Reviews and Dissemination (CRD) guide for undertaking systematic reviews in healthcare, there is no justification summary provided to clarify why the opted method of quality appraisal was selected. The EAG reminds authors that it is important to provide information and clarity to ensure that limitations, risks of bias, and likelihood of error can be appropriately considered. It is also not clear by which manner the assessment was conducted. An optimal approach would be two independent reviewers each conducting an appraisal, with any disagreements then resolved through consensus or by the arbitration of a third independent reviewer.

- The EAG sought clarification[6] and in their response, the company stated that, *"The quality assessment of each included study was conducted by a single reviewer. The results of the quality assessment for each included study were verified by an independent reviewer. Any discrepancies were discussed by the two reviewers until consensus was reached or were referred to and resolved by a third independent reviewer not involved in the appraisal process. In total, three independent reviewers were involved in the quality appraisal process. As described in Section D.1.2 of the Company Appendices, in line with NICE's preferred checklist, the quality of all included RCTs, non-randomised comparative trials and single-arm trials was assessed using the University of York Centre for Reviews and Dissemination criteria."*[7]
- The EAG thanks the company for their clarification.

The CS[5] provides the results of the quality appraisal which are detailed below in Table 3.3.

Table 3.3: Critical appraisal of non-randomised clinical trials included in the SLR

	FOENIX-CCA2[12]	FIGHT-202[13-15]	FIGHT-101[16]	FIGHT-207[17]	NCT04256980[18]
Was the cohort recruited in an acceptable way?	Yes	Yes	Yes	Yes	Yes
Was the exposure accurately measured to minimise bias?	Yes	Yes	Yes	Unclear	Unclear
Was the outcome accurately measured to minimise bias?	Yes	Yes	Yes	Yes	Yes
Have the authors identified all important confounding factors?	Unclear	Unclear	Unclear	Unclear	Unclear
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Unclear	Unclear	Yes	Unclear
Was the follow-up of patients complete?	Yes	Yes	Yes	Unclear	Unclear
How precise (for example, in terms of CI and p values) are the results?	Trial results were precise	Trial results were precise	No	No	Unclear

Based on Table 18, Appendices of CS[9]
CI = confidence interval; CS = company submission; SLR = systematic literature review

3.1.5 Evidence synthesis

Five non-randomised studies were found by the search: FOENIX-CCA2, FIGHT-202, FIGHT-101, FIGHT-207 and NCT0425698021. FOENIX-CCA2 evaluated futibatinib and the latter four evaluated pemigatinib. These five studies comprised seven separate outcome-based papers.[12-17, 19] The company provided an indirect treatment comparison (ITC) to compare futibatinib and pemigatinib in terms of

PFS and OS, using the FOENIX-CCA2 and FIGHT-202 clinical trials. In line with the precedent from the pemigatinib NICE appraisal, a MAIC was conducted. Further details of the ITC are provided in Sections 3.3 and 3.4.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Details of the included trials

Only one study was found evaluating futibatinib. This study was FOENIX-CCA2, a multinational open-label, single arm, phase II study, which evaluates the effects of futibatinib on adults with locally advanced, metastatic, unresectable intrahepatic cholangiocarcinoma (iCCA), with FGFR2 gene fusions or other fusion growth factor receptor (FGFR) rearrangements. Patients must have progressed after at least one prior systemic therapy.

Futibatinib was provided at a starting dose of 20 mg, and outcomes were as outlined in the decision problem. There is no comparator.

One hundred and three patients were enrolled in the trial, with a median follow up of 25 months. Ninety-six (93.2) patients had discontinued treatment by the time of the data cut off (DCO). The reasons for discontinuation were radiological disease progression (78/96), clinical progression (6/96), adverse events (AEs) (7/96), withdrawal of consent (2/96), investigator decision (3/96). None were lost to follow up, died or became pregnant.

Sub-group analyses were not requested by the NICE final scope.[8] However, the pre-specified sub-group analyses carried out by the company appear to be appropriate.

Table 3.4 summarises the study methodology.

EAG comment:

- The trial population, intervention and outcomes concur with the decision problem.
- The lack of a comparator means that it is not possible to eliminate threats to internal validity, and therefore any changes in the outcome after intervention cannot be wholly or even partially assumed to be treatment effects. Fortunately, an MAIC has been undertaken, which is described and discussed in Sections 3.3 and 3.4. A well-conducted MAIC should permit a better estimation of the (relative) treatment effect.
- For the five patients that discontinued due to withdrawal of consent or investigator decision, the reasons are not reported. The company were asked to clarify this[6] as these five constitute a significant proportion of the small cohort.
- The company responded by stating that, *"Of these five patients, two patients discontinued treatment due to withdrawal of consent and three discontinued treatment due to investigator decision. Of the patients who discontinued treatment due to withdrawal of consent, one patient requested to stop taking the treatment due to overall deterioration/feeling unwell (SAE: clinical PD). No additional information was collected in terms of the precise reasons for the discontinuation for the other patient. Of the three patients who discontinued treatment due to investigator decision, no additional information was recorded for the precise reason for discontinuation, however the decision for one patient coincided with the date of radiological progression."*[7]
- The EAG thanks the company for the clarification.

Table 3.4 Summary of the methodology of the trial

Methodology	Summary
Location	Multinational study, conducted in 47 sites across UK, USA, France, Spain, Australia, Canada, Italy, Germany, Netherlands, Portugal, Republic of Korea, Taiwan R.O.C., Hong Kong and Japan
Trial design	Open-label, single-arm, Phase II study in patients with iCCA with FGFR2 gene fusions or other FGFR2 rearrangements
Inclusion criteria	• Provided written informed consent • Age ≥18 years (or according to the country's regulatory definition for legal adult age) • Histologically or cytologically confirmed, locally advanced, metastatic cancer meeting the following criteria: o Histologically or cytologically confirmed, locally advanced, metastatic, unresectable iCCA harbouring FGFR2 gene fusions or other FGFR2 rearrangements o Patient has been treated with at least one prior systemic gemcitabine and platinum-based chemotherapy o Documentation of radiographic disease progression on the most recent prior therapy • Patient has measurable disease as defined by RECIST guidelines (version 1.1, 2009) 79 for advanced solid tumours • ECOG PS 0 or 1 on day 1 of cycle 1 • Able to take medications orally (e.g., no feeding tube) • Adequate organ function • Creatinine clearance (calculated [using the Cockcroft-Gault formula] or measured value): ≥40 mL/min • Women of child-bearing potential must have a negative pregnancy test (urine or serum) within 7 days prior to administration of the first dose of futibatinib. Both males and females of reproductive potential must agree to use effective birth control during the study prior to the first dose and for 6 months after the last dose • Willing and able to comply with scheduled visits and study procedures
Exclusion criteria	• History and/or current evidence of clinically significant non-tumour related alteration of calcium-phosphorus homeostasis • History and/or current evidence of clinically significant ectopic mineralisation/calcification • History and/or current evidence of clinically significant retinal disorder confirmed by retinal examination • History or current evidence of serious uncontrolled ventricular arrhythmias • Fridericia's QTcF >470 ms on ECG conducted during screening • Treatment with any of the following within the specified time frame prior to the first dose of futibatinib: o Major surgery within the previous 4 weeks o Radiotherapy for extended field within 4 weeks or limited field radiotherapy within 2 weeks o Locoregional therapy within 4 weeks

Methodology	Summary
	○ Any non-investigational anticancer therapy within 3 weeks or have not recovered from side effects of such therapy prior to futibatinib administration (mitomycin within prior 5 weeks). Targeted therapy or immunotherapy within 3 weeks or within 5 half-lives (whichever is shorter) ○ Any investigational agent received within 5 half-lives of the drug or 4 weeks, whichever is shorter. Concurrent participation in an observational study may be allowed after review by the Sponsor's Medical Monitor ○ Patients with prior FGFR-directed therapy • A serious illness or medical condition(s) including, but not limited to, the following: ○ Known brain metastasis (not including primary brain tumours) unless patient is clinically stable for ≥1 month ○ Known acute systemic infection ○ Myocardial infarction, severe/unstable angina, symptomatic congestive heart failure within the previous 2 months ○ Chronic nausea, vomiting, or diarrhoea considered to be clinically significant in the opinion of the investigator ○ Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death ○ Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that in the judgment of the investigator would make the patient inappropriate for entry into this study • Patients with a history of another primary malignancy that is currently clinically significant, and has potential for metastases or currently requires active intervention (except for GnRH or LH-RH agonists in prostate cancer or adjuvant hormonal therapy in breast cancer) • Pregnant or lactating female
Duration of study	The first patient was screened on 16 April 2018. Patients received futibatinib in continuous 21-day cycles without treatment breaks between cycles. Treatment continued until disease progression, drug intolerance, withdrawal of consent, or death. At the point of the primary analysis (DCO: 1 October 2020) the median follow-up was 17.1 months; median duration of treatment was 9.1 months. At the point of the final analysis (DCO: 29 May 2021) the median follow-up was 25.0 months; median duration of treatment was 9.1 months. Safety follow-up was conducted at end of treatment (+0–7 days) and 30 days after last dose.
Method of randomisation	N/A – FOENIX-CCA2 is a single arm study.
Method of blinding	N/A – FOENIX-CCA2 is a single arm study.

Methodology	Summary
Trial drugs and method of administration	Patients received futibatinib at a starting dose of 20 mg once daily (QD) via the oral route of administration. Futibatinib was administered continuously, in 21-day cycles. A maximum of two dose reductions (to 16 mg and then to 12 mg) were permitted to manage TEAEs Treatment was discontinued if TEAEs did not resolve after two dose modifications or if the next cycle of treatment was delayed >21 days.
Permitted and disallowed concomitant medication	Patients were not permitted to receive any other investigational or any other anticancer therapy, including chemotherapy, immunotherapy, biological response modifiers, or antineoplastic endocrine therapy during the study treatment period. The following therapies were permitted: Bisphosphonate Denosumab Concomitant treatment with GnRH agonists or LH-RH agonists is permitted in prostate cancer patients Non enzyme-inducing anticonvulsants such as: gabapentin, lamotrigine and levetiracetam Steroids are allowed for patients with primary brain tumours and brain metastases. Steroid use in other patients with other tumour types should be discussed between the investigator and the Sponsor's Medical Monitor Local or regional palliative cryotherapy or radiation, e.g., for bone pain or palliative surgery (non-anti-neoplastic intent) Guidelines for the use of radiation for brain metastasis, therapy for bone metastasis and locoregional therapy are described in the study protocol The medications/therapies for the following causes could be given concomitantly under the guidelines set out in the study protocol: Hematologic Support Management of diarrhoea Management of nausea/vomiting Management of hyperphosphatemia A complete list of the permitted, disallowed and concomitant medications can be found in the study protocol (Amendment 10, Section 7.7–7.8)
Primary endpoints (including scoring methods and timings of assessments)	ORR according to RECIST 1.1 guidelines, defined as the proportion of patients who had BOR of CR or PR based on central radiological assessment by an IRC

Methodology	Summary
Secondary endpoints (including scoring methods and timings of assessments)	DOR: defined as the time from the first documented response (CR or PR) to the first documented objective PD or death due to any cause DCR: the proportion of patients with objective evidence of CR, PR, or SD, except that there is no requirement for a confirmation of an SD response PFS: the time from the first dosing date to the date of the first documented progression or death due to any cause, whichever occurs first OS: the time between the first dosing date and the date of death. ORR, DOR, DCR and PFS endpoints will be calculated based on IRC and based on investigator assessment Safety and tolerability: analysed through the incidence of death, adverse event, concomitant medications, physical examination, vital sign measurements, clinical laboratory results, ECG results, ECOG PS, and other safety observations PROs: EQ-5D, EQ-VAS and EORTC QLQ-C30 Patient's overall health state on a EQ-VAS at each assessment time point was summarised using descriptive statistics. Proportion of patient's reporting problems for the 5 EQ-5D dimensions at each assessment time point was summarised by level of problem. Percentages were based on number patients assessed at each assessment time point A by-patient listing of EQ-5D with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number) and EQ-VAS was provided For EORTC QLQ-C30, all scales and single items were scored on a categorical scale and linearly transformed to 0-to-100 scales with higher scores for a functional scale representing higher levels of functioning, higher scores for the global health status/QoL representing higher levels of global health status/QoL, and higher scores for a symptom scale representing higher level of symptoms Baseline and change from baseline in EORTC QLQ-C30 global health status/ QoL composite scale data and the remaining EORTC QLQ-C30 scale data were summarised by time point using descriptive statistics for each cohort. In addition, the percentage of patients demonstrating a clinically meaningful deterioration (defined as a 10-point change from baseline) was presented for each scale at each assessment time point. Percentages were based on number patients assessed at each assessment time point PROs were evaluated at screening and as close as possible to the tumour assessment schedule: at the end of every 2 cycles (up to +2 weeks) through cycle 4 and every 3 cycles (±7 days) thereafter until disease progression or initiation of new anticancer therapy (whichever is first)
Exploratory objective	To investigate the pharmacokinetics and to explore the relationship between pharmacokinetics and efficacy or toxicity of futibatinib
Pre-specified subgroup analyses	To assess consistency of treatment effect, the primary endpoint was analyses by several demographic and disease variables for iCCA patients enrolled in the trial: • Age (<65 versus ≥65 years)

Methodology	Summary
	• Gender (male versus female) • Race (Caucasian/White, Black, Asian, other) • Baseline ECOG PS (0 versus 1) • Prior systemic therapy 1 line, 2 lines, and 3 or more lines for advanced/metastatic disease • North America, Europe, Asia Pacific (excluding Japan), Japan • Prior surgical resection of primary tumour (Yes versus No) • Prior (neo) adjuvant treatment (Yes versus No) • Baseline FGFR rearrangements status by local lab (commercial test provided to clinician as standard of care based on tumour tissue) and/or central lab (clinical trial assay performed on tumour tissue) • Patients with solid tissue sample and report
Based on Tables 4 and 5, CS[5]. BOR = best overall response; CR = complete response; DCO = data cut-off; DCR = disease control rate; DOR = duration of response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L = Euro-QoL-5 dimensions-3 levels; EQ VAS = EuroQoL visual analogue scale; FGFR2 = fusion growth factor receptor 2; GnRH = gonadotropin-releasing hormone; HRQoL = health-related quality of life; iCCA = intrahepatic cholangiocarcinoma; IRC = Independent Review Committee; LH-RH = luteinizing hormone-releasing hormone; N/A = not applicable; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; PS = Performance Status; PRO = patient-reported outcomes measures; QD = once daily; QoL = quality of life; QT = interval between start of Q wave and end of t wave; QTcF = Fridericia's corrected QT interval; RECIST = Response Evaluation Criteria in Solid Tumours; R.O.C. = Republic of China; SD = stable disease; TEAE = treatment-emergent adverse events; UK = United Kingdom; USA = United States of America	

3.2.2 Statistical analysis of the included trials

A summary of the analysis sets in the FOENIX-CCA2 trial is provided in Table 3.5.

Table 3.5: FOENIX-CCA2 analysis set definitions

Analysis set	Description	Number of patients
Safety set	All patients who received at least one dose of futibatinib	N=103
Efficacy set	All patients with iCCA with FGFR2 gene fusions or other rearrangements who received at least one dose of futibatinib	N=103
PRO set	All patients who received futibatinib treatment and had EQ-5D or EORTC QLQ-C30 assessment at baseline and at least one subsequent post-baseline assessment	N=92
Per-protocol set	All treated patients who had no relevant protocol deviations. For patients who had a relevant deviation during the study, data collected before the point of deviation could be included in the analysis preformed on this population	N=100

Based on Table 10, CS[5]
CS = company submission; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L = Euro-QoL-5 dimensions-3 levels; FGFR2 = fusion growth factor receptor 2; iCCA = intrahepatic carcinoma

The primary efficacy endpoint of FOENIX-CCA2 was the ORR (per the primary endpoint in FOENIX-CCA2 are presented in Table 3.6.

Table 3.6: Statistical methods for the primary analysis of FOENIX-CCA2

	FOENIX-CCA2 primary analysis
Hypothesis	The null hypothesis for the primary endpoint of the FOENIX-CCA trial was that the true ORR would be ≤10%.
Statistical analysis	**Primary efficacy analyses** The primary endpoint, ORR, was defined as the proportion of patients who achieved BOR of PR or CR0 per RECIST 1.1 based on IRC in the Efficacy Population, was summarised by a binomial response rate). ORR was calculated from the best of overall response recorded from the start of treatment until progression disease or start of subsequent new anticancer treatment. The BOR, CR and PR, was confirmed with at least 4 weeks intervals of two consecutive time points. A minimum of 6-week interval between initial of treatment (first dose date) and tumour measurement was required for SD. 95% CI (binomial proportion CI) for ORR was constructed with Clopper-Pearson 95% CI. The null hypothesis would be rejected if the 2-sided 95% CI lower bound was greater than 10%. This translates in observing at least 17 responders out of 100 in the efficacy set. ORR would be assessed by both IRC and investigator review. **Secondary efficacy analyses** DOR was defined as the time between the date of first response and the subsequent date of objectively documented progression of disease or death. The CR or PR would be derived based on investigators or independent radiologist assessment.

	FOENIX-CCA2 primary analysis
	OS was defined as the time between the first dosing date and the date of death. PFS was defined as the time from the first dosing date to the date of the first documented progression or death due to any cause, whichever occurs first. DOR, PFS, and OS would be analysed using KM product-limit estimates. Median PFS and OS would be presented with 2-sided 95% CI if estimable. The cumulative PFS and OS would be plotted over time. DCR was defined as the proportion of patient with objective evidence of CR, PR, or SD, except that there is no requirement for a confirmation of an SD response. DCR would be calculated and a 2-sided Clopper–Pearson 95% CI will be constructed. All the analyses of efficacy, safety, and pharmacodynamics data for this study were performed using SAS® statistical software package, Version 9.3 or a later version.
Sample size, power calculation	Sample size considerations were based on differentiating a historical control ORR of 10% or less with a target ORR of 20%, based on the patient cohort that was being evaluated in the Phase 1 FOENIX-101 study. Assuming the true ORR is 20%, 100 patients would be required to provide 81% power to reject the null hypothesis that the true ORR is ≤10%, using a 2-sided Fishers exact test (alpha=0.05). As such, approximately 100 iCCA patients with FGFR2 gene fusions or other rearrangements were planned to be enrolled in the FOENIX-CCA2 trial.
Data management, patient withdrawals	Missing data were not imputed in the patient level listings. The listings only presented the data recorded on the original CRF. If an AE had a completely missing onset date, then the AE was considered a TEAE. A medication with a completely missing start date was considered a prior medication. A medication with a completely missing stop date was considered a concomitant medication. Data handling rules for partially missing dates are described in the CSR Appendix 16.1.9.
Based on Table 11, CS[5]. AE = adverse event; BOR = best overall response; CR = complete response; CR0 = complete response; CI = confidence interval; CRF = case report form; CS = company submission; CSR = Clinical Study Report; DCR = disease control rate; DOR = duration of response; FGFR2 = fusion growth factor receptor 2; iCCA = intrahepatic carcinoma; IRC = Independent Review Committee; KM = Kaplan-Meier; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease; TEAE = treatment-emergent adverse event	

EAG comment: No comments.

3.2.3 Baseline characteristics of the included trials

Table 3.7 summarises the general demographic data, and Table 3.8 summarises the baseline disease characteristics.

Table 3.9 describes the concomitant medications (reported for ≥ 50% of patients) at the time of study entry. These were as expected for this population

All patients received at least one systemic cancer therapy prior to inclusion. Table 3.10 describes prior cancer therapy.

Table 3.7: General demographic data

	All treated patients (N=103)
Age (years)	
N	103
Mean (SD)	55.7 (12.23)
Median (min, max)	58.0 (22, 79)
Age groups	
<65 years	80 (77.7)
≥65 years	23 (22.3)
Sex, n (%)	
Male	45 (43.7)
Female	58 (56.3)
Race, n (%)	
Caucasian/White	51 (49.5)
Black or African American	8 (7.8)
Asian/Oriental	30 (29.1)
Native Hawaiian or Other Pacific Islander	1 (1.0)
Unknown	13 (12.6)
Region, n (%)	
North America	47 (45.6)
Europe	28 (27.2)
Asia Pacific (excluding Japan)	14 (13.6)
Japan	14 (13.6)
Ethnicity, n (%)	
Hispanic or Latino	2 (1.9)
Not Hispanic or Latino	89 (86.4)
Unknown	12 (11.7)

Based on Table 6, CS[5]
CS = company submission; SD = standard deviation

Table 3.8: Baseline disease characteristics

	All treated patients (N=103)
Time since initial diagnosis (months)	
n	103
Mean (SD)	17.46 (13.116)
Median (min, max)	12.70 (2.0, 61.4)
Age at initial diagnosis (years)	
n	90
Mean (SD)	55.2 (11.81)
Median (min, max)	57.5 (21, 78)
Time since most recent progression (months) to first dose date	
n	100
Mean (SD)	2.81 (4.427)
Median (min, max)	1.50 (0.2, 28.3)
Age at most recent progression (years)	
n	87
Mean (SD)	56.5 (11.6)
Median (min, max)	60.0 (22, 78)
ECOG PS, n (%)	
0	48 (46.6)
1	55 (53.4)
Summary of FGFR2 status	
Patients with sample for FGFR2 status	103 (100.0)
FGFR2 status	
FGFR2 fusion	80 (77.7)
FGFR2 rearrangement	23 (22.3)

Based on Table 7, CS[5].
Notes: One patient had both liquid sample and tissue sample from the primary tumour site. FGFR2 final status was derived from the results by FMI central, results by FMI local, and results by local laboratory, in order of precedence.
CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FGFR2 = fusion growth factor receptor 2; FMI = Foundation Medicine, Inc; SD = standard deviation

Table 3.9: Concomitant medications and therapies at the time of study entry reported for >50% of the safety population

Anatomical therapeutic chemical class WHO drug name (preferred term)	All treated patients (N=103) n (%)
Patients who took at least one concomitant medication	103 (100.0)
All other therapeutic products	**96 (93.2)**
Sevelamer	66 (64.1)
Lanthanum carbonate	27 (26.2)
Analgesics	**76 (73.8)**
Paracetamol	56 (54.4)
Oxycodone	18 (17.5)
Drugs for acid related disorders	**64 (62.1)**
Omeprazole	20 (19.4)
Drugs for constipation	**55 (53.4)**
Sennoside A+B	16 (15.5)

Based on Table 8, CS[5].
Notes: Patients with 2 or more medications within a class level and drug name are counted only once within that class level and drug name. Concomitant medications include medications that either (1) started before first dose of study drug and were continuing at the time of first dose of study drug, or (2) started on or after first dose of study drug. Medications terms were coded using WHO Drug Dictionary version 2016 or current
CS = company submission; WHO = World Health Organization

Table 3.10: Prior treatments (safety population)

	All treated patients (N=103) n (%)
Patients having at least one prior anticancer therapy	103 (100.0)
Treatment type	
Neoadjuvant	4 (3.9)
Adjuvant	14 (13.6)
Advanced	101 (98.1)
Maintenance therapy	3 (2.9)
Number of regimens	
1	48 (46.6)
2	31 (30.1)
≥3	24 (23.3)
Best response to prior anticancer therapy	
CR	[redacted]
PR	[redacted]
SD	[redacted]
PD	[redacted]
Not evaluable	[redacted]
Unknown	[redacted]
Time from the last prior anticancer therapy to the first dose date of futibatinib (months)	
n	103
Mean (SD)	[redacted]
Median (min, max)	1.51 (0.1, 22.5)
Patients who had at least one prior radiation therapy for primary disease	**28 (27.2)**
Patients who had at least one prior anti-cancer surgery	**41 (39.8)**

Based on Table 9, CS[5].
CR = complete response; CS = company submission; PD = progressive disease; PR = partial response; SD = stable disease; SD = standard deviation

The CS[5] reports that, "*The median age at iCCA diagnosis was 57.5 years (range: 21 to 78 years) with a median time since initial diagnosis of 12.7 months (range: 2.0 to 61.4 months). ECOG PS was 0 for 46.6% and 1 for 53.4% of patients. UK clinical experts in CCA confirmed that the baseline characteristics of the FOENIX-CCA2 trial were broadly generalisable to UK clinical practice.*"

EAG comments:

- Clinical expert guidance, though useful, may not be sufficient for such an important issue as the similarity between trial and target populations in England and Wales.
- If characteristics of the target population are different to those in the trial, then the trial results may not represent the results that might be expected in clinical practice in England and Wales. Furthermore, if the characteristics that differ are those that are amongst those included as variables in the pre-specified sub-group analyses, then it may be possible to infer how outcomes in clinical

practice will be affected by these differences. Therefore, knowledge of any differences is potentially very useful.

- The EAG thus requested detailed information[6] from the company on the characteristics of the target population, which should ideally cover the variables included in the pre-specified sub-group analyses.
- The company responded by stating that, *"Cholangiocarcinoma (CCA) is a relatively rare cancer, with an estimated age-standardised incidence rate of 4.3 per 100,000 in England. Thus, as is a common limitation in rare diseases, the evidence base for this disease area is limited and, in particular there is a paucity of evidence in the patient population of relevance to this submission in the UK. To the best of the Company's knowledge, there are no cohort studies reporting on the demographic and/or disease characteristics of patients with advanced and pretreated CCA with FGFR2 fusions or gene rearrangements in the UK. Therefore, where quantitative data are not available, UK clinical expert feedback presents an important evidence source, that reflects the most up-to-date information on patients with CCA in the UK. In the absence of alternatives, the Company considers clinical expert feedback to present the best available means of judging whether the data collected from the FOENIX-CCA2 trial is suitable for decision-making. UK clinical experts in CCA consulted at a recent Advisory Board confirmed that the baseline characteristics of patients enrolled in the FOENIX-CCA2 trial were broadly generalisable to the relevant population in UK clinical practice. In particular, median age and ECOG performance status were noted to be closely aligned."*[7]
- In response to the above, the EAG note that objective data were not found that described the characteristics of the target population. However, the company did not specify the search strategies used in their quest for such objective data, so it remains unconfirmed that objective data do not exist. If it is assumed that objective data does not exist, resorting to clinical expert opinion appears reasonable, but is not, of course, an ideal substitute for objective data. The reliance on subjective opinion means uncertainty remains in terms of the similarity in trial and target population characteristics, and therefore there is uncertainty in the representativeness of trial results to the target population.
- The company continued by stating that, *"Additionally, the baseline patient characteristics in FOENIX-CCA2 were in line with the patient population in the FIGHT-202 trial (Table 3.11 below). Of note, the FIGHT-202 trial population is aligned with the anticipated population that futibatinib would be used in UK clinical practice and was deemed appropriate for decision-making by the NICE Committee (Section 3.4 of the NICE FAD). Furthermore, two separate clinical experts who submitted input into the NICE submission for pemigatinib confirmed that the FIGHT-202 trial was reflective of the population of CCA patients treated in UK clinical practice. Considering the variables included in the pre-specified subgroup analyses, all variables were aligned between trials except the proportion of white patients and the proportion of patients receiving >1 prior therapy line, which were both higher in the FIGHT-202 trial versus the FOENIX-CCA2 trial. As race was demonstrated to have no significant impact on OS and PFS outcomes in the sensitivity analyses performed on the ITC comparing futibatinib to pemigatinib (see Company submission Section B.2.9.2; Tables 21 and 23), the difference in proportion of white patients between trials is not anticipated to impact the generalisability of the results of the FOENIX-CCA2 trial to UK clinical practice. Furthermore, the only prior treatment variables that would be anticipated to impact efficacy and safety outcomes are FGFR2 treatments and prior surgery, and prior treatment with an FGFR2 treatment was a key exclusion criterion in both trials, whilst prior surgery rates were similar between trials (39.8% in FOENIX-CCA2 versus 35.5% in FIGHT-202, respectively). As such, this difference in prior treatments is not anticipated to reduce the generalisability of the FOENIX-CCA2*

trial results to UK clinical practice. This view is supported by feedback received from UK clinical experts who noted that prognostic factors and treatment effect modifiers were "remarkably similar with no key differences" between the FIGHT-202 and FOENIX-CCA2 trials observed. Finally, the similarities between the baseline characteristics between the FOENIX-CCA2 and the FIGHT-202 trial is supported by the fact that there were was no statistically significant differences between the results of the naïve and adjusted ITCs between futibatinib and pemigatinib presented in the Section B.2.9.2 of the Company submission. Overall, in the absence of real-world data for CCA patients in UK clinical practice, the similarities in the baseline patient characteristics between the FOENIX-CCA2 and FIGHT-202 trials, which was deemed suitable for decision-making in the UK, provide confidence in the generalisability of the results of the FOENIX-CCA2 trial to UK clinical practice. A view which is supported by feedback received from UK clinical experts in CCA."[7]

- In the reply above, the company uses the similarity of the populations in the FOENIX-CCA2 and the FIGHT 202 trials to imply that the FOENIX-CCA2 trial is similar to the UK target population. It does this by assuming that the FIGHT-202 trial had a population that was similar to the target populations in England and Wales. In turn, this assumption is based upon the fact that FIGHT-202 was deemed appropriate for decision making by NICE. However, given the company's assertion that objective data on the target population does not exist, the previous NICE decision to use the FIGHT-202 data must be assumed to have also been based on expert clinical opinion that its population was similar to the target population. Thus, the company's assertion that the FOENIX-CCA2 population is similar to the UK target population because it was similar to the FIGHT-202 trials, which in turn were deemed by clinical experts to be similar to the clinical population, is no better than using the more direct clinical opinion about the similarities between FOENIX-CCA2 trial and the target population. Therefore, the EAG is unconvinced by the company's response, and this remains a key issue.

Table 3.11: Baseline patient characteristics for FOENIX-CCA2 and FIGHT-202

Characteristic	Futibatinib (FOENIX-CCA2)	Pemigatinib (FIGHT-202)[b]
Median age (range), years	58 (22–79)	56 (26–77)
Male (%)	43.7	39.3
ECOG PS 0 (%)	46.6	42.0
Albumin <35 g/L (%)	19.4	19.6
One prior therapy line	46.6	60.7
Prior surgery(%)	39.8	35.5
TP53 alteration(%)	12.6	8.4
White[a] (%)	49.5	73.8
Prior neoadjuvant treatment (%)	3.9	NR
Patients with solid tissue (%)	96.1	NR
Baseline FGFR2 status		
FGFR2 fusion (%)	77.7	95.3%
FGFR2 rearrangement (%)	22.3	4.7%

Based on Table 3, company response to clarification[7]
[a] Race (% white versus other) was used in a sensitivity analysis
[b] Informed by the Cohort A (n=107, FGFR2 fusions or rearrangements) of the FIGHT-202 trial.
ECOG PS = Eastern Cooperative Oncology Group Performance Status; FGFR2 = fusion growth factor receptor 2; NR = not reported; TP53 = tumour protein p53

3.2.4 Risk of bias in the included trials

On the basis of the risk of bias tool used (developed by York University CRD, but not otherwise specified) the trial was deemed at 'low risk' of bias (Table 3.12).

EAG comment: Notwithstanding the grading yielded by the tool, a single arm study will always be at extremely high risk of bias because without a control group it is impossible to know what proportion of the changes in outcome after treatment (if any) are actual treatment effects and what proportion are due to intervening variables such as the placebo effect or regression to the mean. However, the EAG understands that the MAIC will alleviate this problem to some extent, by creating a propensity-matched comparison with an active control (see Sections 3.3 and 3.4).

Table 3.12: Overview of quality assessment for FOENIX-CCA2

	FOENIX-CCA2 (NCT02052778[12]	Rationale
Was the cohort recruited in an acceptable way?	Yes	The trial included a number of patient recruitment locations, and the trial protocol had clear pre-specified inclusion and exclusion criteria that matched the aim of the study. However, the open-label single-arm design could introduce selection bias.
Was the exposure accurately measured to minimise bias?	Yes	The futibatinib dosage allowed dose reductions and reasons for discontinuation were pre-specified in the study protocol. All dose reductions and discontinuations within the study were recorded.
Was the outcome accurately measured to minimise bias?	Yes	Outcome measures were prespecified in the study protocol, including the specific criteria to be used to measure tumour response. Validated tumour response measurements (RECIST version 1.1) and standard safety monitoring and grading using CTCAE (version 4.03) were used. The primary endpoint included response assessment by an IRC; researcher assessment outcomes were compared to the IRC outcomes as part of the trial sensitivity analyses. However, neither patients nor assessors were blinded to study treatment.
Have the authors identified all important confounding factors?	Unclear	All confounding factors relevant to the disease area of interest were not explicitly specified.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	The study contained pre-specified subgroup and sensitivity analyses, which explored a range of potentially relevant confounding factors.
Was the follow-up of patients complete?	Yes	Follow-up of all patients was completed in line with the trial protocol as of the final DCO (29 May 2021).
How precise (for example, in terms of CI and p values) are the results?	Trial results were precise	The primary endpoint was met with a high level of certainty relative to the pre-specified null hypothesis (null hypothesis: ORR ≤10%; ORR per IRC at final DCO: 41.7% [95% CI: 32.1, 51.9]).

	FOENIX-CCA2 (NCT02052778[12]	Rationale
Based on Table 12, CS[5]. CI = confidence interval; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; IRC = Independent Review Committee; NCI = National Cancer Institute; ORR = objective response ratio; RECIST = Response Evaluation Criteria in Solid Tumours		

3.2.5 Efficacy results in the included trials

Results for DOR and disease control rate are provided in the CS,[5] but these are not included below, as these are not prescribed in the NICE final scope.[8]

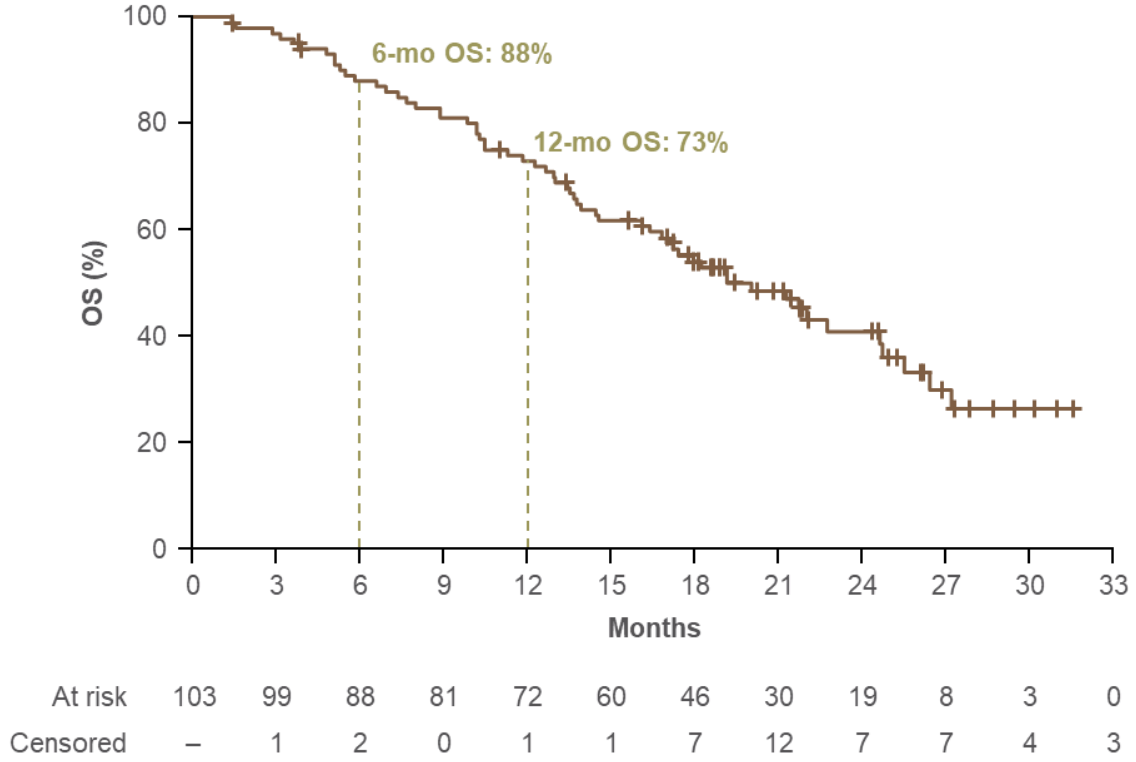
3.2.5.1 Overall Survival (OS)

At the final DCO, [redacted] patients had died. The remaining [redacted] had been censored due to treatment discontinuation for any cause. Table 3.13 summarises this information, and Figure 3.1 provides the survival curve.

Table 3.13: Summary of OS (efficacy population): final DCO

	All treated patients (N=103)
Deaths, n (%)	[redacted]
Censored patients, n (%)	**45 (43.7)**
Patient discontinued treatment due to any reason before DCO	[redacted]
OS (months)	
Median (95% CI)	20.0 (16.4, 24.6)
1st Quartile (95% CI)	[redacted]
3rd Quartile (95% CI)	[redacted]
OS rate (%) (95% CI)	
At 3 months	[redacted]
At 6 months	88.1 (80.0, 93.1)
At 9 months	[redacted]
At 12 months	73.1 (63.2, 80.7)
Based on Table 16, CS[5] Point estimates of OS rate are based on KM method and 95% CIs are based on the Greenwood Formula. CI = confidence interval; CS = company submission; DCO = data cut-off; KM = Kaplan-Meier; NE = not estimable; OS = overall survival		

Figure 3.1: KM curves for OS: final DCO



Based on Figure 10, CS[5]
CS = company submission; DCO = data cut-off; KM = Kaplan-Meier; OS = overall survival

3.2.5.2 Progression Free Survival

At the DCO, [redacted] patients had experienced disease progression or death. The remaining 25 (24.3%) were censored. This is summarised in Table 3.14 and Figure 3.2.

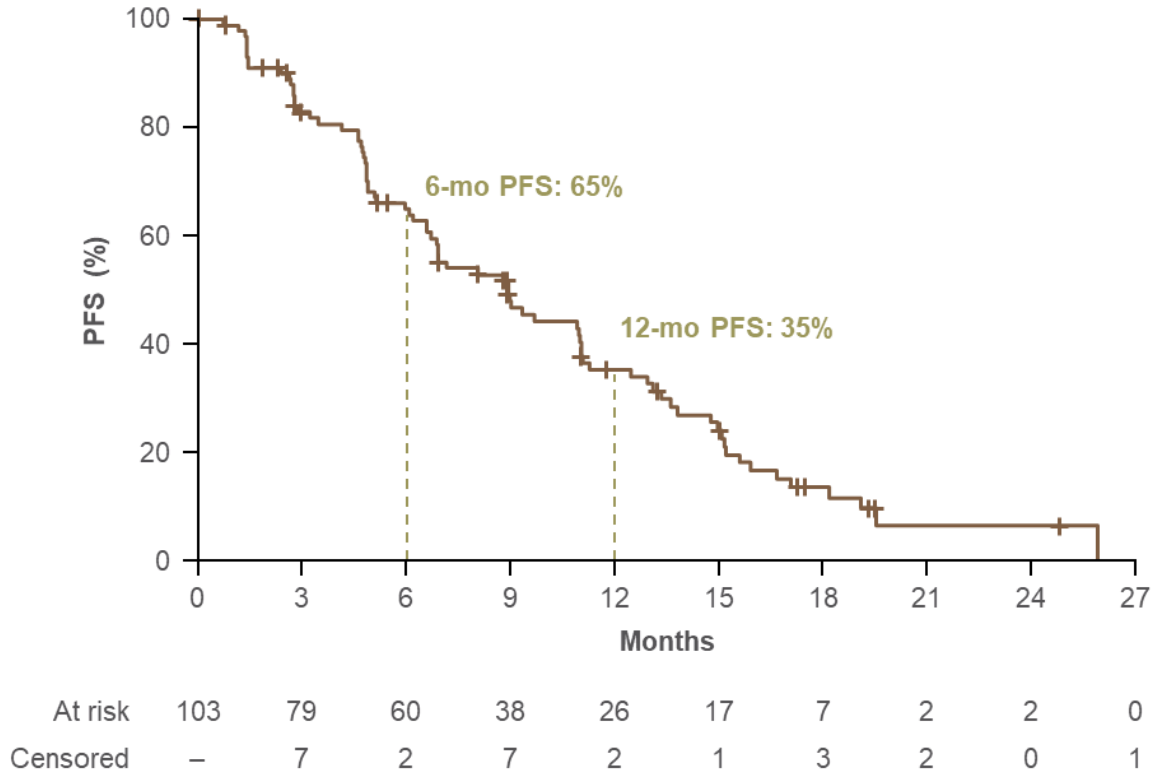
Table 3.14: Summary of PFS by IRC (efficacy population): final DCO

	All treated patients (N=103)
Disease progression or deaths, n (%)	[redacted]
Censored patients, n (%)	**25 (24.3)**
No baseline assessment	[redacted]
No post-baseline assessment	[redacted]
New anticancer treatment	[redacted]
Two or more missed assessment	[redacted]
Treatment discontinued without PD/death	[redacted]
PD/death greater than 21 days after the last dose	[redacted]
Patient still on treatment without PD	[redacted]
PFS (months)	
Median (95% CI)	8.9 (6.7, 11.0)
1st quartile (95% CI)	[redacted]
3rd quartile (95% CI)	[redacted]
PFS rate (%) (95% CI)	
At 3 months	[redacted]

	All treated patients (N=103)
At 6 months	65.0 (54.6, 73.6)
At 9 months	[redacted]
At 12 months	35.4 (25.5, 45.4)

Based on Table 15, CS[5]
PFS is calculated from the date of the first dose of study drug to the date of 1st objective evidence of disease progression or date of death due to any cause, whichever occurs first. Point estimates of PFS rate are based on KM method and 95% CIs are based on the Greenwood Formula.
CI = confidence interval; CS = company submission; DCO = data cut-off; IRC = Independent Review Committee; KM = Kaplan-Meier; PD = progressive disease; PFS = progression-free survival

Figure 3.2: KM curve for PFS: final DCO



Based on Figure 9, CS[5]
CI = confidence interval; CS = company submission; DCO = data cut-off; KM = Kaplan-Meier; PFS: progression-free survival

3.2.5.3 Response Rates

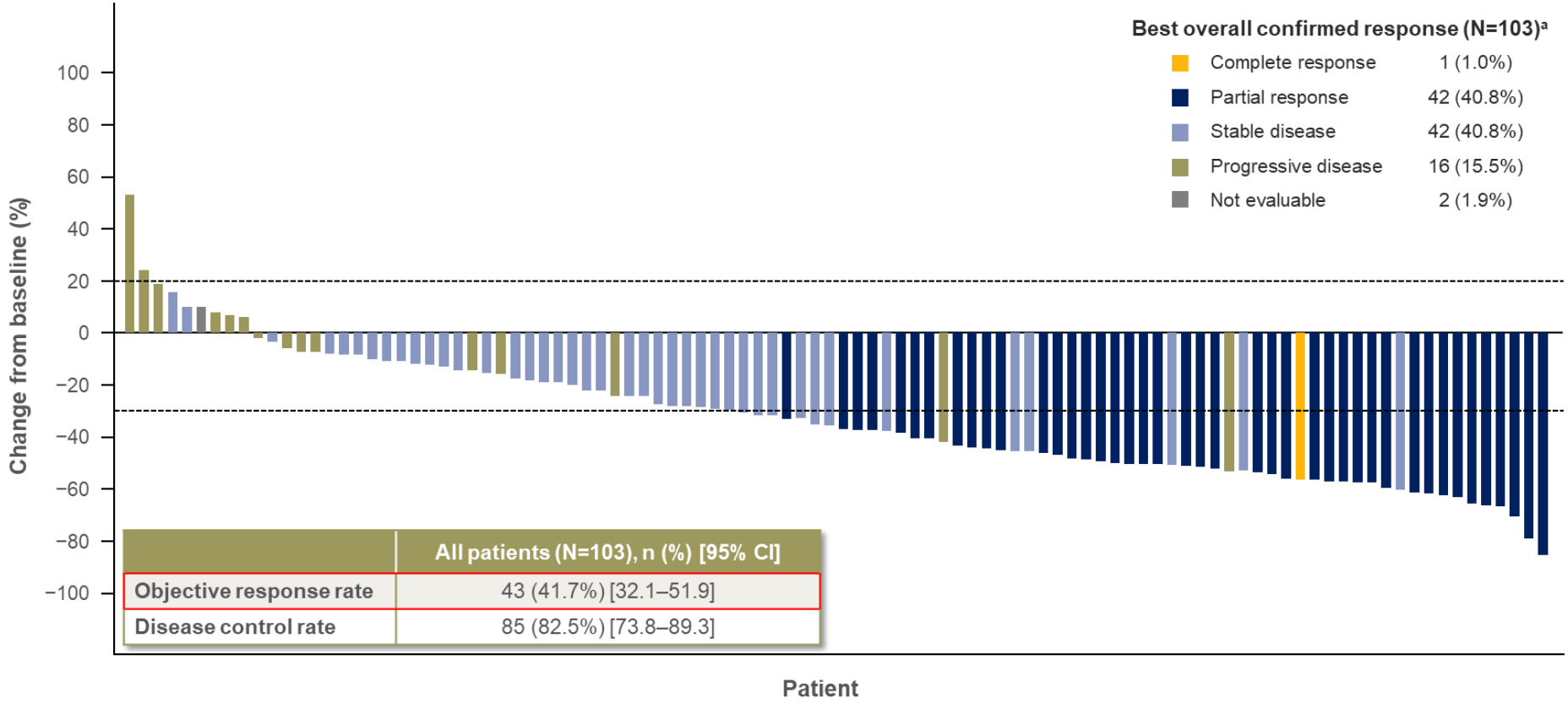
Objective response rate (ORR) was defined as the proportion of patients with objective evidence of confirmed complete response (CR) or partial response (PR) according to RECIST version 1.1 per IRC. Results are summarised in Table 3.15 and Figure 3.3 below.

Table 3.15: Tumour response rate by IRC (efficacy population): final DCO

	All treated patients (N=103) n (%)
BOR	
CR	1 (1.0)
PR	42 (40.8)
SD	42 (40.8)
PD	16 (15.5)
Not evaluable	2 (1.9)
Unconfirmed CR or PR	**6 (5.8)**
ORR	**43 (41.7)**
95% CI	32.1, 51.9
DCR, n (%)	**85 (82.5)**
95% CI	73.8, 89.3

Based on Table 13, CS[5]
ORR is based on confirmed PR/CR. Disease control rate is based on confirmed PR/CR/SD.
BOR = best overall response; CI = confidence interval; CR = complete response; CS = company submission; DCO = data cut-off; DCR = disease control rate; IRC = Independent Review Committee; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease

Figure 3.3: Waterfall plot of patients target lesion sum of diameters percent change from baseline and BOR (efficacy population): final DCO



[a] Assessed by IRC. One patient was not displayed because of no post-baseline assessments. Two patients were not displayed in Independent Review plot because there was no accepted Sum of Diameter information for these two patients.

BOR = best overall response; CI = confidence intervals; CR = complete response; DCO = data cut-off; IRC = Independent Review Committee; NE = not estimable; PD = progressive disease; PR = partial response; SD = stable disease

3.2.5.4 HRQoL

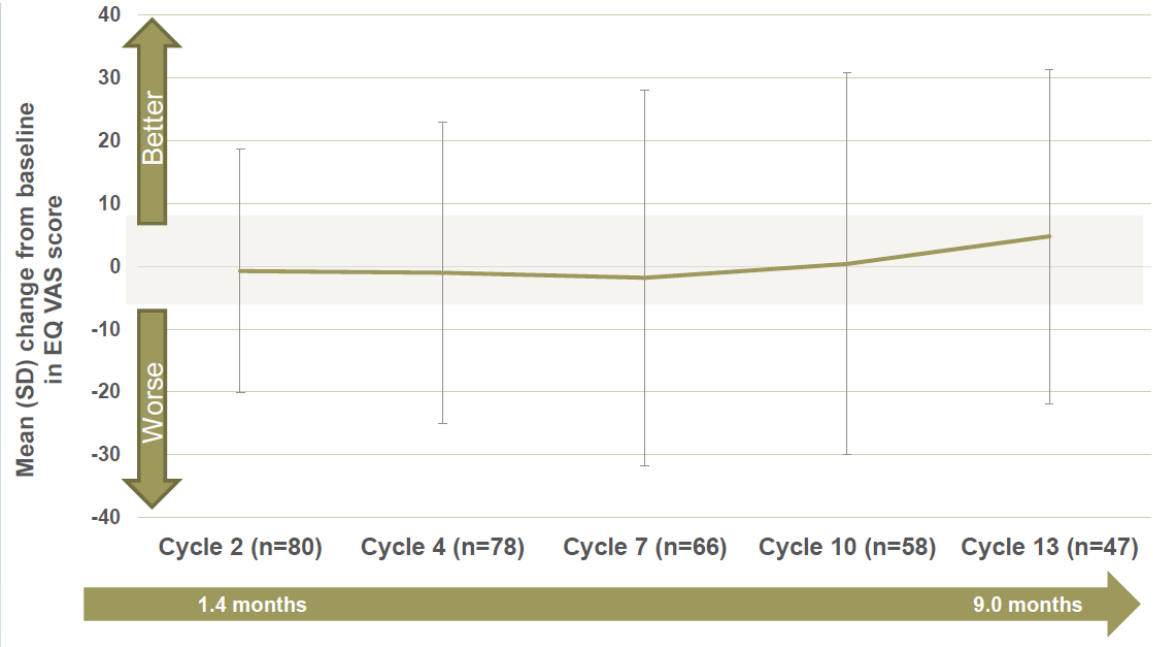
Three HRQoL outcomes were measured. Table 3.16 and Figure 3.4 summarises these results.

Table 3.16: EQ VAS – mean and mean change from baseline by visit to the PRO primary assessment timepoint (PRO population)

	All treated patients (N=92)	
Screening	**Actual**	
n	88	
Mean	71.72	
SD	20.307	
Median	80.00	
Min, Max	6.5, 100.0	
Cycle 13	**Actual**	**Change from baseline**
n	[redacted]	[redacted]
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

Based on Table 17, CS[5]
Only patients with data at both baseline and the relevant post-baseline visit are included in the change from baseline summary statistics.
CS =company submission; EQ VAS = EuroQoL visual analogue scale; PRO = patient reported outcomes; SD = standard deviation

Figure 3.4: Mean change from baseline in EQ VAS scores over time

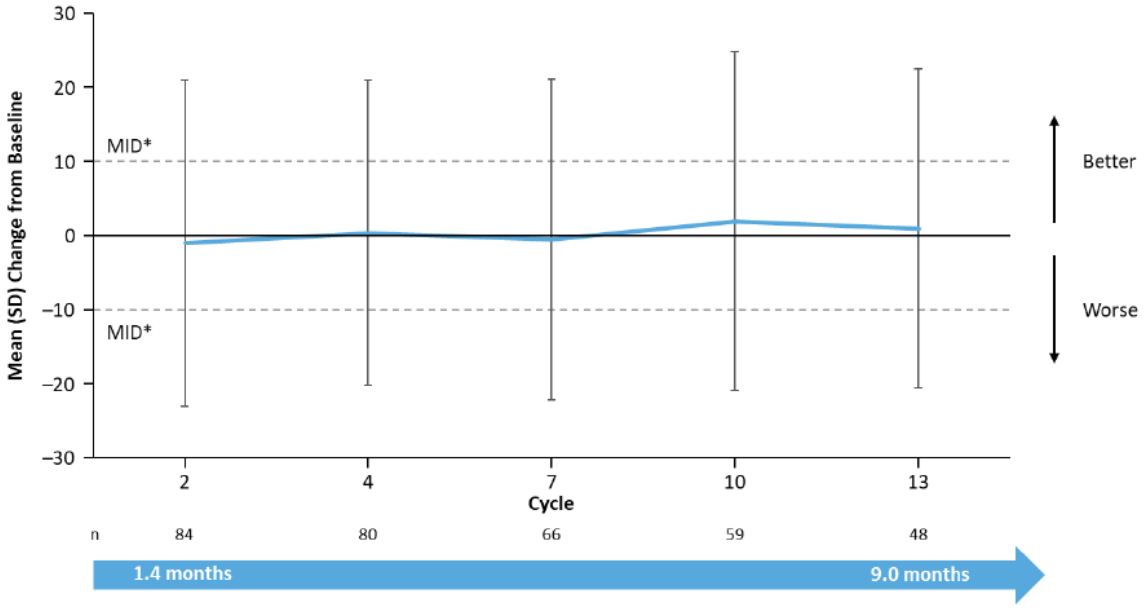


Based on Figure 11, CS[5]
The shaded box indicates scores with no clinically meaningful change from baseline based on a change of +7 for improvement, and −7 for worsening. Error bars represent SD.
CS = company submission; EQ VAS = EurQoL visual analogue scale; SD = standard deviation

EAG comment:

- Several measures of HRQoL were reported to be measured - EORTC QLQ-C30, EQ-5D-3L, EQ VAS. All of these measures appear to be relevant and appropriate, as they measure different aspects of QoL. Therefore, despite the use of three outcomes for one construct, the propensity for over-analysis with a subsequent increase in risk of type I errors is reduced.
- Only results for EQ VAS were fully reported in the CS[5] or Appendices.[9] Failure to report all planned outcomes constitutes outcome reporting bias. The company was asked[6] why it had not reported the QoL data for the EORTC QLQ-C30 and EQ-5D-3L measures.
- The company responded by stating that, *"As reported in Section B.2.6.6 of the submission document, HRQoL outcomes collected in the FOENIX-CCA2 trial included EORTC QLQ-C30 (5 functional and 9 physical measures), EQ-5D-3L (utility index and 5 dimensions: anxiety/depression, mobility, pain/discomfort, self-care, and usual activity) and EQ-VAS. Primary analysis for HRQoL outcomes was assessed using predefined clinically meaningful thresholds; since after Cycle 13 less than 50% of the patient population provided PRO data, the primary analyses were conducted up to Cycle 13.The EORTC-QLQ-C30 Global Health Status Score change from baseline through Cycle 13 and EQ-5D-3L Dimensions Status change from baseline at Cycle 13 are presented in Figure 3.5 and Figure 3.6 respectively, reproduced from the Goyal et al. (2023) publication reporting the results of the FOENIX-CCA2 trial. The change from baseline in the EORTC QLQ-C30 Scales are provided in Table 3.17. Overall, the outcomes of EORTC-QLQ-C30 and EQ-5D-3L were consistent with the results for EQ-VAS, indicating stable quality of life for most patients. The HRQoL assessments for the final DCO (21 May 2021) were consistent with those from the preliminary DCO (1 October 2020)."*[7]
- The EAG thanks the company for this additional information, which confirms that QoL did not change positively or negatively after treatment with futibatinib.

Figure 3.5: EORTC QLQ-C30 Global Health Status Score change from baseline through cycle 13



Based on Figure 1 in company response to clarification questions.[7]
The error bars indicate one SD and the dashed lines MIDs; changes from baseline between the dashed lines were not considered clinically meaningful.

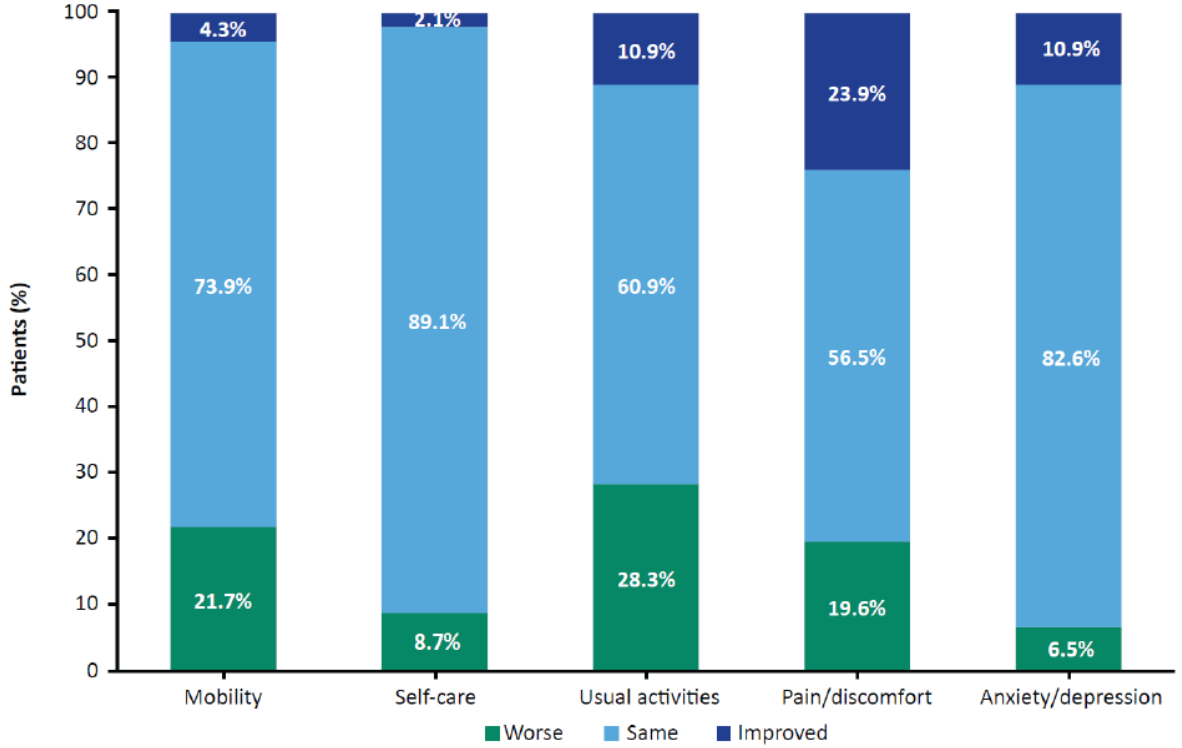
*A ≥10-point change from baseline in QLQ-C30 scores was predefined as the MID to designate a change as clinically meaningful.
EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; MID = minimally important difference; SD = standard deviation

Table 3.17: EORTC QLQ-C30 Scales, Mean (SD) change from baseline

Scale[a]	Cycle 2 n=84	Cycle 4 n=80	Cycle 7 n=66	Cycle 10 n=59	Cycle 13 n=48
Global health status	−1.0 (22.0)	+0.4 (20.6)	−0.5 (21.6)	+1.9 (22.8)	+0.9 (21.5)
Functional scales					
Physical	−1.1 (17.9)	+0.8 (15.0)	−0.4 (14.1)	−1.4 (15.4)	−2.0 (14.0)
Role	−1.2 (26.0)	−2.3 (24.0)	−0.8 (24.2)	−3.7 (23.6)	−1.4 (25.7)
Cognitive	−3.8 (15.9)	−5.7 (15.1)	−3.3 (12.2)	−4.0 (14.1)	−5.2 (12.5)
Emotional	+3.0 (19.7)	+4.7 (17.6)	+3.7 (16.2)	+2.9 (16.6)	+4.9 (15.6)
Social	+4.4 (27.9)	+0.6 (23.9)	+0.8 (19.9)	+2.9 (23.6)	−0.3 (20.5)
Symptom scales/single items					
Appetite loss	+0.4 (30.6)	+0.8 (31.8)	0.0 (35.1)	−3.4 (30.1)	−5.6 (31.0)
Constipation	+9.6 (31.5)	**+10.0 (34.9)**	+9.1 (31.8)	+5.1 (35.5)	+7.1 (34.7)
Diarrhoea	+7.1 (26.9)	+5.4 (28.8)	+2.5 (25.0)	−0.6 (26.6)	+4.2 (21.3)
Dyspnoea	−4.0 (26.2)	−5.4 (24.6)	−7.1 (23.0)	−9.0 (22.2)	−6.3 (20.2)
Fatigue	−2.3 (23.7)	−2.4 (20.5)	−2.9 (22.6)	−5.2 (21.3)	−3.2 (20.9)
Insomnia	+0.8 (29.8)	−0.4 (27.1)	+2.6 (25.9)	−2.9 (27.4)	−2.8 (29.0)
Nausea/vomiting	−1.8 (20.8)	−1.2 (22.5)	−1.5 (19.3)	−2.5 (20.0)	−3.8 (16.9)
Pain	−0.8 (23.4)	+2.1 (21.6)	+2.8 (22.4)	+4.5 (29.0)	+4.9 (29.0)
Financial difficulty	+0.8 (29.6)	−1.7 (27.3)	+1.1 (26.8)	−1.2 (28.2)	−3.5 (35.6)

Based on Table 4 in Company response to clarification questions.[7]
Positive values for functional scales and global health status represent improvement, whereas positive scores for symptom scales/items and financial impact represent increased symptomatology/financial impact.
[a] A 10-point change from baseline for EORTC QLQ-C30 scores was predefined as the MID to designate a change as clinically meaningful (shown in bold).
EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; MID = minimally important difference; SD = standard deviation

Figure 3.6: EQ-5D-3L dimensions status change from baseline at cycle 13



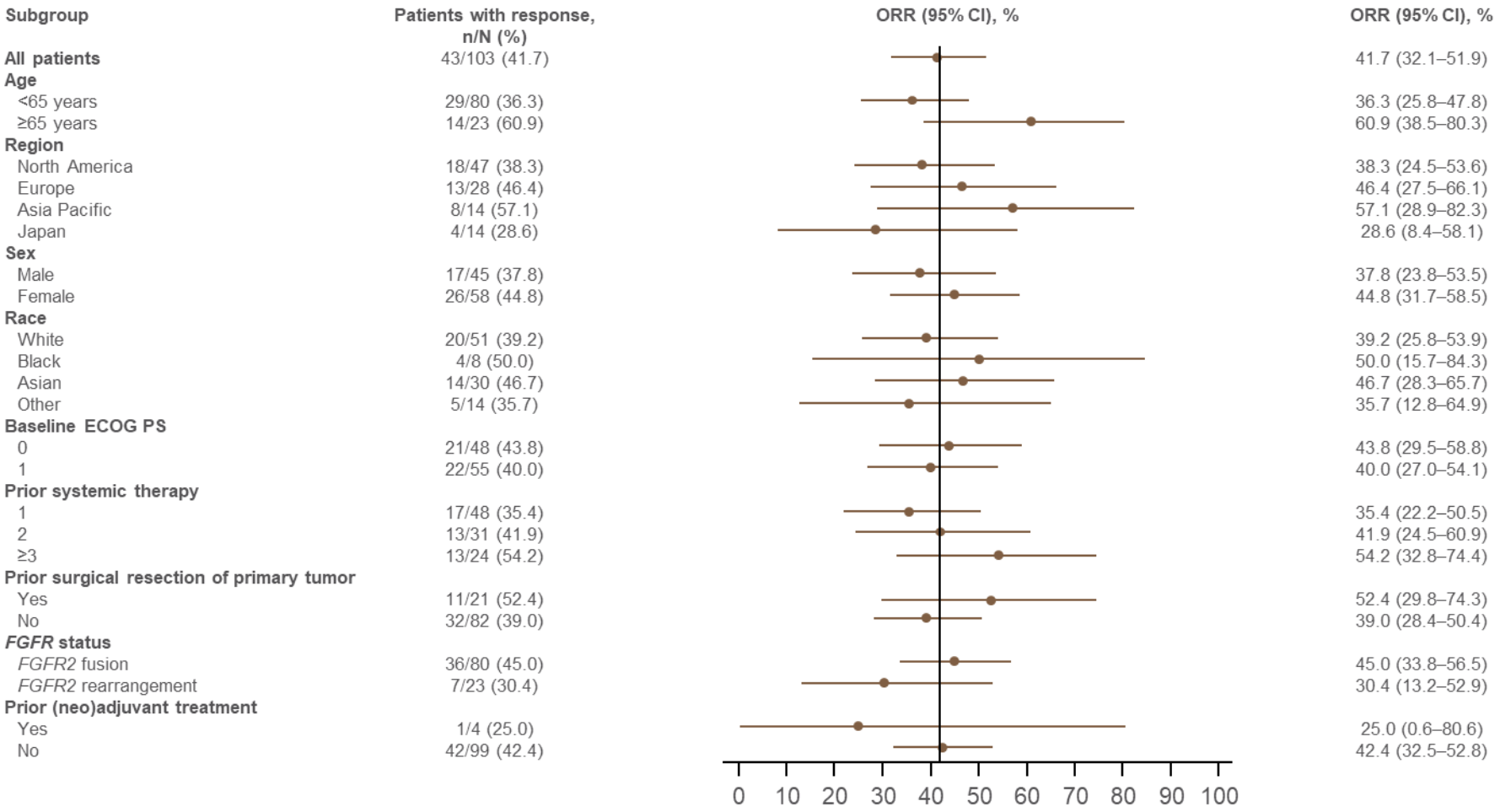
Based on Figure 2 in company response to clarification questions.[7]
EQ-5D-3L = Euro-QoL-5 dimensions-3 levels

3.2.5.5 Sub-groups

The company carried out 10/11 of the pre-planned sub-grouping analyses for ORR. The analysis omitted was defined by 'patients with solid tissue sample and report'.

The sub-group analyses are summarised in Figure 3.7.

Figure 3.7: ORR subgroup analysis (based on IRC): efficacy population



Based on Figure 12, CS[5].

CI = confidence interval; CS = company submission; ECOG = Eastern Cooperative Oncology Group; FGFR = fusion growth factor receptor; FGFR2 = fusion growth factor receptor 2; IRC = Independent Review Committee; ORR = overall response rate

EAG comment:

- The company implies that the sub-group analyses suggest no effect modification from the chosen variables. However, this is not necessarily the case. The sub-group analyses show a trend for age to be an effect modifier, with older age being associated with a more robust response to treatment. For 'prior systemic therapy' there was an apparent dose-response effect, which supports the possibility that efficacy may increase with increased prior systemic therapy. It was unclear if other sub-grouping variables are effect-modifiers. The 95% CI for the strata in all sub-grouping analyses overlap, but this does not necessarily mean that the differences are 'non-significant', as it is quite possible for overlapping 95% CIs to be consistent with significant difference at an alpha of 0.05.
- The EAG would also add that the sub-group analysis is probably underpowered: the groups may be so small that detection of 'significant' differences will be difficult. This implies that any significant results are to be taken seriously, because they will probably require a large effect size to be so detected. On the other hand, there may be a high risk of type II errors if the statistical analyses show a marginally 'non-significant result', and therefore it would make sense to pay attention to strong but non-significant trends in the data. Normally the emphasis in statistical testing is conservative; that is, the null hypothesis will only be rejected if there is a very low probability that the null hypothesis is consistent with the sample statistics. This is because the harms of falsely rejecting the null hypothesis (type I error) are often greater than the harms of falsely accepting the null hypothesis (type II error). However, in this case the harms of falsely accepting the null hypothesis may be greater. The impact of possible effect modification on external validity is potentially important if some of these variables are shown to differ between the trial and the target populations in England and Wales. For example, a real effect modification for the variable of 'race', in conjunction with the target population having a different proportion of ethnic identities to the trial, might mean that results for the trial are not representative of the target population. Therefore, the onus should be on vigilance for *possible* effect modification, rather than the more conservative approach of only accepting the presence of effect modification when statistical significance is reached.
- The EAG requested[6] that the company perform statistical analyses to clarify this. The company responded by stating that, *"Formal statistical subgroup analyses were not conducted for the FOENIX-CCA2 trial owing to the fact that any results would be associated with substantial uncertainty owing to the small sample sizes. Furthermore, the power calculations conducted to identify the target enrolment number for the FOENIX-CCA2 trial were not powered for subgroup analyses. As a result, any formal statistical subgroup analyses conducted would be underpowered and therefore any resulting p-values would not be statistically meaningful. This is supported by Barraclough et al. (2010), who note that a key limitation of subgroup analyses is that they are often underpowered owing to the sample size of the clinical trial being calculated to evaluate the primary study objective as opposed to in specific subgroups. Barraclough (2010) goes on to highlight that unplanned subgroup analyses (subgroup analyses not pre-specified in the protocol) frequently lack statistical power and therefore results are often over interpreted and misused. For these reasons, the conduct of formal statistical subgroup analyses on the FOENIX-CCA2 trial population was not considered appropriate"*.[7]
- The EAG are not satisfied with the above response because it fails to consider the points made in the clarification question – that the likely underpowering of the analysis means that any significant effects would represent a large magnitude of effect, and that any non-significant trends would indicate variables requiring consideration (given the greater need to avoid type II errors than type I errors in this particular context). The EAG would also question why a sub-group analysis was

conducted at all if the company were not inclined to take findings from it seriously. The EAG have noted possible differences in effect resulting from differing age and differing prior systemic therapy, which clearly need to be considered. The company appear to disregard these clear trends because there is no statistical evidence that the sub-groups are different, whilst simultaneously refusing to conduct any statistical analyses to examine the probability of any difference on the grounds of an underpowered analysis. This, along with the references to Barraclough (2010),[20] gives the impression that the company willingly carried out the (knowingly underpowered) sub-group analyses without any intention of utilising the information gained from them. This remains a key issue.

- The EAG is also concerned that the sub-group analysis for the omitted variable ('patients with solid tissue sample and report') was carried out, but not reported. The EAG requested[6] that the results of this analysis be provided.
- The company responded by stating that, *"Per the primary analysis (DCO 1st October 2020) of ORR and DOR for patients with solid tissue sample and report, 96.1% (99/103) of patients were classified as having a solid tissue sample with a report available. Therefore, a subgroup analysis based on "patients with solid tissue sample and report" was not performed, as only four patients did not meet this criterion, therefore the results of any such subgroup analysis would be subject to substantial uncertainty resulting from the extremely imbalanced distribution of patient numbers."*[7]
- In relation to the above company response, the EAG would note that for the sub-group analysis of 'prior neo-adjuvant treatment' there are also only four patients in one sub-group. The EAG is therefore unclear why the rationale for exclusion of one variable (the omitted variable) would not apply to another ('prior neo-adjuvant treatment'). This remains a key issue.
- 'Concomitant treatments' is not a sub-grouping variable. The company was asked[6] to explain why this was omitted, given that it has the potential to be an important covariate.
- The company stated that, *"Since the population of the FOENIX-CCA2 trial included patients with advanced CCA, most of the patients were expected to receive concomitant medications at the time of the trial design. Therefore, a subgroup analysis of patients based on whether they received concomitant treatments was not considered to be meaningful. Indeed, all patients in the FOENIX-CCA2 trial received at least one concomitant medication – therefore, a subgroup analysis split by patients receiving versus not receiving concomitant treatment would not be feasible. It is also important to note that the concomitant medications permitted by the FOENIX-CCA2 protocol were principally intended for the mitigation of AEs, or in some cases, palliative treatment, and were not expected to have any significant anti-cancer activity. As per the FOENIX-CCA clinical trial protocol, the following concomitant medications were permitted:*
  - *Bisphosphonate*
  - *Denosumab*
  - *Non enzyme-inducing anticonvulsants*
- *Gonadotropin-releasing hormone (GnRH) agonists, luteinizing hormone–releasing hormone (LH-RH) agonists, steroids and local or regional palliative cryotherapy or radiation were allowed for certain patients*

  Guidelines were also provided for concomitant treatments for haematologic support and management of diarrhoea, nausea/vomiting and hyperphosphatemia. In addition, it was considered that concomitant treatments do not present an effect modifier by themselves, instead reflecting on other patient characteristics that do present treatment effect modifiers, and it was considered that all principal effect modifying variables were considered in subgroup analyses. For all of the above reasons, a subgroup analysis based on concomitant medications was not considered feasible nor appropriate."[7]

- The EAG's response to the above statement is that consideration of concomitant treatments did not need to be made in a simple binary (yes/no) manner. Consideration of concomitant treatments could have been made by categorising the given concomitant treatments into three or four bins, based on type. Though such categorisation may have been difficult it is something that could have been considered by the company, given that concomitant treatments may influence outcomes (even if these are only adverse outcomes, they are still important) and it is plausible that concomitant treatment choice may differ in the UK target population to that in the trial. This remains a key issue.

A post-hoc sub-analysis was also undertaken, of ORR and PFS by 'co-alteration'. It is unclear if alteration in the included genes makes a difference to the effects. This is summarised in Table 3.18.

Table 3.18: Post-hoc subgroup analysis of ORR and PFS by co-alteration

Gene	Molecular status (n)	ORR (95% CI), %	Median PFS (95% CI), months
All patients (n=93)	—	43.0 (32.8–53.7)	8.9 (6.6–13.1)
BAP1	Unaltered (53)	49.1 (35.1–63.2)	8.0 (4.9–13.8)
	Altered (40)	35.0 (20.6–51.7)	9.0 (5.1–13.3)
CDKN2A	Unaltered (73)	43.8 (32.2–55.9)	9.7 (6.9–13.8)
	Altered (20)	40.0 (19.1–63.9)	4.9 (3.4–13.3)
CDKN2B	Unaltered (77)	42.9 (31.6–54.6)	11.0 (7.2–15.1)
	Altered (16)	43.8 (19.8–70.1)	4.8 (3.4–4.9)
TP53	Unaltered (80)	43.8 (32.7–55.3)	9.0 (6.6–13.3)
	Altered (13)	38.5 (13.9–68.4)	7.0 (1.4–13.8)
ARID1A	Unaltered (81)	42.0 (31.1–53.5)	9.0 (6.2–13.1)
	Altered (12)	50.0 (21.1–78.9)	8.8 (4.9–18.2)

Based on Table 18, CS[5]
Analysis performed for the preliminary DCO (1 October 2020)
CI =confidence interval; CS = company submission; DCO = data cut-off; ORR = objective response rate; PFS = progression-free survival.
Note that although the gene names resemble abbreviations, they are in the correct form to completely define the identity of each gene and so do not require further explanation.

EAG comment: Post-hoc sub-group analyses are prone to bias, as the choice of sub-groups may be influenced by the desire to create a particular result. The EAG recommends that the results from this analysis are not used for decision-making.

3.2.6 Adverse effects in the included trials

The CS[5] states that, "*In the FOENIX-CCA2 trial, most patients experienced mild-to-moderate AEs which were manageable. The most common TRAE (85.4%), and the most common grade 3–4 TRAE (30.1%) was hyperphosphatemia, which aligns with expectation for an FGFR2 inhibitor. Other adverse events commonly reported in patients who receive FGFR inhibitors were generally mild, including nail toxic effects and retinal disorders.*"

A summary of treatment-emergent adverse events (TEAEs) in the FOENIX-CCA2 trial is presented in Table 3.19.

Table 3.19: Summary of TEAEs

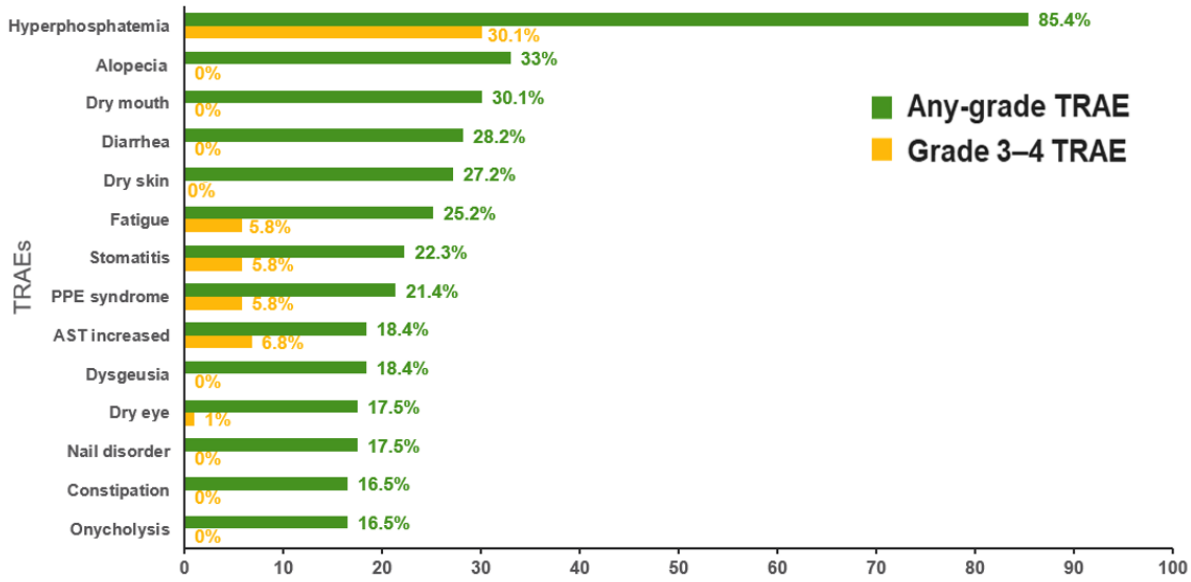
	Safety population (N=103), n (%)	
	Any grade	**Grade ≥3**
TEAEs (any cause)	[redacted]	[redacted]
SAEs	[redacted]	
Dose modification due to AE:		
Dose interruption	[redacted]	
Dose reduction	[redacted]	
Drug discontinuation	[redacted]	
TRAEs	[redacted]	[redacted]
SAEs	[redacted]	
Dose modification due to AE:		
Dose interruption	[redacted]	
Dose reduction	[redacted]	
Drug discontinuation	4 (3.9)	
AEs with outcome of death	0	

Based on Table 24, CS[5]
AE = adverse event; CS = company submission; SAEs = serious adverse events; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event

3.2.6.1 Summary of treatment-related adverse events

The CS[5] reports that, *"All TRAEs were grade ≤3 in severity, except for two grade 4 events (increased ALT [n = 1] and eye disorder [n = 1]). The frequency of serious TRAEs was low, and no treatment-related deaths occurred. Only four patients discontinued treatment due to TRAEs. The most common TRAEs included hyperphosphatemia, alopecia, dry mouth, and diarrhoea."* A summary of most common (≥15%) treatment-related adverse events (TRAEs) in FOENIX-CCA2 is given in Figure 3.8.

Figure 3.8: Most common (≥15%) TRAEs



Based on Figure 15, CS[5]
N=103 patients; AEs were graded using CTCAE Version 4.03 except for hyperphosphatemia and blood phosphorus increased; incidence of cataracts was 4% (4; all grade), of which 3% (3) were ≥grade 3; grade 3 hyperphosphatemia defined as serum phosphate level ≥7 mg/dL. Two grade 4 events were reported (increased ALT [n=1] and eye disorder [n=1]), and no grade 5 TRAEs occurred.
AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; PPE = palmar–plantar erythrodysesthesia; TRAE = treatment-related adverse event

3.2.6.2 Deaths

The CS[5] states that*: "A total of [redacted] patients died on study treatment or within 30 days of their last dose of futibatinib. No deaths were assessed to be treatment-related."*

EAG comment:

- The seven deaths are described as not 'assessed to be treatment related'. The company were asked[6] to provide more details of these deaths, and their assumed cause. The company responded by stating that, *"Of the [redacted] deaths due to AEs:* [redacted]"[7]
- The EAG thanks the company for this clarification. It is clear that the six patients dying from radiologic disease progression did not die from treatment-related effects. However, based on the limited information provided, the possibility remains that the death secondary to oesophageal varices could have been due to an adverse treatment effect affecting the hepatic system.

3.2.6.3 Adverse events of special interest

Table 3.20 summarises the adverse events of special interest (AESI).

Table 3.20: Overview of AESIs

AESI by group term	Safety population (N=103), n (%)		
	Any grade	Grade 3	Grade 4
Hyperphosphataemia[a]	94 (91.3)	32 (31.1)	0

AESI by group term	Safety population (N=103), n (%)		
	Any grade	Grade 3	Grade 4
Nail toxicities[b]	54 (52.4)	2 (1.9)	0
Increased ALT and AST[c]	28 (27.2)	12 (11.7)	1 (1.0)
PPE syndrome	23 (22.3)	6 (5.8)	0
Rash[d]	9 (8.7)	0	0
Retinal disorders[e]	8 (7.8)	0	0

Based on Table 25, CS[5]
No Grade 5 AESIs were reported
[a] Includes increased blood phosphorus.
[b] Includes nail discoloration, disorder, dystrophy, hypertrophy, infection, pigmentation, or toxicity, and onychalgia, onycholasis, onycholysis, onychomadesis, onychomycosis, and paronychia.
[c] Also includes two events of increased GGT.
[d] Includes macular, maculopapular, or papular rash.
[e] Includes chorioretinopathy, detachment of retinal pigment epithelium, maculopathy, serous retinal detachment, and subretinal fluid.
AESI = adverse event of special interest; ALT = alanine transaminase; AST = aspartate transaminase; CS = company submission; PPE = palmar–plantar erythrodysesthesia

EAG comment:

- The AEs Section in Document B is brief, with no report of the individual AEs that were not deemed treatment emergent or of special interest. The reader is directed to Appendix F for more information, but Appendix F is empty apart from a note that AE data is available in Document B. A fuller list of all AEs is required, and the company were asked to provide this.[6]
- The company responded by providing a summary of AEs and a summary of TRAEs. These can be found in Tables 10 and 11 of the company's clarification response[7]
- The EAG thanks the company for the full list of AEs provided, which do not contradict the company's overall conclusion that AEs were manageable.

3.2.7 Ongoing studies

The CS[5] states that, *"Two studies of futibatinib in CCA are ongoing:*

1. *A study of futibatinib in patients with advanced CCA with FGFR2 fusion or rearrangement (TAS-120-205, FOENIX-CCA4, NCT05727176), which is an open-label, multinational, randomised Phase II study confirming the clinical benefit of 20 mg futibatinib and evaluating the safety and efficacy of 16 mg futibatinib, is recruiting patients.*

2. *A clinical trial FOENIX-CCA3 (TAS-120-301, NCT04093362) is ongoing. FOENIX-CCA3 is a Phase III study comparing the efficacy and safety of futibatinib versus gemcitabine plus cisplatin chemotherapy as first-line treatment in adults with unresectable or metastatic CCA with FGFR2 rearrangement."*

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Apart from finding evaluations of futibatinib, the SLR described in Section 3.1 was also used to find pemigatinib evaluations that could be used in the indirect comparison between futibatinib and pemigatinib. The CS[5] reports that *"Only one trial reporting data on futibatinib (FOENIX-CCA2) was identified…. Four trials were identified reporting evidence on pemigatinib: FIGHT-202, FIGHT-101,*

FIGHT-207 and NCT04256980. Among these, FIGHT-202 was the only relevant trial for inclusion in the ITC, as its eligibility criteria aligned closely with the patient population of interest to this submission, the approved dosing schedule of pemigatinib was used and it reported results specifically in the population of interest; patients with CCA and FGFR2-fusions or other rearrangements with at least one previous systemic treatment. In trials FIGHT-101 and FIGHT-207, eligibility criteria were substantially broader, and results reported specifically in the relevant population were limited; in particular, PFS and OS KM data were not reported. The NCT04256980 trial was set in China and is therefore of limited relevance to the UK clinical practice. For these reasons, only the FIGHT-202 trial was included in the ITC for pemigatinib."

EAG comment:

- The company needs to provide a more thorough and complete rationale for the omission of FIGHT-101, FIGHT-207 and NCT04256980 than that provided in the CS.[5] For FIGHT-101 and FIGHT-207, it appears that there were relevant sub-groups in the data, which could be utilised. In particular, the assumption that the study from China (NCT04256980) is not relevant because of the study's location is very weak, given that the company have already asserted in their sub-group analysis that race and nationality do not have a significant effect on outcome, and given the fact that the futibatinib trial was multinational. The EAG asked for a fuller rationale, along with a summary of the outcomes from these studies.[6] If the relevant portions of these other studies provided superior effect sizes to the study selected for the ITC (FIGHT-202) then this might suggest the possibility of bias.
- The company responded by stating that, "*The characteristics and outcomes from the FIGHT-101, FIGHT-207 and NCT04256980 clinical trials … are briefly summarised in* [Table 3.21] *below. Health-related quality of life outcomes were not reported for the FIGHT-101, FIGHT-207 and NCT04256980 trials. A matching-adjusted indirect comparison (MAIC) is a pairwise analysis, meaning it is necessary to select one study to inform the comparator. Therefore, it is essential to select the study that is most relevant for the population of interest. Additionally, it is necessary for the trial to provide detailed baseline characteristics data for the population of relevance to this appraisal, and KM data for the outcomes of interest within this patient population, to allow for appropriate adjustment of the trials and to provide relevant efficacy inputs that can be used in the MAIC analysis and subsequently incorporated into an economic model. In this submission, the FIGHT-202 study (n=108, Cohort A) was selected as the most relevant source of evidence for pemigatinib to inform the MAIC, since it provides evidence for pemigatinib in a population of patients directly of relevance to this appraisal. The FIGHT-202 trial presents detailed baseline characteristics data, and PFS and OS KM curves that are directly relevant to the patient population of interest to this submission. The FIGHT-202 trial, Cohort A, was used to inform the efficacy of pemigatinib as part TA722, and was considered suitable for decision-making by the committee."*[7]
- The EAG thanks the company for the above explanation, which justifies the use of only one comparator trial in a MAIC and demonstrates that FIGHT-202 was an appropriate comparator.
- The company continued by providing additional rationale for not using FIGHT-101, FIGHT-207 and NCT04256980, as follows: *"The FIGHT-101 trial was delivered in two parts – the first part did not restrict to patients with CCA, nor to patients with FGFR2 fusions or rearrangements and was not considered relevant for this submission, whereas the second part of the trial reported outcomes for patients with FGFR2 fusions or rearrangements. The FIGHT-101 trial was further set up as a dose escalation study (part 1, with different dose levels and dose intervals) and dose expansion study (part 2), where only part 2 applied the approved dosing schedule of pemigatinib. In part 2 of FIGHT-101, the FGFR2 CCA-patient population was much smaller (in total 20, treated with various*

dosing schemes of pemigatinib) than FIGHT-202, and KM data for OS or PFS of the CCA population were not separately reported. Due to the limitations of the small sample size and the paucity of KM data, it was not possible to conduct a MAIC analysis using the FIGHT-101 trial of the relevant patient population for this appraisal. Similarly, the overall population in the FIGHT-207 trial is broader than the indication of relevance to this submission, since it did not restrict to patients with CCA only, nor to FGFR2 fusions or rearrangements. The trial did report results for a smaller subgroup of patients with solid tumours and FGFR1–3 fusions (n=49), however, this indication is still broader than the population with CCA with a FGFR2 fusion or rearrangement as specified in the decision problem for this submission. Additionally, the study did not report OS or PFS KM data for the overall population or the FGFR1–3 fusion population. Consequently, due to the limited relevance of the patient population and lack of KM data, it was not possible to conduct a MAIC analysis versus FIGHT-207. The NCT04256980 trial was conducted in a small sample of Chinese patients (n=31); the sample size is notably lower than in FIGHT-202 (n=108), which reduces the power of the study and limits its external and internal validity. Furthermore, the NCT04256980 trial was restricted to patients from China, and it is reasonable to assume that, compared to the FIGHT-202 study which included patients from the UK, the NCT04256980 trial population is less representative of the population anticipated to receive futibatinib in UK clinical practice. Additionally, the median follow-up for the final DCO was 25.6 months which is shorter than the final DCO of FIGHT-202 (42.9 months). For these reasons, while it would be theoretically feasible to conduct a MAIC versus NCT04256980, there would be extremely limited rationale to prefer the use of the NCT04256980 when compared to FIGHT-202, and any MAIC versus NCT04256980 would be associated with substantial additional uncertainty, when compared to the MAIC versus FIGHT-202 For these reasons, FIGHT-202 was considered to be the most relevant study for pemigatinib with respect to the population of interest (patients with advanced CCA with an FGFR fusion or rearrangement) and consequently, was used to inform the ITC analysis and subsequently, the efficacy of pemigatinib in the economic model. This approach is consistent with TA722, where the FIGHT-202 trial was considered suitable to provide evidence for pemigatinib for the population of interest to this submission, i.e., patients with advanced cholangiocarcinoma with FGFR2 fusion or rearrangement."[7]

- The EAG thanks the company for this further explanation and agrees that the FIGHT-202 study was the most relevant study for the MAIC.

Table 3.21: Characteristics of the FIGHT-101, FIGHT-207 and NCT04256980 clinical trials, compared with FIGHT-202

Trial	Study design and patient population	Sample size	Availability of baseline patient characteristics data	Availability of OS KM data	Availability of PFS KM data	Median follow-up
FIGHT-202 (NCT02924376)[13-15]	Phase II, open-label multicohort study in locally advanced/ metastatic or unresectable CCA harbouring FGF/FGFR alterations, translocations or no FGF/ FGFR alterations (USA only)	N=147 Cohort A: FGFR2 fusions or rearrangements (n=108)	Available for population of interest (Cohort A)	Available for population of interest (Cohort A)	Available for population of interest (Cohort A)	42.9 months
FIGHT-101 (NCT02393248)[16]	Phase I/II, open-label in pan-cancer patients with FGF/FGFR alterations and advanced disease	N=128	Not available for the subgroup of interest	No	No	NR
FIGHT-207 (NCT03822117)[17]	Phase II, single-arm, open-label, multiple cohort study in patients with locally advanced/metastatic or unresectable solid tumour malignancies harbouring FGFR1-3 gene mutations or translocations	N=107 Cohort A: FGFR 1-3 in-frame fusions or FGFR2 rearrangements (n=49)	Available for cohort A, which does not fully align with the population of interest (patients with FGFR2 fusions or rearrangements)	No	No	NR
NCT04256980[18]	Phase II, single-arm, open-label study in patients with advanced/metastatic CCA with FGFR2 fusions or rearrangements	Efficacy set: N=30 (preliminary DCO)	Available for population of interest	Available for population of interest, however most of the data only available for the preliminary DCO	Available for population of interest, however most of the data only available for the preliminary DCO	Preliminary DCO: 5.1 months Latest DCO: 25.6 months

Based on Table 5, company response to clarification.[7]
CCA = cholangiocarcinoma; DCO = data cut-off; FGF = fibroblast growth factor; FGFR = fusion growth factor receptor; FGFR2 = fusion growth factor receptor 2; KM = Kaplan–Meier; NR = not reported; OS = overall survival; PFS = progression free survival; USA = United States of America

Table 3.22: Baseline patient characteristics for FOENIX-CCA2 and FIGHT-202

Treatment (study)	Sample size or estimated sample size	Mean/ median age	% Male	% ECOG PS 0	% Albumin <35 g/L	% One prior therapy line	% Prior surgery	% TP53 alteration	% White[b]
Futibatinib unadjusted (FOENIX-CCA2)	N=103	55.7	43.7	46.6	19.4	46.6	39.8	12.6	49.5
Futibatinib population-adjusted (FOENIX-CCA2)	ESS=91.3	56.0	39.3	42.0[a]	19.6	60.7	35.5	8.4	73.8
Pemigatinib (FIGHT-202)[c]	N=108	56.0	39.3	42.0[a]	19.6	60.7	35.5	8.4	73.8

Based on Table 19, CS[5]
[a] Five patients (5%) had ECOG PS 2 in the pemigatinib group compared with no patients in the futibatinib group.
[b] Race (% white versus other) was used in a sensitivity analysis.
[c] Informed by the cohort A (n=107, FGFR2 fusions or rearrangements) of the FIGHT-202 trial.
CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ESS = effective sample size; OS = overall survival; PFS = progression-free survival; TP53 = tumour protein p53; % = percentage

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The effects from the single-arm trials FOENIX-CCA2 (Futibatinib) and FIGHT-202 (pemigatinib) were compared using a MAIC. An MAIC works by adjusting the sample in the study for which the individual patient data are available, to match the aggregate evidence in the other study drawn from the literature. It is therefore an analogous procedure to propensity-matching. Once the studies are matched it can be assumed that individuals in both studies will have similar prognostic characteristics (i.e., similar disease severity or age), and be exposed to (and respond to) any intervening variables (such as the placebo effect) in a similar way, thus allowing cancelling of extraneous effects, and revelation of the true treatment difference. Without such matching, the observed difference in effect may not equate to the true treatment difference, as the observed difference in effect may also be wholly or partially due to differences in extraneous effects.

The CS[5] describes the company's MAIC model as follows: "In a MAIC analysis, adjustments are made to the baseline characteristics of the study population of the intervention so they align more closely to the baseline characteristics of the study population of the comparator. This process of adjustment is referred to as propensity score weighting (PSW). In line with best practice (NICE TSD 18), the goal is to adjust for all potential prognostic factors and treatment effect variables that may confound the relationship between treatments and study outcomes, which is essential for a MAIC to be valid.

The MAIC analysis comparing futibatinib and pemigatinib utilised the individual patient data (IPD) from the final DCO of the FOENIX-CCA2 trial, and the pseudo-IPD data generated from the published final data for the FIGHT-202 trial. To account for potential differences between the studies, seven confounding factors were included in the base case Cox regression model (age, gender, ECOG status, prior lines, prior surgery, baseline hypoalbuminemia status, and TP53 alteration status). A sensitivity analysis was also performed additionally including the race covariate (White vs other). UK clinical experts in CCA indicated that all relevant treatment effect modifiers and prognostic variables had been adjusted for."

EAG comment:

- The seven confounding factors chosen are relevant and appropriate. The factors chosen for the sub-group analyses would appear to be relevant to the Cox model, as these are all factors believed to interact with outcome. However, race, region, FGFR status and prior (neo)adjuvant treatment, which were sub-group analysis factors, are not included in the Cox model. In addition, the potentially important variable of concomitant treatments was not included. The company were asked to explain this in the clarification letter.[6]
- The company responded by stating that, *"Firstly, it is important to note that clinical experts consulted as part of the May 2023 Advisory Board confirmed that the key prognostic factors and treatment effect modifiers were adjusted for in the ITC analysis. Furthermore, the clinical experts observed how the population characteristics were "remarkably similar" between the FIGHT-202 and FOENIX-CCA2 trials, with the Health Economist expert highlighting how this presents an advantage for the ITC analysis, since the populations are likely to be similar in unobservable characteristics. As such, the exclusion of these additional factors is unlikely to have any meaningful impact on the results of the ITCs. Further details on the exclusion of each of these factors is provided below."*[7]
- The EAG agrees with the statements above. The company then discussed each of race, region, FGFR status, prior (neo)adjuvant treatment, and concomitant treatments in turn. Beginning with 'race', the

company stated that, *"The impact of race on OS and PFS has already been explored as sensitivity analyses in the MAIC; these analyses demonstrated that the addition of race as a covariate had minimal impact on the ITC results (see Tables 22–23, Document B). Similar to OS and PFS, race was considered in sensitivity analyses of ORR in the MAIC for the earlier DCO and was not considered to be a covariate that has a substantial impact on the results. Additionally, subgroup analyses for ORR revealed treatment effects were consistent across the four race groups investigated (see Section B.2.7.1 of Document B). Consequently, race was not considered to be a prognostic factor or treatment effect modifier and, to maximise the effective sample size, it was not adjusted for in the base case ITC analysis."*[7]

- Based on the explanation above, the EAG agrees that race did not need to be included in the MAIC. The company then discussed 'region', as follows: *"There is no biologically plausible reason that region, as a standalone covariate, would represent a prognostic factor or treatment effect modifier. Instead, regional differences indirectly result in differences in outcomes – for example, due to differences in race or the treatment pathway in different countries. Therefore, as a standalone factor, it was not considered appropriate to adjust for region in the ITC analysis."*[7]
- Based on the explanation above, the EAG also agrees that region did not need to be included in the MAIC. The company then discussed 'FGFR status', as follows: *"FGFR2 status refers to the specific type of FGFR genetic aberration which was explored in the FOENIX-CCA2 trial – patients were categorised as having a "FGFR2 fusion" or "FGFR rearrangement". As part of the Advisory Board, clinical experts were consulted regarding the difference in treatment outcomes experienced by patients with FGFR2 fusions versus rearrangements. Clinical experts confirmed that in reality, all patients with FGFR rearrangements have FGFR fusions and the difference in labelling is simply due to the accuracy of the test. As such, FGFR fusion versus rearrangement status would not have an effect on either disease prognosis or treatment effect and, therefore, FGFR2 status is not a prognostic factor or treatment effect modifier. Based on this feedback, FGFR2 status was not adjusted for in the ITC analysis."*[7]
- Based on the above explanation, the EAG concurs with the decision not to include FGFR status in the MAIC. The company then discussed 'prior neoadjuvant treatment, as follows: *"The number of prior lines of therapy and prior surgery were adjusted for as part of the ITC meaning, overall, the impact of prior treatments was extensively explored as part of the MAIC. Prior (neo)adjuvant treatment was not directly adjusted for in the ITC analysis due to data limitations; these data were not reported in the primary or final publication for FIGHT-202 and consequently, it was not possible to adjust for differences in prior neoadjuvant treatment between the FOENIX-CCA2 trial and the FIGHT-202 trial. Furthermore, clinical experts consulted as part of the Advisory Board identified that prior FGFR2 therapy is the only prior treatment, other than surgery, that would be anticipated to impact efficacy outcomes. Since the FIGHT-202 and FOENIX-CCA2 trials excluded patients who had received prior FGFR2 therapy, and prior surgery was adjusted for in the ITC, it is deemed appropriate to not adjust for differences in the specific types of prior treatment that patients received."*[7]
- Based on the explanation above, the EAG agrees that prior treatment did not need to be included in the MAIC. The company then discussed 'concomitant treatments', as follows: *"Concomitant treatments were not reported in the primary or final publication for FIGHT-202 and consequently, it was not possible to adjust for any differences in concomitant treatments in the ITC analysis. Additionally, as described in the response to Question A13, most patients with advanced cholangiocarcinoma would be expected to receive concomitant treatments and it would not be statistically meaningful to conduct analyses based on this covariate."*[7]

- The EAG thanks the company for this clear justification for the omission of some of the sub-grouping variables from the ITC analysis. However, some uncertainty remains over the possible confounding effect of different types of concomitant treatments – although it was not possible for the company to adjust for this, these effects may introduce some uncertainty into the model. This remains a key issue.
- As recommended in Technical Support Document (TSD) 18, the company were asked in the clarification letter[6] to provide evidence that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects, and to present an estimate of the likely range of residual systematic error in the "adjusted" unanchored comparison.
- The company responded by stating that, *"In the absence of data for futibatinib and pemigatinib in UK clinical practice, there is no way of knowing whether 'absolute outcomes' for futibatinib and pemigatinib can be predicted with sufficient accuracy. However, given that the impact of the population adjustment in the MAIC is very minimal compared with the unadjusted results, this should not be considered to represent a source of uncertainty. NICE TSD 18 recommends at least two common methods for quantifying the residual error from unobserved prognostic variables or effect modifiers in an unanchored ITC: the out-of-sample method and the in-sample method. The out-of-sample method involves identifying a set of external studies with aggregate data on the relevant outcome in the target population, followed by a random effect pooling of absolute outcomes from each study arm. However, since the unanchored MAIC between futibatinib and pemigatinib relied on FOENIX-CCA2 and FIGHT-202 studies, and no further relevant studies involving pemigatinib were identified in the target population (as detailed in response to QA15), calculating the between study variance was not possible. In the absence of between-studies variation, quantification of residual error is not feasible. On the other hand, the in-sample method compared with the out-of-sample method may underestimate the true amount of residual variation and may not be a suitable method for quantifying the residual heterogeneity. With small sample size, the performance metric could significantly fluctuate across different runs which could lead to potentially misleading conclusions about the model performance. Previous literature suggests serious deficiencies in using in-sample methods for the validation of time to event outcomes and no clear methods are available for cross validation of estimates from Kaplan-Meier curves*.[Company reference 24]*To better account for uncertainty from all sources in the treatment effect, we relied on bootstrapping, which is also a method noted in the NICE TSD 18 document.*[Company reference 25] *The empirical distribution obtained from bootstrapping was used to estimate confidence intervals (CIs) for the treatment effect. These intervals inherently reflect the variability in the data due to sampling, as well as the uncertainty introduced by the matching and weighting process, and they were provided alongside the analysis results in the Submission document. In line with the reasoning above, this bootstrapping analysis was considered to be the most appropriate method of estimating uncertainty with the data available."*[7]
- The company were also asked[6] to present the details of the simulated treatment comparison (STC) given the lack of reliability of any form of population adjustment in an unanchored comparison. The company stated that, *"While an STC was not conducted as part of the Company submission, an STC was previously conducted to assess the efficacy of futibatinib against pemigatinib using data from an early data cut of both the FOENIX-CCA2 (October 2020) and FIGHT-202 (PFS; March 2019, OS: April 2020) trials. The MAIC presented in Document B utilised data from the final DCO of FOENIX-CCA2 (May 2021) and the most recently published data from the FIGHT-202 trial. The results from the MAIC and STC analyses using the early DCOs, and a comparison with the results of the MAIC analysis using the later DCOs of both trials (as presented in Document B) are provided in Table 3.23. Overall, the results of the MAIC and STC analyses point towards futibatinib and*

pemigatinib having a very similar efficacy profile, with no statistically significant differences identified across any of the analyses. Given the similarity between the MAIC and STC results at the time of the earlier DCOs, it was considered appropriate to only conduct MAICs for the final ITC (utilising the latest DCOs for FOENIX-CCA2 and FIGHT-202). It should be noted that the results of the STCs were more favourable than the MAICs with respect to both PFS and OS at the time of the earlier DCO, indicating that the use of MAICs for the final DCO could be considered conservative. Health economic experts consulted as part of the May 2023 Advisory Board confirmed that MAIC is an appropriate methodology for the ITC since it aligns with the approach used in TA722, whereby only a MAIC was conducted. The use of a MAIC was considered appropriate for decision-making as part of NICE TA722. Additionally, MAICs offer the advantage of producing marginal treatment effect estimates, since, by assigning differential weights to IPD for futibatinib, the aggregate measures on the modelled prognostic and treatment effect variables match (or as close as possible to) the values in the matched aggregate studies.[company reference 27] This weighting approach results in a marginal (population-level) treatment effect which consequently allows for a population-level ITC. In comparison, STCs only produce conditional (patient-level) treatment effects. As such, the use of the MAICs to inform the base case ITCs and economic analysis should not be considered to represent a source of uncertainty in this appraisal."[7]

- In response to the above, the EAG accept that it might not be possible to establish that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects and thus the effect of the MAIC or the STC on the amount of bias. However, the company make a false distinction between a MAIC and STC in that both MAIC and STC produce estimates at the marginal (population) level and that both suffer the same disadvantage of only being able to use the marginal covariate distribution because of the lack of Individual Participant Data (IPD) in the comparator dataset (see TSD 18). In fact, as the EAG pointed out in the clarification letter, *"MAICs perform poorly in simulation studies, and in some scenarios perform worse than standard NMA with no population adjustment"* (page 12).[21] Nevertheless, it is some reassurance that the naïve comparison and both methods of population adjustment produce similar results.

Table 3.23: ITC results for the early and final DCOs

ITC	Model	HR for PFS	95% CI	HR for OS	95% CI
Early DCO					
N/A	Cox-naïve/unadjusted	0.812	0.579–1.138	0.897	0.595–1.352
MAIC	Base-case	0.827	0.584–1.170	0.881	0.580–1.338
	Sensitivity analysis	0.840	0.585–1.206	0.852	0.547–1.329
STC	Base-case	0.821	0.576–1.170	0.823	0.530–1.277
	Sensitivity analysis	0.831	0.574–1.201	0.823	0.511–1.324
Final DCO					
N/A	Cox-naïve/unadjusted	1.02	0.75–1.39	0.96	0.67–1.36
MAIC	Base-case	1.07	0.86–1.30	0.95	0.72–1.21
	Sensitivity analysis	1.11	0.89–1.36	0.96	0.71–1.25

Based on Table 6, company response to clarification.[7]
CI = confidence interval; DCO = data cut-off; HR = hazard ratio; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; N/A = not applicable; OS = overall survival; PFS = progression free survival; STC = simulated treatment comparison

The MAIC was only performed for OS and PFS, as these would inform the economic model. The CS explains that *"A safety ITC was also explored, but it was not considered feasible due to the differences in AE reporting definitions between FOENIX-CCA2 and FIGHT-202. In addition, UK clinical experts in CCA confirmed that the safety profiles of futibatinib and pemigatinib were very similar, and they did not expect there to be any meaningful difference in AE profiles, meaning that the absence of a safety ITC should not be considered to represent a major source of uncertainty".*

EAG comment:

- In Appendix D (Table 16) the AE of hyperphosphatemia appears to be reported in both studies. As this is an AESI, it appears feasible that this specific AE outcome could be used in an MAIC. Given the importance of AEs in the estimation of the relative benefits and harms of two treatments, the company were asked[6] to consider an adjusted MAIC for this outcome.
- In response, the company stated that, "*Since the PFS and OS outcomes were the key outcomes of interest to the submission and they informed the economic model, the MAICs were focused on these two outcomes. This aligns with the approach taken by the NICE evaluation of pemigatinib (TA722), which provided PFS and OS MAIC results only for the treatments of interest. It should also be noted that AEs have a very limited impact on the economic model results, as demonstrated by the sensitivity analyses presented in Document B, Section B.3.11. Deterministic sensitivity analyses (DSA) were conducted for a variety of inputs, including AEs, by varying all parameters for which there were single input values in the model by ±20% of their mean value. The results of the DSA showed that the AEs input variation had a negligible effect on the model outcomes, measured in terms of incremental costs, QALYs and incremental net health benefit (INHB) (please refer to the Section B.3.11.2 in the submission document). Notably, variation of the incidence of hyperphosphatemia was also included in the DSA, however it was not shown in the results in Section B.3.11.2 since it was not in the top ten variables that impacted the INHB outcome of the model. Varying the incidence of hyperphosphataemia for futibatinib by 20% changed the NHB by a negligible amount of ~0.0001. Further to this, the results of the PFS and OS MAICs demonstrated that population-adjustment had a very limited impact on the results. This potentially reflects the fact that, as highlighted by the UK clinical experts, the patient populations in the FOENIX-CCA2 and FIGHT-202 trials were similar. Therefore, while in theory it would be feasible to conduct MAICs for specific safety outcomes, it would be expected to have a negligible impact on the economic model, as demonstrated by the DSA analyses. As such, the exclusion of MAICs for safety outcomes should not be considered to represent a source of uncertainty in this submission. This is aligned with the conclusions of the NICE committee as part of NICE TA722 for pemigatinib, where 'The Committee concluded that there was a lack of comparative safety evidence for pemigatinib and its comparators, but that this was unlikely to have much effect on the cost-effectiveness estimates.'* "[7]
- The EAG is satisfied with the above response, given that the deterministic sensitivity analysis (DSA) showed that incidence of hyperphosphatemia would have little impact on net health benefits (NHBs).
- No justification is given for the omission of HRQoL or response rates from the MAIC analyses, apart from the implicit suggestion that they were not to be used for economic modelling. These outcomes have been requested by the NICE final scope,[8] and are therefore important aspects of the clinical evidence, which is important for clinical decision-making even if not carried through to economic modelling. They should therefore also be subjected to an MAIC, as without comparison to a reference treatment the meaning of the single arm results for these outcomes is questionable. The CS Appendices contain data comparing the FOENIX-CCA2 (Futibatinib) and FIGHT-202 (pemigatinib) trials for response rates (Table 15 in CS Appendices[9]), HRQoL (Table 17

in CS Appendices[9]) but these do not appear to be adjusted and so do not constitute MAICs. The company were asked[6] to consider performing MAICs for these two outcomes.

- The company responded in terms of response rate outcomes by stating that, "*A MAIC analysis for ORR was previously performed for the final DCO of the FOENIX-CCA2 trial versus a previous DCO of the FIGHT-202 trial. The ORR was evaluated as a binary outcome, in contrast to the methods used for PFS and OS MAICs, which evaluated PFS and OS as continuous variables. The results of this analysis are provided below. The unadjusted ORR in FOENIX-CCA2 was 41.7% and from FIGHT-202 was 37.0% (Table 3.24). There remained only a small reduction from the trial sample size after matching, suggesting good overlap in baseline characteristics between studies. No patient received a very large weighting, with the maximum rescaled weight being 1.78 (minimum 0.33). The results from the unadjusted binomial model and covariate-adjusted MAIC analyses are shown in Table 3.25. Seven base-case prognostic factors were included in the base-case adjusted model (age, gender, ECOG status, prior lines, prior surgery, baseline hypoalbuminemia status, TP53 alteration status). In the base case, the OR estimate shows a non-statistically significant but numerically higher rate of ORR for futibatinib compared with pemigatinib (OR: 1.15; 95% CI: 0.66–2.02). This effect remained statistically non-significant in the sensitivity analysis. Calculations have been made to provide a rough estimate of the sample size that might be required to differentiate ORR between futibatinib and pemigatinib, assuming that the probability of experiencing a response at the end of follow-up was as observed in the FOENIX-CCA2 (42%) and FIGHT-202 trial (37%) primary DCOs. These calculations suggested that approximately 3,000 patients would be required in total, which is 15 times greater than the current numbers enrolled in FOENIX-CCA2 and FIGHT-202."*[7]
- The EAG thanks the company for the above response, which provides a clear account of the methodology and results of a MAIC for objective response rates.
- In relation to the outcome of HRQoL, the company added that, "*The HRQoL MAIC was considered for this submission, however it was decided that this MAIC would result in negligible impact on the economic model results due to futibatinib and pemigatinib resulting in similar efficacy and safety profiles (as discussed throughout this submission and confirmed by UK clinical experts), and due to the two treatments having the same mode of administration. Consequently, it was considered that a HRQoL MAIC would not provide any new information compared with the PFS and OS MAICs which are presented in the Submission document*."[7]
- The EAG does not accept this rationale for the omission of an MAIC for HRQoL It cannot be assumed that similar efficacy and safety profiles, alongside a similar mode of administration will lead to similar effects of QoL. This appears to be based on a simplistic model of how efficacy outcomes and AEs may interact in real-world patients. This is a key issue.

Table 3.24: Unadjusted ORR for futibatinib and pemigatinib

Source	N	Median follow-up, months	ORR events, n (%)
FOENIX-CCA2, May 2021 DCO	102	25	43 (41.7)
FIGHT-202, April 2020 DCO	108	30.4	40 (37.0)

Based on Table 7, Company response to clarification.[7]
DCO = data cut-off; ORR = objective response rate

Table 3.25: Unadjusted and adjusted ORR model results

Model	HR for ORR	95% CI; p value	Notes
Cox-naïve/unadjusted	1.22	0.70–2.13; p=0.487	No covariate adjustment

Model	HR for ORR	95% CI; p value	Notes
Adjusted Cox MAIC model analyses			
Base-case covariates	1.15	0.66–2.02; p=0.618	Adjusted for age, gender, ECOG PS, prior lines, prior surgery, baseline hypoalbuminemia status, TP53 alteration status
Sensitivity analysis	1.11	0.63–2.10; p=0.7195	Base-case + race

Based on Table 8, company response to clarification.[7]
CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; ORR = objective response rate; TP53 = tumour protein p53

Results of the MAIC are provided for PFS and OS in Section 3.4.1 and 3.4.2, respectively.

3.4.1 Progression-free survival

The median PFS from FOENIX-CCA2 (futibatinib) was 8.9 months (95% confidence interval (CI): 6.7–11.0 and the median PFS from FIGHT-202 (pemigatinib) was 7.0 months (95% CI: 6.1–10.5; Table 3.26).

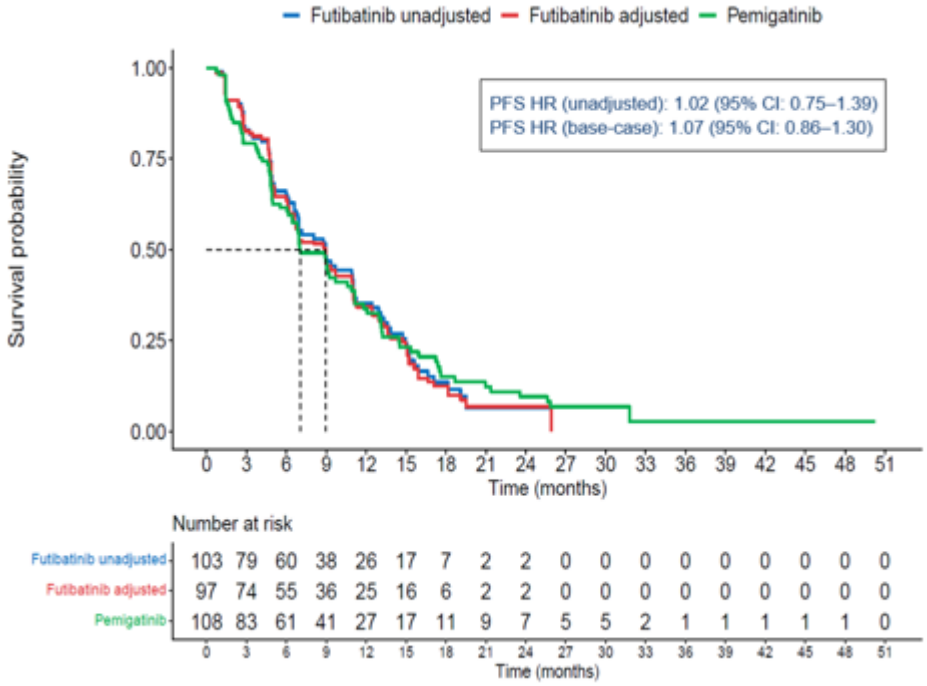
Table 3.26: Unadjusted KM estimates of PFS for futibatinib and pemigatinib

Model	N	Events, n (%)	Median, months (95% CI)	Estimated PFS events from recreated KM, n (%)	Estimated median, months (95% CI) from recreated KM
FOENIX-CCA2	103	[redacted]	8.94 (6.74, 11.00)	N/A	N/A
FIGHT-202	108	85 (78.70)	7.0 (6.1, 10.5)	88.00 (81.48)	7.03 (6.14, 10.60)

Based on Table 20, CS[5]
CI = confidence interval; CS = company submission; KM = Kaplan–Meier; N/A = not applicable; PFS = progression-free survival

The CS[5] reports that, "*The Cox model was used to calculate HRs for the relative effect of futibatinib versus pemigatinib. Table 3.29 summarises the results from the unadjusted Cox model and covariate-adjusted MAIC analyses for PFS. This analysis resulted in an adjusted PFS HR of 1.07 (95% CI: 0.86, 1.30), with no statistically significant difference between the two treatment groups (Figure 3.9). In addition to HRs, restricted mean survival time (RMST) analyses were conducted for the base case analysis, based on the length of PFS follow-up in the FOENIX-CCA2 trial ([redacted] months). The results of the RMST analyses similarly indicated no statistically significant difference in PFS survival for futibatinib and pemigatinib, with the futibatinib RMST PFS being slightly higher than that for pemigatinib ([redacted]months versus [redacted]months). A sensitivity analysis was also conducted, with the race covariate added to the base-case analysis covariates. The results of this analysis were similar to those in the base case (Table 3.27*)".

Figure 3.9: KM plot of unadjusted and MAIC-weighted PFS for futibatinib and pemigatinib



Based on Figure 13, CS.[5]

CI = confidence interval; CS = company submission; HR = hazard ratios; KM = Kaplan–Meier; MAIC = matching-adjusted indirect comparison; PFS = progression-free survival

Table 3.27: Unadjusted and adjusted PFS model results

Model	HR for PFS	95% CI; p value	RMST (months) for PFS at 25.92 months	RMST difference (months) for PFS (95% CI; p value)	Notes
Unadjusted analyses					
Cox-naïve/unadjusted	1.02	0.75–1.39; p=0.918	Futibatinib unadjusted: 10.01 Pemigatinib 9.997	0.02 (-2.07, 2.11); p=0.988	No covariate adjustment
Adjusted Cox MAIC model analyses					
Base-case	1.07	0.86–1.30; p=0.520	Futibatinib adjusted: 10.17	0.17 (-1.12, 1.56); p=0.804	Adjusted for age, gender, ECOG PS, prior lines, prior surgery, baseline hypoalbuminemia status, TP53 alteration status
Sensitivity analysis	1.11	0.89–1.36; p=0.335	N/A	N/A	Base-case covariates + race

Based on Table 21, CS[5]

CI = confidence interval; CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; N/A = not applicable; PFS = progression-free survival; RMST = restricted mean survival time; TP53 = tumour protein p53

3.4.2 Overall survival

There was a median OS of 20.0 months for futibatinib (95% CI: 16.4, 24.6), compared with a median OS for pemigatinib of 17.5 months (95% CI: 14.4–22.9; Table 3.28).

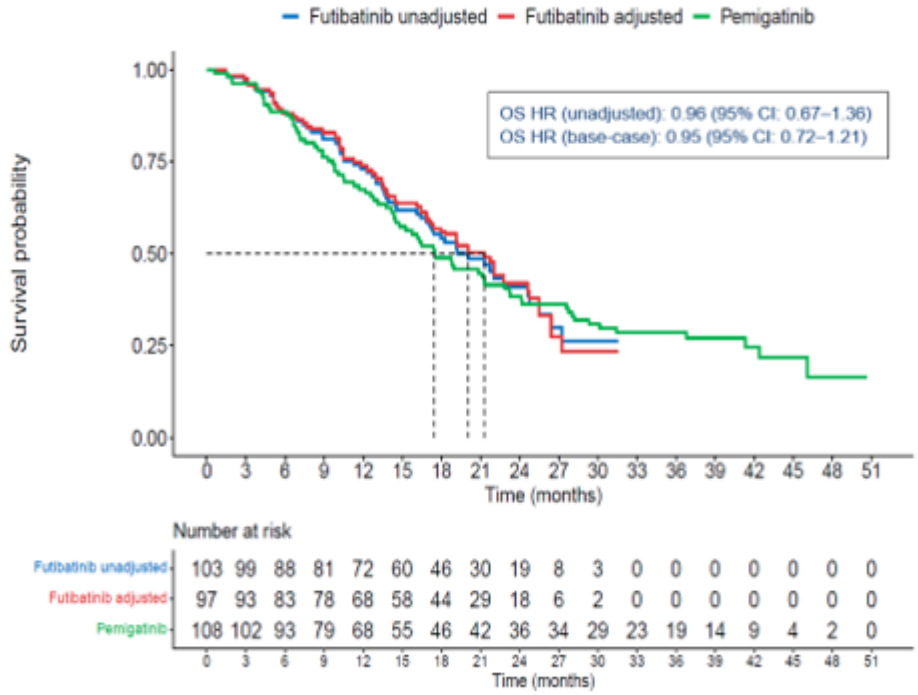
Table 3.28: Unadjusted KM estimates of OS for futibatinib and pemigatinib

Model	N	Events, n (%)	Median, months (95% CI)	Estimated OS events from recreated KM, n (%)	Estimated median, months (95% CI) from recreated KM
FOENIX-CCA2	103	[redacted]	20.0 (16.4–24.6)	N/A	N/A
FIGHT-202	108	76 (70.37)	17.5 (14.4–22.9)	75.00 (69.44)	17.50 (14.40–22.90)

Based on Table 22, CS[5]
CI = confidence interval; CS = company submission; KM = Kaplan–Meier; N/A = not applicable; OS = overall survival

The CS[5] states that: *"The unadjusted and weighted futibatinib OS curves compared with the recreated pemigatinib OS curve are shown in Figure 3.10. The unadjusted and adjusted futibatinib OS curves appear to show that futibatinib is associated with a slight OS benefit versus pemigatinib from Month ~6 to Month ~27; after this point, extremely low numbers of patients at risk remain in the futibatinib data due to the length of follow-up of the futibatinib trial. Table 3.29 summarises the results from the unadjusted Cox model and covariate-adjusted MAIC analyses. The MAIC base-case HR estimate shows a comparable risk of death for futibatinib versus pemigatinib patients (HR: 0.95; 95% CI: 0.72–1.21), with no statistically significant differences between the two treatments. This effect remained statistically non-significant in the sensitivity analysis, which explored the addition of race to base-case covariates.Additionally, results of the RMST analysis are presented in Table 3.32 based on the follow-up time for OS in the FOENIX-CCA2 trial (27.24 months). Based on RMST calculation, futibatinib slightly extended restricted mean OS when compared to pemigatinib across all analyses considered, with an increase of 0.87 months (95% CI: -0.85, 2.52) in the base case ITC".*

Figure 3.10: KM plot of unadjusted and MAIC-weighted OS for futibatinib and pemigatinib



Based on Figure 14, CS.[5]
CI = confidence interval; CS = company submission; HR = hazard ratios; KM = Kaplan–Meier; MAIC = matching-adjusted indirect comparison; OS = overall survival

Table 3.29: Unadjusted and adjusted OS model results

Model	HR for OS	95% CI; p value	RMST (months) for OS at 27.24 months	RMST difference (months) for OS (95% CI; p value)	Notes
Unadjusted analyses					
Cox-naïve/unadjusted	0.96	0.67–1.36; p=0.799	Futibatinib unadjusted: 18.41 Pemigatinib: 17.59	0.82 (-1.59, 3.22); p=0.505	No covariate adjustment
Adjusted Cox MAIC model analyses					
Base-case covariates	0.95	0.72–1.21; p=0.699	Futibatinib adjusted: 18.46	0.87 (-0.85, 2.52); p=0.312	Adjusted for age, gender, ECOG PS, prior lines, prior surgery, baseline hypoalbuminemia status, TP53 alteration status
Sensitivity analysis includes race covariate (white vs other)	0.96	0.71–1.25; p=0.777	N/A	N/A	Base-case covariates + race
Based on Table 23, CS[5]					

Model	HR for OS	95% CI; p value	RMST (months) for OS at 27.24 months	RMST difference (months) for OS (95% CI; p value)	Notes
CI = confidence interval; CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; N/A = not applicable; OS = overall survival; RMST = restricted mean survival time; TP53 = tumour protein p53					

EAG comment: Although population adjustment of any kind in an unanchored ITC has highly questionable validity, it is some reassurance that both methods produced similar results to the naïve comparison, which seem to show that there is little difference in PFS and OS between futibatinib and pemigatinib. This means that an assumption of equal effectiveness seems reasonable, at least in terms of these two outcomes.

3.5 Additional work on clinical effectiveness undertaken by the EAG

None.

3.6 Conclusions of the clinical effectiveness section

The CS[5] and response to clarification[7] provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence on the efficacy and safety of futibatinib and pemigatinib for the treatment of adult patients with locally advanced or metastatic CCA with FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy. Searches were conducted in September-October 2023. Searches were transparent and reproducible, and comprehensive strategies were used. Bibliographic databases, conference proceedings and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted, although searches could have been more sensitive in order to minimise the risk of relevant records being missed.

The NICE final scope[8] dictated a comparison between futibatinib and the comparators pemigatinib, mFOLFOX or BSC, in terms of survival, response, safety and HRQoL for adults with locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or rearrangement that has progressed after at least one prior systemic therapy. The decision problem differed from this in its restriction of comparators to pemigatinib alone. The omission of BSC was justified, but the company were unable to give a strong rationale for the omission of mFOLFOX as a comparator. For mFOLFOX to be justifiably omitted, it would need to be shown to be inferior to pemigatinib in the same population, but the company were unable to provide sufficiently strong evidence that pemigatinib was superior to mFOLFOX. This was a concern because it meant that any demonstration of superiority for futibatinib over pemigatinib would not necessarily indicate futibatinib was better than mFOLFOX.

The trial data were restricted to a single arm study of 103 patients in the specified population. This demonstrated futibatinib was associated with an OS at 12 months of 73.1%, a PFS of 35.4% at 12 months, CR in 1% and PR in 40.8% at the final DCO (median 25 months), and a mean improvement of EQ VAS of [redacted] points at 9 months. Because of the single arm data, it was not possible to eliminate extraneous effects and attribute these findings solely to treatment effects. It was unclear how representative these trial results were to the target population as no characteristics of the target population were available for comparison with the trial baseline characteristics. Despite the company's confidence in expert clinical opinion, it was not possible to exclude population differences in age and

prior systemic therapy, which had shown trends in the sub-group analysis for outcome modification. It was also not possible to exclude population differences in concomitant medication types or population differences in patients with solid tissue samples, which had not been included in the sub-group analysis but were plausible effect modifiers. The company's rationale for omitting these from the sub-group analysis was insufficiently strong, according to the opinion of the EAG. It is possible therefore that the trial results might not precisely apply to the target population, although the EAG accepts that any effect of population differences in these variables on outcomes is likely to be small.

As the trial results did not involve a comparator, an MAIC was used to facilitate comparison of futibatinib with pemigatinib. The single arm trial used for the pemigatinib data was appropriate, and although the covariates used for adjustment of the data were appropriately chosen, 'types of concomitant therapy', which is a plausible effect modifier, was not included in the MAIC model. The MAIC results demonstrated that the treatments were similar in terms of OS and PFS. Given the methodology used by the company, and the company's clear responses to clarification questions, the EAG has reasonable confidence that the MAIC results reflect the equipoise of futibatinib and pemigatinib. However, the EAG have concerns that the submission did not exclude the fact that mFOLFOX may have been superior to pemigatinib and therefore also superior futibatinib. The EAG also have concerns about the external validity of the results to the target population, though this is of lesser magnitude.

AEs from futibatinib were generally manageable, with 11 serious TRAEs in 103 patients, and no deaths. It is unclear how these would compare to those for pemigatinib.

4. Cost effectiveness

4.1 EAG comment on company's review of cost effectiveness evidence

This Section pertains mainly to the review of cost effectiveness analysis (CEA) studies. However, the search Section (4.1.1) also contains summaries and critiques of other searches related to CE presented in the CS. Therefore, the following Section includes searches for the CEA review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for CE Section

The following paragraphs contain summaries and critiques of all searches related to CE, HRQoL and resource use identification presented in the CS.[5, 9] The CADTH evidence-based checklist for the PRESS, was used to inform this critique.[10, 11] The EAG has presented only the major limitations of each search strategy in the report.

Appendix G of the CS provides details of an SLR conducted to identify relevant studies on CE, HRQoL and cost/health care resource use in adult patients treated with futibatinib and pemigatinib.[9] Searches were undertaken in October 2023.

A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources searched for economic evaluations (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	1974-3.10.23	3.10.23
MEDLINE	Ovid	1946-3.10.23	3.10.23
Additional resources			
NHS EED	CRD website	Not stated	5.10.23
International HTA Database	Internet	Not stated	5.10.23
CEA Registry	Internet	Not stated	24.10.23
ScHARRHUD	Internet	Not stated	24.10.23
EQ-5D Publications Database	Internet	Not stated	24.10.23
HTA websites			
• AWMSG • CADTH • NCPE • NICE • PBAC • SMC	Internet	Last 10 years	12.10.23
Conferences			
• ASCO • ESMO	Internet	2021-2023	11.10.23

Resource	Host/Source	Date Ranges	Date searched
• ESMO World Congress on Gastrointestinal Cancer • ISPOR Annual Meetings			

ASCO = American Society of Clinical Oncology; AWMSG = All Wales Medicines Strategy Group; CRD = Centre for Reviews and Dissemination; CEA Registry = Cost-Effectiveness Analysis Registry; CADTH = Canadian Agency for Drugs and Technology in Health; ESMO = European Society of Medical Oncology; HTA = Health Technology Assessment; NCPE = National Centre for Pharmacoeconomics; NHS EED = National Health Service Economic Evaluation Database; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; ScHARRHUD = University of Sheffield Health Utilities Database; ISPOR = International Society for Pharmacoeconomics and Outcomes Research

EAG comment:

- A single set of searches was undertaken in October 2023 to identify relevant studies on CE, HRQoL and cost/health care resource use in adult patients treated with futibatinib and pemigatinib. The CS, Appendix G and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[5, 7, 9]
- In addition to bibliographic database searches, a good range of Health Technology Assessment (HTA) organisation websites, grey literature resources and conferences proceedings were searched. Reference checking was conducted. Searches were well structured, transparent and reproducible.
- Database searches were limited to CE references published since 2020 and cost/resource use studies published since 2013. No date limit was applied to the HRQoL searches. Searches were not limited by language of publication.
- Conference proceedings were handsearched for four key international conferences between 2021 and 2023. The rationale for this was that:

  > 'Abstracts from congresses prior to 2021 were excluded, under the assumption that congress abstracts that have not been published as journal articles within two years are of low quality.' (Appendix G[9])

  Embase however, which also contains conference proceedings, was limited to conferences proceedings from 2022-2023, rather than 2021-2023 (Appendix G, Table 20; Lines 58-59[9]). The EAG feels that more extensive conferences proceedings searches could have been conducted on Embase, and that this might have retrieved additional useful records.
- The CE searches contained a population facet for metastatic CCA. This was then combined with an intervention/comparator facet for futibatinib/pemigatinib, and a study design filter containing terms for economic evaluations.
- The HRQoL searches contained a population facet for CCA. This was then combined with a study design filter containing terms for HRQoL.
- The cost/resource use searches contained a population facet for metastatic CCA. This was then combined with a study design filter containing terms for cost and resource use.
- Low numbers of records were found by all searches. As with the clinical effectiveness searches (see comments in Section 4.1.1), a number of approaches could have been taken to increase the sensitivity of the searches, such as the use of additional synonyms within each facet and omitting the 'neoplasm metastasis' limit from the CE and cost/resource use searches.
- None of the study design filters used were referenced, however all contained an extensive combination of subject heading terms and free text terms, and the EAG considered them appropriate.

4.1.2 Inclusion/exclusion criteria

In- and exclusion- criteria for the review on CE studies, utilities and costs and resource use are presented by the company in appendix G of the CS.[9] The EAG agrees that the in- and exclusion- criteria are suitable to fulfil the company's objective to identify relevant CE studies.

4.1.3 Conclusions of the CE review

The CS[5] and response to clarification[7] provided sufficient details for the EAG to appraise the literature searches conducted to identify economic, HRQoL and cost data on adult patients treated with futibatinib and pemigatinib. Searches were conducted in October 2023. Searches were transparent and reproducible, and comprehensive strategies were used. Databases, conference proceedings and HTA resources were searched. Overall, the EAG has no major concerns about the literature searches conducted, although searches could have been more sensitive in order to minimise the risk of relevant records being missed. Since no economic models to address the current decision problem were identified by the company, a de novo model was built, which is discussed in the remainder of this section.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.2: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	As per the reference case
Perspective on costs	NHS and PSS	As per the reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	As per the reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	As per the reference case
Synthesis of evidence on health effects	Based on systematic review	As per the reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	As per the reference case
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	As per the reference case
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	PROs collected in FOENIX-CCA2 included EQ-5D-3L data. As per the reference case, the utility values derived from these data used the UK tariff
Equity considerations	An additional QALY has the same weight regardless of the	As per the reference case

Element of HTA	Reference case	EAG comment on CS
	other characteristics of the individuals receiving the health benefit	
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	As per the reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	As per the reference case

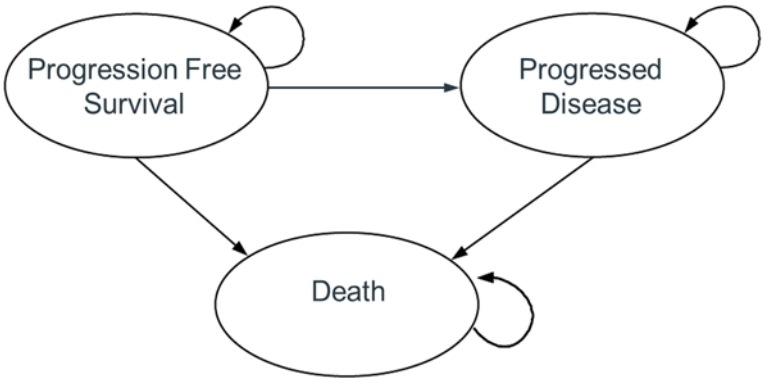
CS = company submission; EAG = External Assessment Group; EQ-5D-3L = EuroQoL-5 Dimensions Three Levels; HTA = Health Technology Assessment; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PRO = patient-reported outcome; PSS = Personal Social Services; QALY = quality-adjusted life year; QoL = quality of life; UK = United Kingdom

4.2.2 Model structure

The company developed a CE model in Microsoft Excel® to assess the CE of futibatinib compared to pemigatinib for treating patients with previously treated locally advanced or metastatic CCA with FGFR2 gene rearrangements and gene fusions.

The model adopts a partitioned survival approach consisting of three mutually exclusive health states; namely progression-free (PF), progressive disease (PD), and death, where patients can only occupy one state at the time and death being an absorbing state. The company chose to use a partitioned survival model (PSM) over a Markov model as this could directly use the OS and PFS data from the FOENIX-CCA2 trial to inform the state occupancy of the futibatinib arm, without the need to estimate transition probabilities.[12] Furthermore, the company noted that, in absence of patient-level data for the comparator arm, published summary survival data could be used within the PSM to re-construct OS and PFS curves and define state occupancy without the need to impose stronger assumptions. This approach was further expected to appropriately reflect locally advanced or metastatic CCA, considering the progressive nature of the disease, which in advanced stages it would typically lead to death. A PSM was previously accepted by NICE in TA722, which also focused on treatment of patients with CCA with FGFR2 fusion or rearrangement.[22] Figure 4.1 shows the schematic model structure.

Figure 4.1: Model structure



Based on Figure 16 of the CS[5]
CS = company submission

Patients were assumed to enter the model in the PF health state and receive either futibatinib or pemigatinib. The proportion of patients in PF was determined by the PFS curves. In the original CS, it was assumed that in each cycle, patients in the PF health state can remain in PF and continue treatment, move to PD health state, or die. That structure was based on the company's assumption that the time on treatment (ToT) curve would be equal to the PFS curve, indicating that patients would remain on treatment as long as they do not progress. Following the clarification phase, the company adjusted the model structure allowing PF patients to remain in PF but stop receiving treatment.[7] This was achieved by modelling the ToT curve independently of the PFS curve as per the EAG's request. PF patients were assumed to incur costs associated with treatment acquisition and administration, monitoring, medical management of the condition and costs related to the management of Grade 3/4 AEs. The proportion of patients in the PD health state was calculated as the difference between the PFS and OS curves. The OS curve was used as an upper bound to constrain the PFS curve, and survival of the general population to constrain both. Progressed patients were assumed to either stay in the PD health state or die. Costs for the medical management of the PD and terminal care were also included in the model.

Costs and utilities were applied to each health state to calculate total costs and quality-adjusted life years (QALYs) per model cycle, which was set at 21 days. A half-cycle correction was implemented to account for events happening at any time during the cycle. The input values of the model and their underlying assumptions are further elaborated in the remaining of Section 4 of the EAG report.

EAG comment: The company argued that the model structure in the current submission aligns with the model structure used in TA722. The EAG noticed that in TA722 the PSM employed five different mutually exclusive health states instead of three that were assumed in the current submission. In response to clarification question B1,[7] the company explained that whilst ToT was modelled independently of PFS in TA722, a structural restriction was included ensuring ToT could not exceed PFS for any modelled treatment arm, such that all patients discontinued treatment prior to or at the point of disease progression. This was considered to be in line with UK clinical practice as well as the licence for pemigatinib. As such, in the clarification response, the company argued that the modelling approaches between the current submission and TA722 are functionally similar. The EAG does not agree with this company's rationale. That is because incorporating actual ToT data in the model can sufficiently impact the estimated treatment costs as explained in the EAG comments in Section 4.2.9. To further elaborate, independent modelling of ToT and PFS curves in TA722 indicated that PF patients on pemigatinib can still remain in PF while not on treatment and can, therefore, have lower treatment costs than the costs that are estimated if ToT is assumed to be equal to PFS. Using the PFS curve as an upper bound of the ToT curve in TA722, as per the company's response above, is not the same as assuming equal ToT and PFS given that the second option may lead to a bias in the estimated costs. In any case, following the clarification phase, the company have added a functionality to allow for independent modelling of ToT curves as requested by the EAG and further comments on the EAG's preferred approach are provided in Section 4.2.9.

4.2.3 Population

Consistent with the NICE final scope,[8] the population considered in the CS was adult patients with previously treated locally advanced or metastatic CCA with FGFR2 gene rearrangements or fusions that have progressed after at least one prior systemic therapy. The patient population aligns with the anticipated licensed indication of futibatinib,[23] and is consistent with the patient population included in the FOENIX-CCA2 trial (see Section 3.2.1).

The key baseline patient characteristics in the economic model are listed in Table 4.3. Patients included in the economic model were assumed to have an average baseline age of 55.7 years, a mean weight of [redacted] kg, a mean body surface area of [redacted] m^2, and consist of a 56.3% female population based on the FOENIX-CCA2 trial population characteristics.[12]

Table 4.3: Key baseline patient characteristics used in the economic model

Parameter	Mean	Source
Percentage female	56.3%	FOENIX-CCA2 CSR; DCO 29 May 2021[12]
Starting age, years	55.7	
Body weight, kg	[redacted]	
Body surface area, m^2	[redacted]	
Based on Table 29 of the CS[5] CS = company submission; CSR = Clinical Study Report; DCO = data cut-off; kg = kilogram; m^2 = square metre		

4.2.4 Interventions and comparators

The intervention considered in the CS was futibatinib, which is a self-administered oral treatment at a dosage of 20 mg once daily (QD) as a continuous therapy, and can be administered until disease progression or unacceptable toxicity occurs, consistent with the licensed indication.[23]

Pemigatinib was deemed to be the only relevant comparator in the economic analyses, with the company referring to feedback from UK clinical experts,[24] and to the NICE recommendation for the treatment of patients with locally advanced or metastatic CCA with a FGFR2 fusion or rearrangement that has progressed after prior systemic therapy.[22] Apart from pemigatinib, the NICE scope also listed modified FOLFOX and BSC as relevant comparators. The company justified that, according to clinical experts, adult patients with previously treated locally advanced or metastatic CCA harbouring FGFR2 gene rearrangements, including gene fusions, would be treated with pemigatinib in the UK, since chemotherapy is not a mutation-specific treatment and the survival gain for these patients is lower than treatment with pemigatinib.[24] Pemigatinib is also a self-administered oral tablet which is offered at a dosage of 13.5 mg QD for 14 days followed by seven days-off treatment. Pemigatinib can be administered until disease progression or unacceptable toxicity occurs.

EAG comment: The main concerns of the EAG relates to the omission of mFOLFOX from the comparators list. Although the EAG accepts the company's decision to omit BSC from the current analyses (see EAG comments in Section 2.4), the EAG does not concur with the company's rationale to disregard mFOLFOX from the relevant comparators claiming superiority of pemigatinib over mFOLFOX based on the unanchored and improperly adjusted MAIC analyses in TA722.[22] As explained in the EAG comments in Section 2.4, the company did not present any new evidence that would support the inferiority of mFOLFOX as compared to pemigatinib, while clinical opinion, although valued by the EAG, it should be used as a complementary to objective evidence.

4.2.5 Perspective, time horizon and discounting

The economic analysis is conducted from the National Health Service (NHS) and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is 21 days with a lifetime time horizon (40 years) and a half-cycle correction applied.

4.2.6 Treatment effectiveness and extrapolation

Survival analyses for the futibatinib arm, were conducted using data from the FOENIX-CCA2 trial. The company followed the recommendations by the NICE Decision Support Unit (DSU) TSD 14 on survival data extrapolation.[25] Six parametric distributions (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) were fitted to extrapolate OS, PFS, and ToT (the latter in response to clarification question B4)[7] data from the FOENIX-CCA2 trial. For the pemigatinib arm, the analyses were based on reconstructed pseudo-IPD from FIGHT-202 (clarification question B2).[7, 14]

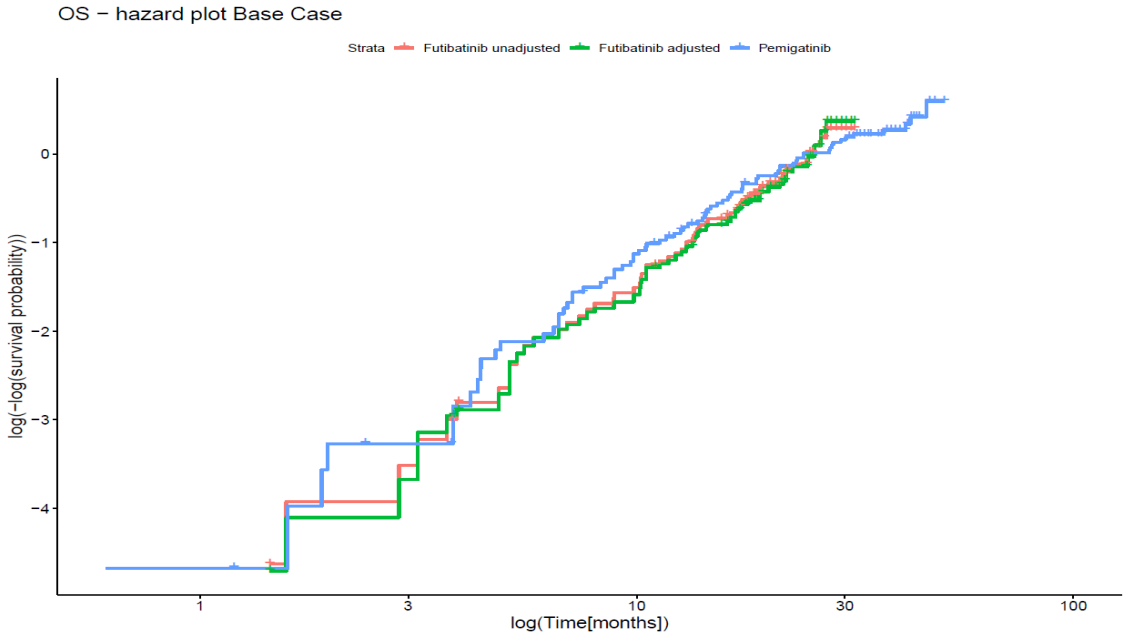
In the absence of head-to-head trial data comparing the clinical effectiveness of futibatinib against pemigatinib, the company relied on an ITC analysis to estimate PFS and OS in the pemigatinib arm of the model. Details on these matching methods are provided and discussed in Section 3.4, while the details specific to the model implementation on the MAIC results are explained below.

4.2.6.1 Overall survival

For the futibatinib arm, six parametric survival models were fitted to unadjusted OS data (FOENIX-CCA2 data not matched to the FIGHT-202 trial) from the FOENIX-CCA2 trial, whereas for the pemigatinib arm OS was informed by implementing relative treatment effects (in the form of a hazard ratio (HR)) on the OS of futibatinib, as estimated from the MAIC analysis.

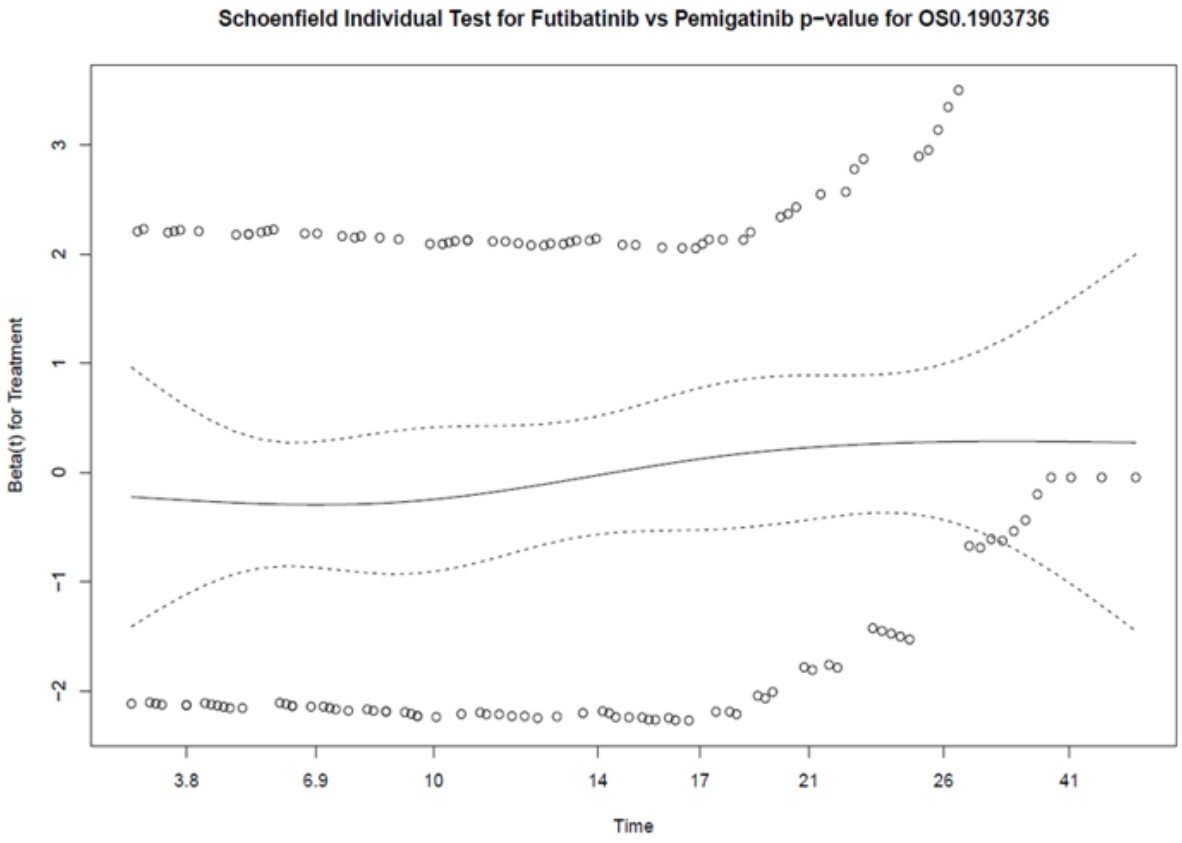
The proportional hazards (PHs) assumption was assessed using the log-cumulative hazard plot (for futibatinib the company presented both unadjusted and MAIC-adjusted survival curves), shown in Figure 4.2, and the Schoenfeld residual plot, shown in Figure 4.3. Referring to these figures and the Schoenfeld test resulting to a p-value of 0.190, the company concluded that there was no evidence to suggest a violation of the PH assumption. The company further commented that the PH assumption was expected to hold considering that both treatments are FGFR2 inhibitors and are characterised by a similar mechanism of action and a similar clinical efficacy based on the MAIC results. Therefore, extrapolation of OS for patients receiving futibatinib was modelled using data obtained from the FOENIX-CCA2 trial, while OS extrapolation for patients receiving pemigatinib was derived by implementing a MAIC-derived HR as explained below.

Figure 4.2: Log-cumulative hazard plot for futibatinib versus pemigatinib for OS



Based on Figure 22 of the CS.[5]
CS = company submission; OS = overall survival

Figure 4.3: Schoenfeld residual plot for futibatinib (adjusted) versus pemigatinib for OS



Based on Figure 23 of the CS.[5]
CS = company submission; OS = overall survival

To select the most appropriate extrapolation option for the futibatinib OS curve, the company used goodness-of-fit statistics, visual inspection, and clinical expert opinion regarding the plausibility of the long-term predictions of the alternative parametric survival models. Table 4.4 summarises the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) model fit statistics for the parametric survival functions of the futibatinib OS data. AIC and BIC values were similar across the different parametric OS curves (difference in points <5), apart from the exponential which scored higher presenting the worst statistical fit. According to the AIC and BIC values the Weibull and log-logistic distributions would be the best options in terms of goodness-of-fit statistics.

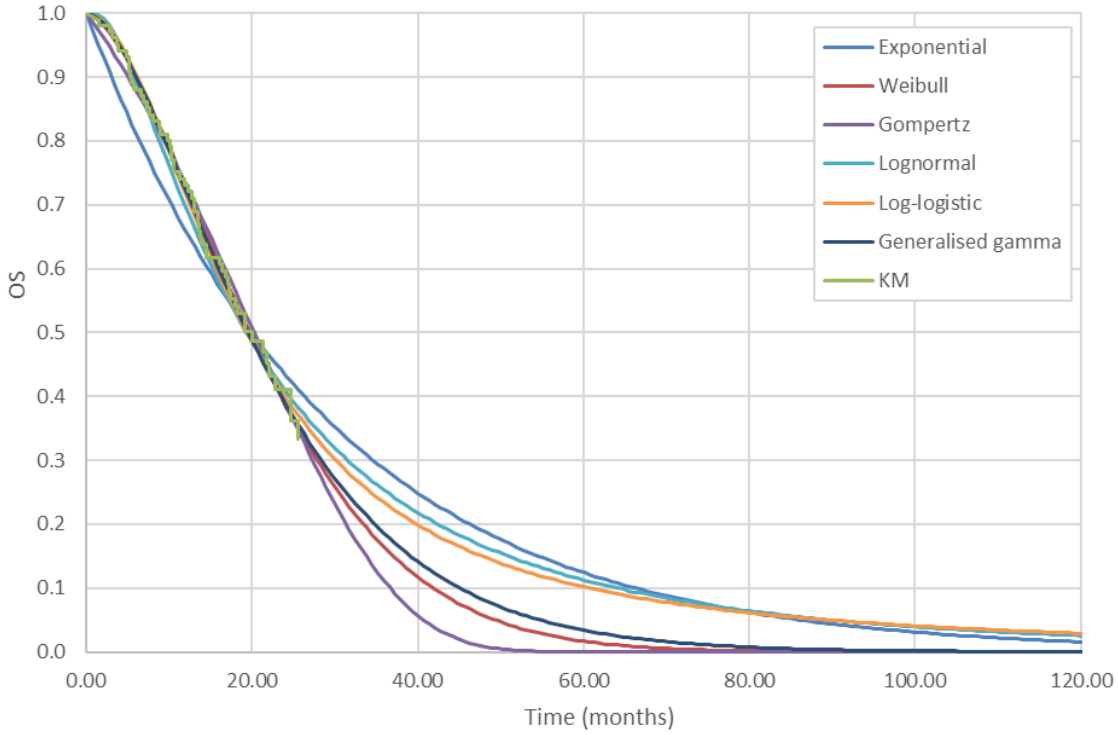
Table 4.4: AIC and BIC statistics for OS parametric survival functions for futibatinib

Model	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	507.65	6	510.29	6
Weibull	495.96	1	501.23	1
Gompertz	499.24	5	504.51	4
Log-normal	497.94	4	503.21	3
Log-logistic	496.66	2	501.93	2
Generalised gamma	497.78	3	505.68	5

Based on Table 32 of the CS.[5]
AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; OS = overall survival

Figure 4.4 presents the OS extrapolations using alternative parametric survival functions combined with the Kaplan-Meier (KM) data for futibatinib. Based on the visual assessment of the goodness of fit, the company concluded that all parametric options presented similar fit to the observed KM data, apart from the previously mentioned exponential model.

Figure 4.4: Futibatinib OS trial data and parametric survival extrapolations

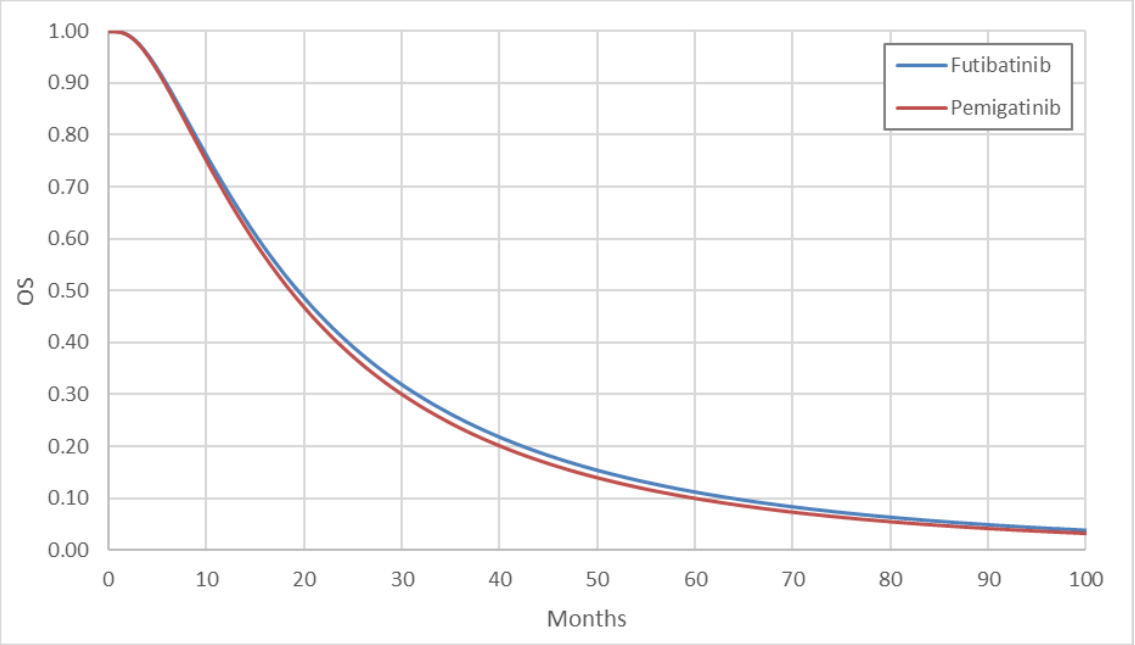


Based on Figure 24 of the CS.[5]
CS = company submission; KM = Kaplan-Meier; OS = overall survival

In the absence of long-term OS data for futibatinib, CCA clinical experts from the UK were consulted to validate the plausibility of the long-term extrapolations of the parametric models. The two clinical experts consulted by the company agreed that '*OS after 3 years should plateau at a value that is a bit higher than 0%, reflecting the patients that may go on to receive curative surgery; however, both experts noted that due to futibatinib being a relatively new drug, the clinicians do not yet have experience of using it in the long term*'.[24] Relying on this experts' opinion and considering the long-term survival predictions of the alternative parametric models, the company considered the log-normal and log-logistic curves as the most clinically plausible choices. As these two models presented a similar statistical fit (<2 points difference), the company used the log-normal survival curve in the base-case analysis, while noting that this option would represent a conservative choice between the two given that OS predictions of the log-normal model were slightly lower compared to the log-logistic model. The impact of using alternative parametric options were also explored in scenario analyses.

To extrapolate the OS curve for pemigatinib, the company used the parametric extrapolation of futibatinib adjusted by a HR of 1.05. This HR was based on the inverse OS HR of 0.95, as was estimated in the MAIC analysis for futibatinib versus pemigatinib (please see Section 3.4 for details). The impact of using different OS HRs were explored in the company's scenario analyses. Figure 4.5 shows the resulting OS extrapolation of pemigatinib versus futibatinib treatment in the company's base-case.

Figure 4.5: Pemigatinib and futibatinib OS extrapolation



Based on Figure 25 of the CS[5]
CS = company submission; OS = overall survival

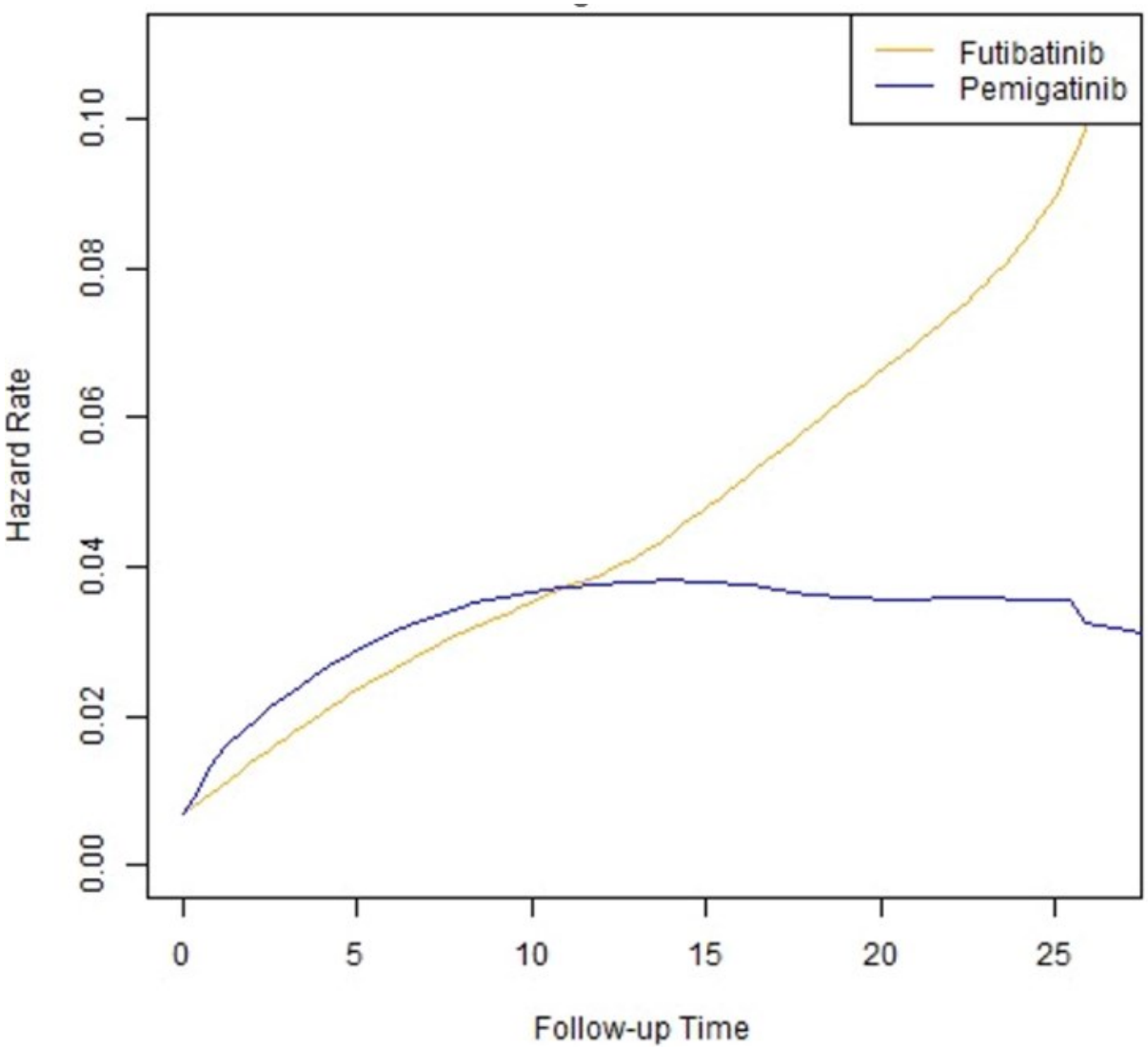
Finally, age- and gender-adjusted background mortality (based on life tables for England from the Office for National Statistics 2017-2019) was used as a lower bound of the disease-specific mortality predictions. The 2017-2019 life tables were preferred to avoid the data skewness caused by coronavirus disease 2019 (COVID-19) excess mortality.

EAG comments:

- The EAG has several concerns regarding the company's approach to estimate OS for patients receiving futibatinib and pemigatinib treatments:
  a) The EAG questions the plausibility of the PH assumption. The PH assumption was assessed using the log-cumulative hazard plot shown in Figure 4.2, and the Schoenfeld residual plot, shown in Figure 4.3. However, the company's main argument for supporting the PH assumption seems to rely on the p-value of the Schoenfeld test, as the company did not comment on the fact the log-cumulative hazards of OS in Figure 4.2 do not seem to be in parallel. That suggests that the log-cumulative hazard plot was not completely considered by the company when deciding regarding the plausibility of the PHs assumption. In response to clarification question B2 on this matter, the company argued that '*the log-cumulative hazard plots for PFS and OS showed that the futibatinib and pemigatinib curves largely ran parallel to each other, with one instance of crossing at 30 months for PFS'*.[7] The EAG does not concur with this assessment. In fact, the log-cumulative hazard OS curves in Figure 4.2 seem to cross at several time points, which is a clear indication of non-PHs, despite the non-significant p-value of the Schoenfeld test.
     Furthermore, in response to the EAG's request in question B2,[7] the company provided the hazard functions over time for the OS of patients on futibatinib and pemigatinib treatments, which are shown in Figure 4.6. The company responded that '*these plots demonstrate that hazard rates for futibatinib and pemigatinib were similar up to ~10 months of follow-up; the tail ends of both curves should be interpreted with caution, given the low numbers of patients at risk at later timepoints*'.[7] The EAG again disagrees with this interpretation, as this reasoning

is dismissing about half of the observed data. Specifically, Figure 4.6 shows that the hazard functions seem to change substantially after ~10 months, but this time point represents less than half of the overall follow-up period for the observed data. Therefore, it cannot be argued that the curves after ~10 months represent the '*tail*' of the curve and '*should be interpreted with caution'*. The EAG's concerns are also confirmed by the number of patients at risk in Figure 3.10, which shows that more than half of the patients remained at risk after ~15 months of follow-up time.

Figure 4.6: Instantaneous hazard over time of futibatinib and pemigatinib observed OS



Based on Figure 4 in clarification letter response.[7]
OS = overall survival

Following the clarification phase, the electronic model was adjusted to allow for independent modelling of OS for futibatinib and pemigatinib treatments, although this option was not preferred by the company for their revised base-case. Considering the above comments, the EAG considers the PH assumption for OS invalid and, therefore, prefers to employ an independent modelling approach to extrapolate the OS of futibatinib and pemigatinib treatments in the EAG base-case analysis.

b) The company's approach to implement a constant HR of 0.95 for the OS of patients receiving futibatinib versus pemigatinib implicitly assumed that patients on futibatinib treatment would receive a survival benefit even when they have stopped receiving treatment. In response to clarification question B5,[7] the company confirmed the EAG's concerns that there should be no survival difference expected between futibatinib and pemigatinib when patients stop receiving treatment. Therefore, the company updated their model by assuming that the hazard rates for OS and PFS for pemigatinib are set equal to those of futibatinib after 24 months, at which time point ~11% and ~12% of patients on futibatinib and pemigatinib treatments, respectively, were still on-treatment based on the PFS curve, which informed ToT in the company's original and revised (following the clarification phase) base-case analysis. The EAG considers that although this approach can partially address the issue, there are still concerns if that would be the most appropriate, especially considering the uncertainty around the PH assumption previously discussed. This approach may still be dismissing and not appropriately aligning with the observed data. Alternative well-established methods may fit better the observed data by allowing for time-varying hazard functions such as use of fractional polynomials,[26, 27] or use of independent modelling. Considering the availability of evidence and the observed survival data, the EAG believes that independent survival modelling would be a more appropriate option for the base-case analysis of the current appraisal. Therefore, the setting in the electronic model that forced the hazard rates of the OS and PFS to be equal at 24 months was turned off in the EAG base-case analysis. Further explanation on this is provided in Section 6.1.2.

c) The selection of extrapolation models for futibatinib was based on unadjusted data. However, the EAG disagrees with this approach, and considers that these should have been based on MAIC-adjusted data. The company selected extrapolation models for futibatinib based on unadjusted survival data (FOENIX-CCA2 data not matched to the FIGHT-202 trial), while for pemigatinib PHs were assumed and the *adjusted* HR as was estimated from the MAIC analysis was applied. The EAG is unclear why the company used the unadjusted curves for the OS of futibatinib while they implemented an HR based on the MAIC analysis for the OS of pemigatinib. The appropriate methodology of a MAIC requires balanced trial populations in terms of baseline characteristics, so using unadjusted curves while implementing an adjusted MAIC-derived HR does not seem to meet this requirement. The EAG's preferred thus extrapolation options for the base-case analysis based on adjusted survival curves for both OS and PFS. For PFS, further details are provided in the EAG comments in the next subsection.

d) The selection of extrapolation models based on clinical feedback was based on futibatinib only (but not on pemigatinib). Clinical experts provided feedback on extrapolations of both futibatinib and pemigatinib treatments. However, the company clarified in response B3 that the '*selection of the survival extrapolation curves was performed solely based on the clinical feedback for futibatinib. This was considered appropriate due to the model approach of applying HRs to the futibatinib parametric extrapolations to obtain PFS and OS predictions for pemigatinib and the consistent feedback from clinicians stated that the survival profile for the two treatments would be very similar*'.[7] The EAG does not agree with this approach. Clinicians would be expected to have more experience from using pemigatinib treatment and hence their feedback on the validation of the pemigatinib extrapolations should have been considered when selecting the appropriate models for extrapolation.

e) The EAG's preferred approach to extrapolate OS would be independent modelling for both futibatinib and pemigatinib. In this scenario, the company selected a log-logistic extrapolation for pemigatinib OS and a log-normal extrapolation for futibatinib OS (scenario 3d in clarification response).[7] This approach (selecting different parametric extrapolations for

different treatment arms) is not recommended by TSD 14,[25] given the similar mechanism of action of futibatinib and pemigatinib treatments. Therefore, the EAG prefers using the same type of distribution for both arms. In terms of goodness of fit, the log-normal and log-logistic options would be the preferred options for pemigatinib OS, as shown in Table 4.5. The EAG notes that for OS in both treatments, clinicians in the company's Advisory Board meeting commented that '*the long-term OS (after 3 years) should plateau at a value that is a bit higher than 0%*', reflecting that a small number of patients can remain alive up to 5–10 years, with the exact range defined between 5-10% from the two experts.[24] However, looking at the KM curve in Figure 4.4, for example, there seems to be no indications of an OS plateau after 3 years. The clinical expert consulted by the EAG indicated that 5-year OS for iCCA patients would be around 3-8% while the 10-year OS would be in the range of 0-2%.[28] These estimates align with the clinical feedback provided both to the current appraisal anticipating a value between 5-10%, and to the clinical input given to the company in TA722 appraisal in which the experts anticipated the 5-year OS to be around 5%.[3, 24] Considering the pemigatinib OS extrapolations in Table 4.5, the log-normal and log-logistic may be overestimating OS. For futibatinib, although the company included the option to model OS curves treatments independently after the clarification phase and mentioned that the adjusted curves should be used for a '*fair comparison'* (response B2),[7] they did not provide a complete assessment for the adjusted OS curves of futibatinib in terms of statistical fit, visual inspection, and clinical plausibility. The EAG noticed that the revised electronic model that included the options to select independent modelling based on adjusted curves or based on the raw trial data (unadjusted), also included AIC/BIC scores for both options. The EAG agrees with the company that adjusted and unadjusted curves for futibatinib should not be very different since the MAIC did not result in losing many patients. However, parametric model selection should be based on the adjusted data. Table 4.5 also presents the AIC and BIC scores of the parametric models fitted to the adjusted survival OS curves for futibatinib, as extracted from the model. In terms of statistical fit, the Weibull and the log-logistic options performed best, although AIC and BIC values for futibatinib were quite similar across the different parametric OS curves (difference in points <5), apart from the exponential which presented the worst statistical fit. In terms of visual inspection and clinical validity, the EAG considers that the Weibull and log-logistic extrapolations may also represent the best fit considering the EAG's clinical feedback, the clinical feedback provided to the company of the current appraisal and the clinical feedback provided to the company in TA722,[2] which as explained above, anticipated a 5-year OS between 3-10%. Therefore, the EAG base-case analysis employed an independent modelling approach for the OS of futibatinib and pemigatinib treatments, using the adjusted trial data for the futibatinib arm (FOENIX-CCA2 data matched to the FIGHT-202 trial data) and a Weibull model for both treatment arms. Alternative extrapolation options, including a log-logistic, generalised gamma, and log-normal models, were explored in the EAG scenario analyses in Section 6.2 of this report.

Table 4.5: AIC and BIC statistics for independent OS parametric survival functions and 5-year OS predictions

Model	AIC	Rank (AIC)	BIC	Rank (BIC)	5- year OS
Futibatinib					
Exponential	473.93	6	476.56	6	[redacted]

Model	AIC	Rank (AIC)	BIC	Rank (BIC)	5- year OS
Weibull	461.51	1	466.78	1	[redacted]
Gompertz	463.56	4	468.83	3	[redacted]
Log-normal	464.60	5	469.87	4	[redacted]
Log-logistic	463.21	2	468.48	2	[redacted]
Generalised gamma	463.50	3	471.40	5	[redacted]
Pemigatinib					
Exponential	652.98	5	655.66	3	[redacted]
Weibull	651.72	4	657.09	5	[redacted]
Gompertz	654.77	6	660.14	6	[redacted]
Log-normal	647.15	2	652.51	2	[redacted]
Log-logistic	646.10	1	651.47	1	[redacted]
Generalised gamma	648.81	3	656.85	4	[redacted]

Based on for pemigatinib: Table 13 of the clarification letter response.[7] For futibatinib: the revised electronic model.[1]
AIC = Akaike information criterion; BIC = Bayesian information criterion; OS = overall survival

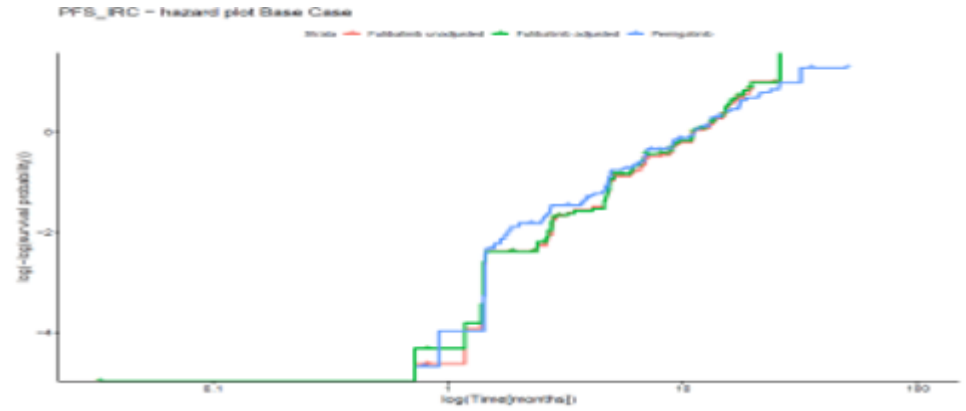
4.2.6.2 Progression-free survival

To extrapolate the PFS data for the futibatinib arm, the company used the same approach discussed for OS. Therefore, less details are reported here for PFS.

Parametric survival models were fitted to unadjusted PFS data from the FOENIX-CCA2 trial (FOENIX-CCA2 data not matched to the FIGHT-202 trial data), whereas for the pemigatinib arm PFS was informed by implementing relative treatment effects on the PFS of futibatinib as estimated from the MAIC analysis.

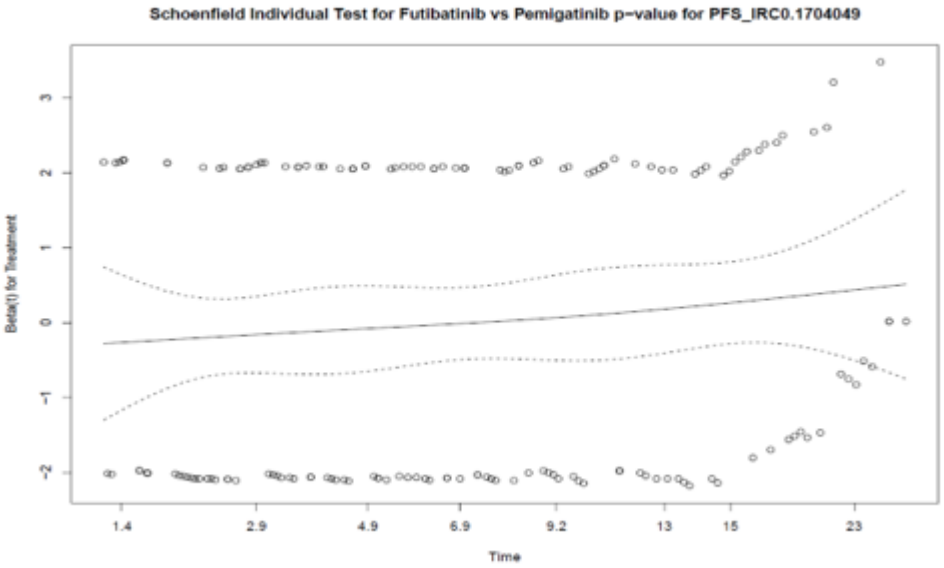
The PH assumption was assessed using the log-cumulative hazard plot (for futibatinib the company presented both unadjusted and MAIC-adjusted curves), shown in Figure 4.7, and the Schoenfeld residual plot (p-value = 0.225), shown in Figure 4.8. Based on these, the company concluded that there was no evidence to suggest a violation of the PH assumption for the PFS analysis.

Figure 4.7: Log-cumulative hazard plot for futibatinib versus pemigatinib for PFS



Based on Figure 18 of the CS[5]
CS = company submission; PFS = progression-free survival

Figure 4.8: Schoenfeld residual plot for futibatinib versus pemigatinib for PFS



Based on Figure 19 of the CS.[5]
CS = company submission; PFS = progression-free survival

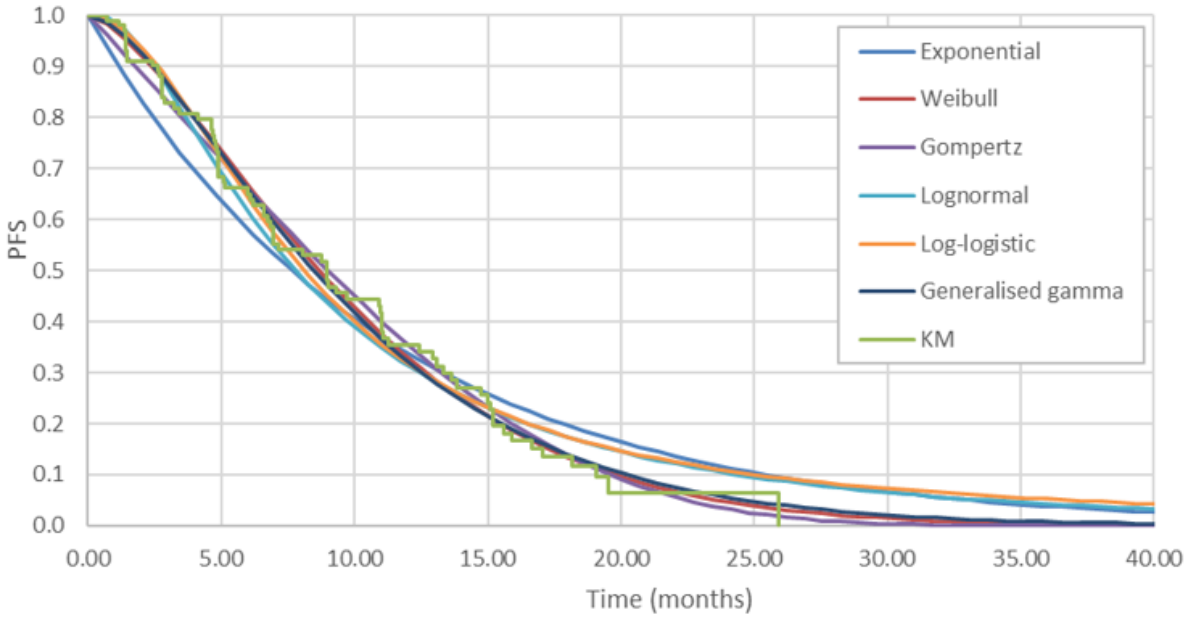
Table 4.6 summarises the AIC and BIC model fit statistics for the parametric models of the PFS data for futibatinib. Based on these, the Weibull and generalised gamma distributions would be the best options in terms of goodness-of-fit statistics. Figure 4.9 presents the alternative parametric survival extrapolations for PFS combined with the KM data for futibatinib. Based on the statistical fit presented in Table 4.6, all parametric options presented similar fit to the observed KM data, apart from the exponential model. Based on the visual assessment, the exponential curve seemed to deviate the most from the observed KM data as compared to the other parametric options, while the log-normal and log-logistic curves presented a poorer fit to the observed data after ~15 months. According to the CS, this latter distinction was not considered meaningful due to the small numbers of patients at risk after 15 months.[5]

Table 4.6: AIC and BIC statistics for PFS parametric survival functions for futibatinib

Model	AIC	Rank (AIC)	BIC	Rank (BIC)
Exponential	532.94	6	535.57	6
Weibull	520.09	1	525.36	1
Gompertz	523.90	3	529.17	2
Log-normal	523.97	4	529.24	3
Log-logistic	524.92	5	530.19	5
Generalised gamma	521.84	2	529.75	4

Based on Table 30 of the CS.[5]
AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; PFS = progression-free survival

Figure 4.9: Futibatinib PFS trial data and parametric survival extrapolations



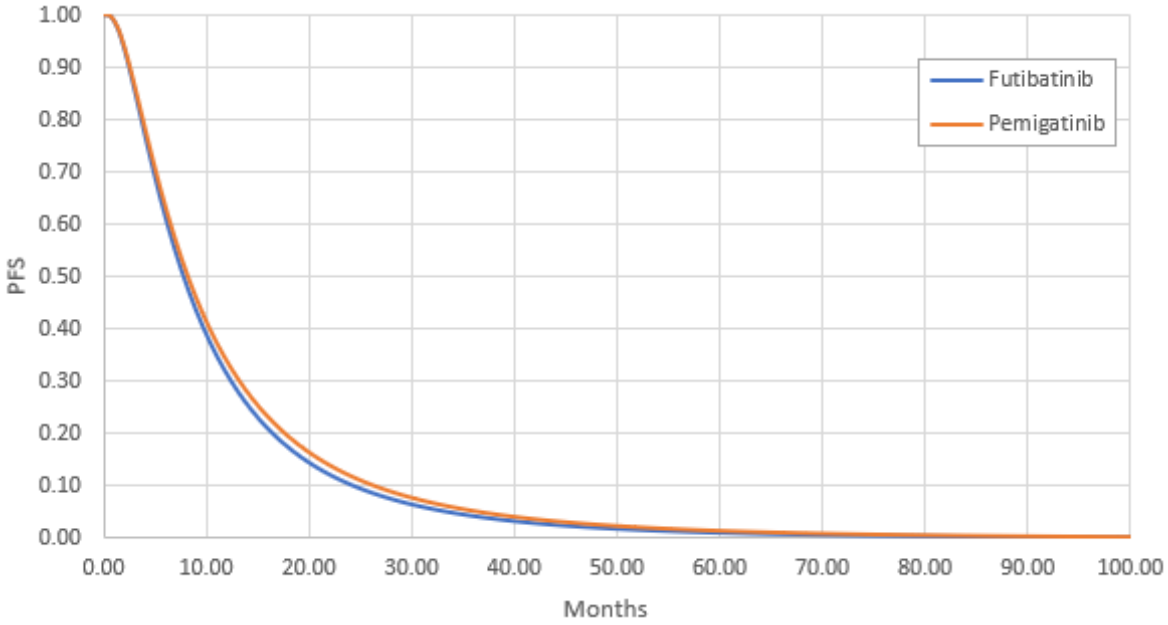
Based on Figure 20 of the CS.[5]
CS = company submission; KM = Kaplan-Meier; PFS = progression-free survival

CCA clinical experts from the UK were also consulted to validate the long-term PFS predictions of the alternative parametric models.[24] Clinical experts highlighted that although 5-year PFS is expected to be small, it would still be greater than 0%. Therefore, based on clinical experts, the log-normal, log-logistic and exponential curves presented the most clinically plausible long-term model fit.[5] As the log-normal and log-logistic parametric models presented a similar statistical fit (<2 points difference), which was better than the exponential, the company considered the log-normal model for the base-case analysis of the futibatinib PFS data. The CS highlighted that this option would represent a conservative choice given that PFS predictions of the log-normal model were lower compared to the log-logistic model. The impact of using alternative parametric options were also explored in scenario analyses.

To extrapolate the PFS for pemigatinib, the company used the parametric PFS extrapolation of futibatinib (based on the unadjusted KM data from the FOENIX-CCA2 trial) adjusted by an HR of 0.93. This HR was based on the inverse PFS HR of 1.07 that was estimated in the MAIC analysis for futibatinib versus pemigatinib (see Section 3.4 for details). The impact of using different PFS HRs was explored in the company's scenario analyses. Figure 4.10 shows the PFS extrapolations of pemigatinib

and futibatinib treatments chosen by the company for their base-case. As OS and PFS were modelled independently, the economic model included a cap for PFS (capped to OS) to avoid negative state occupancy in the progressed disease health state.

Figure 4.10: Pemigatinib and futibatinib PFS extrapolation

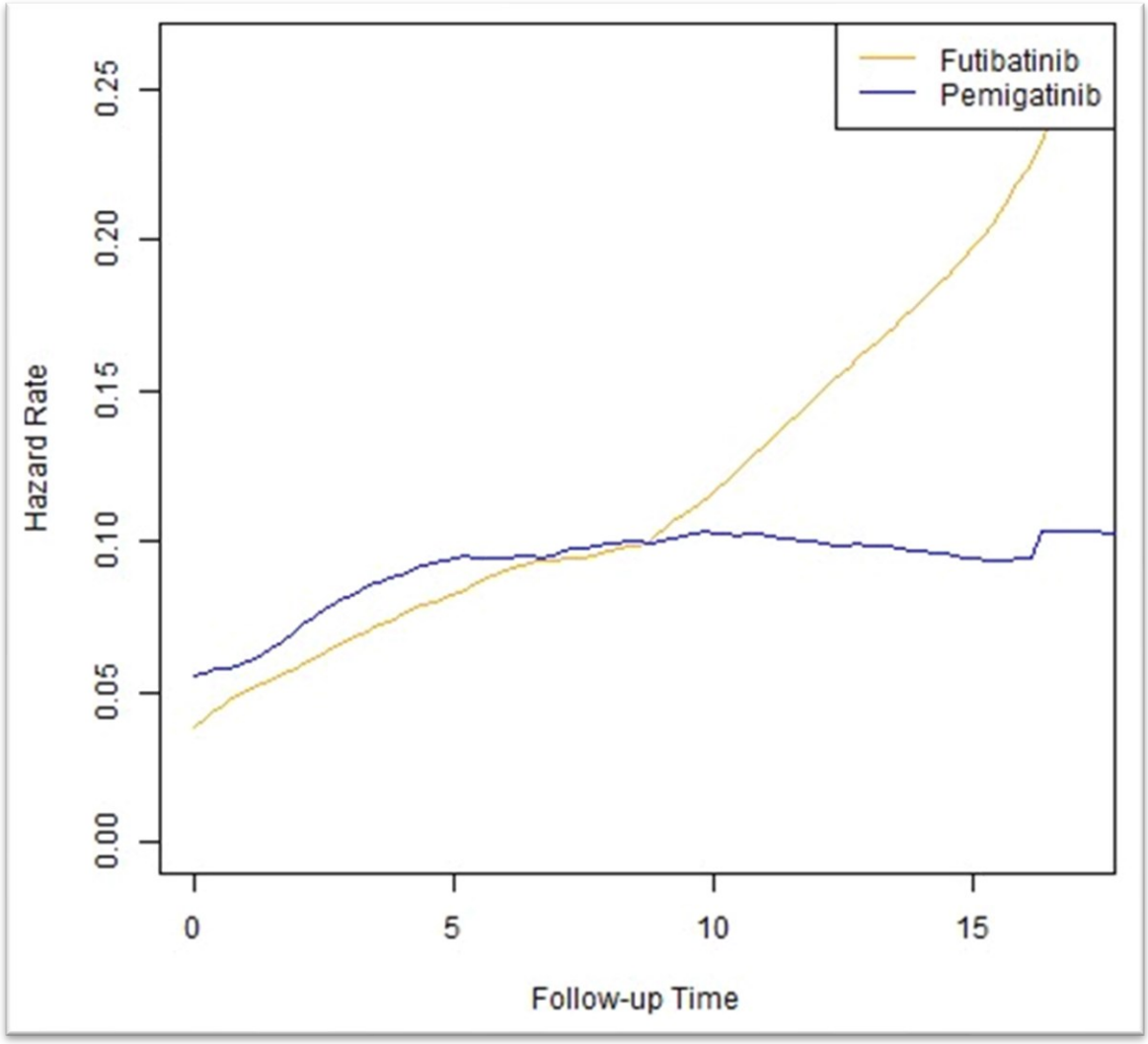


Based on Figure 21 of the CS.[5]
CS = company submission; PFS = progression-free survival

EAG comments:

- The EAG has also several concerns regarding the company's approach to extrapolate PFS for patients receiving both futibatinib and pemigatinib treatments. These are similar to those discussed for OS extrapolations above:
  a) The EAG questioned the plausibility of the PH assumption for PFS. The company relied again on the log-cumulative hazards plot (Figure 4.7) and the p-value of the Schoenfeld test (Figure 4.8) The EAG does not agree with this assessment as the log-cumulative hazard plots for PFS in Figure 4.7 seem to cross at several time points despite the non-significant p-values of the Schoenfeld tests. Similarly, the plot of the hazard functions in Figure 4.11 suggests a violation of the PH assumption since the crossing does not happen at the tails of the curves (it can be seen in Figure 3.9, there are still about 1/3 of patients at risk after ~12 months of follow-up time). Therefore, the EAG prefers using an independent modelling approach for PFS as well (for both futibatinib and pemigatinib treatments).

Figure 4.11: Instantaneous hazard over time of futibatinib and pemigatinib observed PFS



Based on Figure 5 in clarification letter response.[7]
PFS = progression-free survival

b) The company selected the PFS extrapolation models for futibatinib based on unadjusted survival data (FOENIX-CCA2 data not matched to the FIGHT-202 trial), while the HR as estimated from the MAIC analysis was used for the pemigatinib PFS curve. In line with the EAG comments in the OS section, the EAG's preferred extrapolation options for the base-case analysis included use of adjusted survival curves for both OS and PFS.
c) Clinical experts feedback to support the choice of extrapolations should have been based on both futibatinib and pemigatinib treatments, not on futibatinib only.
d) The EAG's preferred approach would be independent modelling of PFS for futibatinib and pemigatinib treatments. The same probability distribution should be used for both treatments as explained for OS. Based on Table 4.7, the EAG concluded that the log-normal would represent the most appropriate choice to model PFS for both treatment arms (resulting in 5-year predictions of about 1-2%), while the impact of using alternative models was explored in the scenario analyses. This survival predictions would also align with the clinical feedback provided to the EAG indicating a 5-year PFS of 1-2%.[28]

Table 4.7: AIC and BIC statistics for independent PFS parametric survival functions and 5-year PFS predictions

Model	AIC	Rank (AIC)	BIC	Rank (BIC)	5-year PFS
Futibatinib					
Exponential	508.83	6	511.46	6	[redacted]
Weibull	497.20	1	502.47	1	[redacted]
Gompertz	501.73	5	507.00	5	[redacted]
Log-normal	500.00	3	505.27	2	[redacted]
Log-logistic	500.61	4	505.88	3	[redacted]
Generalised gamma	498.59	2	506.49	4	[redacted]
Pemigatinib					
Exponential	602.78	5	605.46	4	[redacted]
Weibull	601.07	4	606.44	5	[redacted]
Gompertz	604.59	6	609.96	6	[redacted]
Log-normal	594.95	1	600.31	1	[redacted]
Log-logistic	597.95	3	603.32	2	[redacted]
Generalised gamma	596.62	2	604.67	3	[redacted]

Based on For pemigatinib: Table 12 of the clarification letter.[7] For futibatinib: the revised electronic model.[1]
AIC = Akaike Information Criterion; BIC = Bayesian Information criterion; PFS = progression-free survival

4.2.6.3 Time on treatment discontinuation

ToT was assumed to be equal to PFS for both treatment arms in the company's base-case analysis, as explained in previous Sections. The company explained that this assumption was appropriately reflecting the FOENIX-CCA2 trial data, as the median PFS for futibatinib was 8.9 months whilst the median duration of treatment was 9.07 months. The CS further highlighted that clinical experts concurred with this approach mentioning that in clinical practice there was no evidence to suggest substantial differences between ToT and PFS although for practical reasons some patients may encounter a short delay from disease progression to treatment discontinuation.

EAG comment: The EAG was unclear why the company did not include the ToT data for futibatinib from the FOENIX-CCA2 trial given their availability, but instead they assumed ToT would be equal to PFS for futibatinib. In their response, the company explained that '*this assumption was required to ensure a fair comparison in the absence of publicly available Kaplan–Meier data for ToT for pemigatinib'*.[7] The company went further on stating that '*this assumption is aligned with the data from the FOENIX-CCA2 trial, where the median PFS for futibatinib was 8.9 months, compared to a median duration of treatment of 9.07 months. Similarly, the median PFS for pemigatinib for the DCO reported in TA722 (6.9 months) was aligned with the median duration of treatment in the safety population of 7.2 months (219 days) reported in TA722. Furthermore, the assumption that ToT is equal to the PFS was validated by UK clinical experts in CCA*'.[7] To address the EAG's concerns, the company presented two scenario analyses where ToT for futibatinib and pemigatinib were modelled independently of PFS. For futibatinib, ToT was modelled via extrapolation of the unadjusted IPD from the FOENIX-CCA2 trial in the company's scenario analyses. The selection of the most appropriate extrapolation for futibatinib ToT was informed by the recommendations of the NICE DSU TSD 14 on survival data extrapolation, as it was done for OS and PFS.[25] The company chose the Weibull model given it had the

best fit according to both AIC and BIC, and good visual fit to the observed KM data, as shown in Table 4.8 and Figure 4.12. In the absence of publicly available KM data for pemigatinib ToT, the inverse of the estimated MAIC PFS HR of 1.07 for futibatinib versus pemigatinib (i.e. a HR of 0.93) was implemented to the futibatinib ToT extrapolation to derive a corresponding ToT extrapolation for pemigatinib used in the company's scenario analyses. The company's rationale was based on the expectation that any delays between disease progression and ToT discontinuation due to practical reasons would apply to both treatment arms equally.

Table 4.8: AIC and BIC statistics for independent ToT parametric survival functions - futibatinib

Model	AIC	Rank (AIC)	BIC	Rank (BIC)
Futibatinib				
Exponential	695.32	6	697.96	6
Weibull	669.85	1	675.11	1
Gompertz	669.97	2	675.24	2
Log-normal	691.98	5	697.25	5
Log-logistic	689.10	4	694.37	4
Generalised gamma	670.35	3	678.25	3

Based on Table 14 of the clarification letter response.[7]
AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; ToT = time on treatment

Figure 4.12: Futibatinib ToT extrapolation

Based on Figure 8 in clarification letter response.[7]
ToT = time on treatment

- In clarification question B4,[7] the EAG also asked the company to provide a comparison of PFS and ToT from the FOENIX-CCA2 trial. However, the company only included these data in the electronic model and did not comment on differences observed in the survival data between ToT and PFS. Based on the revised electronic model, the EAG produced Figure 4.13, which presents the KM data for ToT and PFS of patients receiving futibatinib in the FOENIX-CCA2 trial. Figure 4.13 shows that the ToT curve for futibatinib treatment lies often above the PFS curve. In the Advisory Board meeting organised by the company clinical experts confirmed that, although in theory patients would discontinue treatment with a FGFR inhibitor as soon as they progressed, in practice patients would discontinue treatment only once they have met with their clinician, which time could translate to up to a couple of weeks post-progression.[24, 29] This expectation aligns with the approach taken in TA722 for pemigatinib, where although ToT was modelled independently of PFS, a structural restriction was imposed to ensure that ToT could not exceed PFS, allowing patients to discontinue treatment either prior to or at the point of disease progression.[22] However, although the company argued that the pemigatinib modelling approach for ToT would be functionally similar to assuming ToT equal to PFS in the current appraisal, the EAG disagrees with this statement as, explained in Section 4.2.2. Moreover, if ToT and PFS curves were modelled independently in TA722 with the restriction that ToT ≤PFS, it can also indicate that PF patients on pemigatinib treatment can still remain PF, while not on treatment and can, therefore, have lower treatment costs

than the costs estimated when ToT is set equal to PFS. To conclude, considering the survival data for PFS and ToT presented by the company for futibatinib, and the company's base-case approach to assume ToT equal to PFS, while using an HR of 1.07 for futibatinib versus pemigatinib to produce the pemigatinib PFS curves, the EAG is concerned around the appropriateness of the company's choice to assume ToT equal to PFS in both arms. That is also because looking at the median ToT values reported above, it seems that ToT for futibatinib might be longer than for pemigatinib. However, by assuming ToT equal to PFS and applying the inverse of the PFS estimated HR the potential difference is likely reduced.

Figure 4.13: ToT and PFS data from the FOENIX-CCA2 trial

Based on Electronic model following the clarification phase.[1]
KM = Kaplan-Meier; PFS = progression-free survival; ToT = time on treatment

- Considering the above response, the EAG finds the modelling approach presented in the company's scenario analysis more suitable for the EAG base-case analysis. Therefore, in the EAG base-case analysis it is assumed that ToT for futibatinib was informed from the FOENIX-CCA2 trial, whilst for pemigatinib the EAG agreed that using the estimated MAIC PFS HR of [redacted] for futibatinib versus pemigatinib would be the best approach considering the lack of the pemigatinib data. The EAG agreed with the company's choice to use the Weibull model for the extrapolation of ToT and used that also in the EAG base-case, while explored the impact of using alternative models in the scenario analyses. Note that to align with clinical feedback provided both in the current appraisal and in TA722, the EAG also set the PFS curves as an upper bound of the ToT curves for both arms.

4.2.7 Adverse events

TRAEs of grade 3 or above, with an incidence rate at least 5% for either futibatinib or pemigatinib observed in the FOENIX-CCA2 and FIGHT-202 trials were included in the economic model. The company included hyperphosphatemia of grade 2 or above since this was experienced by a large proportion of patients in the FOENIX-CCA2 trial. The AEs (and their frequency) included in the economic model can be seen in Table 4.9.

In the cost-comparison scenario presented by the company, in which equal efficacy between futibatinib and pemigatinib is assumed, it is also assumed that AEs for pemigatinib are the same as those for futibatinib. This assumption was supported by UK clinical experts who confirmed that the safety profiles of both treatments are very similar.[24]

Table 4.9: AEs (and observed frequency) included in the economic model

	Futibatinib (FOENIX-CCA2)	**Pemigatinib (FIGHT-202)**
Arthralgia	0.0%	5.6%
Aspartate aminotransferase increased	6.8%	0.0%
Fatigue	5.8%	4.6%
Hyperphosphatemia (Grade 2+)	82.5%	51.9%
Hypophosphatemia	0.0%	0.0%
Stomatitis	5.8%	8.3%

Based on Table 35 in the CS.[5]
AEs = adverse events; CS = company submission

EAG comment:

- In response to clarification question B6,[7] the company explained that grade 2+ hyperphosphatemia was additionally included, given the high proportion of patients experiencing it in the FOENIX-CCA2 trial. Hypophosphatemia was originally included in the model, but the incidence was set to [redacted]% for futibatinib and pemigatinib, since this AE was not reported in the latest DCO FIGHT-202 or the FOENIX-CCA2 trial.[14]
- The company also noted that not all AEs included in TA722 meet the inclusion criteria for either the FOENIX-CCA2 or the FIGHT-202 trials or were not reported in the latest DCO for FIGHT-202,[14] and for that reason were not included in the model. By using the incidences reported in Vogel et al. (2022),[14] some relevant AEs for pemigatinib were excluded from the model. For example, Abou-Alfa et al. (2020) includes data from the October 2020 DCO FIGHT-202 and reported that grade 3 hypophosphatemia occurred in 6.8% of patients.[13] To avoid using different data cuts to inform AE incidences, the company used those reported in Vogel et al. (2022) only.[14] The company considered this a conservative assumption, as relevant AEs associated with pemigatinib may have been excluded from the model. However, the impact of this assumption on the CE results is expected to be minor seeing how the AEs contribute to both the cost and QALY calculations.

4.2.8 Health-related quality of life

Patient-reported outcomes (PROs) collected in the FOENIX-CCA2 trial included EQ-5D-3L data,[12, 30] from which the utility values used in the economic model were derived. Since EQ-5D-3L data were collected in the FOENIX-CCA2 trial, no additional mapping was required. In response to clarification

question B7,[7] the company confirmed that the utility values from the FOENIX-CCA2 trial were derived using the UK tariff.[31] PROs were collected at screening, cycles 2 and 4, every 3 cycles after cycle 4, and at the end of treatment. Effect on HRQoL was assessed as change in mean score from baseline using predefined clinically meaningful thresholds for each time point with at least 19 observations (through cycle 13). We refer to Section 3.2.5.4 for additional details.

4.2.8.1 Health-related quality of life data identified in the review

According to the CS, an SLR was conducted in October 2023 to identify all relevant literature published on HRQoL outcomes in adult patients treated with futibatinib or pemigatinib. The SLR identified one study reporting utility values from the ABC-06 trial.[32, 33] However, the company considered this study to be appropriate for the economic model because the ABC-06 trial did not include patients with FGFR2 gene rearrangements or fusions. Furthermore, utility values were only reported at baseline and after 4 months. Full details of the HRQoL SLR search can be found in Appendix H of the CS. [9]

4.2.8.2 Health state utility values

As mentioned above, utility values were derived from the FOENIX-CCA2 trial and were applied to the PF and PD health states of the model.[12, 30] The company used a mixed model for repeated measures (MMRM) to derive the utilities, with progression status as covariate in the base-case analysis. Additional analyses were conducted to explore the impact of including additional covariates, such as treatment status, but the company did not consider these to generate plausible results. However, it seems that all these analyses were not included in the CS. The health state utility values (HSUVs) included in the model are summarised in Table 4.10.

The company indicated that the HSUVs were validated by UK CCA clinical and economic experts who noted that the utility value for PD may be (slightly) higher than expected. According to the company, this potentially high value for PD could be explained by highly symptomatic patients who did not complete the questionnaire regularly following disease progression.[24, 29] The company explored the impact of the utility values on the model results as part of sensitivity and scenario analyses.

In addition, the base-case analysis includes age-adjusted utility decrements based on the UK population norm values for EQ-5D as reported in the HSE 2014 dataset by the NICE DSU.[34]

Table 4.10: HSUVs

Health state	Utility value	References	Justification
PF	[redacted]	FOENIX-CCA2[35]	EQ-5D-3L data in line with NICE reference case
PD	[redacted]		

Based on Table 37 in the CS.[5]
CS = company submission; EQ-5D-3L = EuroQoL-5 Dimensions Three Levels; HSUVs = health state utility values; NICE = National Institute for Health and Care Excellence; PD = progressive disease; PF = progression free

EAG comment:

- In clarification question B8,[7] the EAG asked the company to discuss the (face) validity of the EQ-5D values presented in Table 4.10. In their response, the company indicated that the utility values from FIGHT-202 used in TA722 are redacted, and therefore cannot be used for validation purposes. The company referred to Lamarca et al. (2022),[32] as the only identified study reporting utility values for patients with CCA. This study, however, did not include patients with FGFR2 fusions or

rearrangements, and the utility values were reported for patients receiving mFOLFOX or ASC at baseline or Month 4. For these reasons, the company considered these values not suitable to inform the current economic model. While the EAG agrees with the company here, in the absence of other data, these values could have been compared with those obtained from FOENIX-CCA2 for validation purposes. Utility values reported for similar conditions, even though not CCA, could have been used for this purpose too. The company also argued that the current model is based on a patient population where the starting age is equal to 55.7 years. Utility values for 56-year old male and female patients age in the general population report are 0.8394 and 0.8627, respectively, according to the HSE 2014 dataset.[34] Therefore, the company considered that the PF HSUV of [redacted] seems clinically plausible compared to these utilities form the general population. Furthermore, this was confirmed by UK clinical experts. Regarding the PD utility value, UK clinical experts considered this value slightly higher than expected. This was based on the hypothesis that this may have been caused by most HRQoL assessments being completed early after disease progression, and highly symptomatic patients not completing the questionnaire regularly after that. However, the company considered that the PD utility value has a minor impact on the model results since both PFS and OS are similar between futibatinib and pemigatinib, and the same utility value is applied to both treatments. While this might be the case, the impact on the results might be relevant if the incremental QALYs become very small. Alternative utilities values based on the literature were not explored by the company in the scenario analyses. The company did vary the PF and PD utilities by ±20% in their DSAs results in a change to the INHB of [redacted] and [redacted], respectively (see Section 5.2).

- The company indicated that a MMRM with progression status as covariate was used to derive the utilities included in the base-case analysis. However, the results of such analyses were not reported in the CS. Therefore, the EAG is unable to comment on the validity of such analyses and, therefore, on the utilities derived from them.

4.2.8.3 Disutility values

As explained in Section 4.2.7 of this report, TRAEs of grade 3 or above, with an incidence rate at least 5% for either futibatinib or pemigatinib observed in the FOENIX-CCA2 and FIGHT-202 trials were included in the economic model. AE disutility values were applied upon treatment initiation as one-off events. These assumptions were validated by UK economic experts.[24, 29] Utility decrements associated to these AEs and their corresponding durations were sourced from previous NICE TAs as indicated in Table 4.11.

The company asked UK clinical experts in CCA to validate the values provided in Table 4.11 and overall, these were considered to be accurate.[24, 29] They indicated though that the duration of hypophosphatemia was longer than what they normally see in clinical practice. However, this parameter has no impact on the model results since this AE is assumed to have no impact on patients' HRQoL. In addition, the experts noted that the duration of arthralgia was also (slightly) higher than expected.

Table 4.11: AE utility decrements included in the economic model

AE	Disutility value	Duration in days	Source
Arthralgia	-0.069	18.7	Disutility: NICE TA391[36] Duration: NICE TA722[22]
AST increased	0[a]	6.8	Disutility and duration: NICE TA722[22]
Fatigue	-0.085	2.625	Disutility: NICE TA439[37]

AE	Disutility value	Duration in days	Source
			Duration: NICE TA722[22]
Hyperphosphatemia (grade 2+)	0[a]	15.5	Disutility and duration: NICE TA722[22]
Hypophosphatemia	0[a]	29.3	Disutility and duration: NICE TA722[22]
Stomatitis	-0.038	9.8	Disutility: NICE TA439[37] Duration: NICE TA722[22]

Based on Table 36 of the CS.[5]
[a] Assumed to have no effect on HRQoL
AE = adverse event; AST = aspartate aminotransferase; CS = company submission; HRQoL = health-related quality of life; NICE = National Institute for Health and Care Excellence; TA = Technology Appraisal

EAG comment:

- There are no major concerns regarding the modelling of the utilities identified by the EAG. The impact of the utility value for PD, which was identified by experts as (slightly) higher than expected, will be explored in scenario analyses.
- In Section B.3.13 of the CS, the company discussed several benefits not captured in the QALY calculation.[5] The company referred to the possibility that treatment resistant mutations arise over the course of treatment with FGFR2 inhibitors such as futibatinib and pemigatinib. The company considered that futibatinib led to significantly fewer resistance mutations than pemigatinib in vitro (see Section B.2.12 of the CS).[5] The company also indicated that UK clinical experts in CCA highlighted that, this difference is not likely to be reflected in the survival results from the clinical trial. However, for individual patients this distinction may be important; considering the comparable efficacy of futibatinib and pemigatinib, patient may prefer futibatinib to reduce the potential for the development of treatment resistance. Thus, the company concluded that it is plausible that futibatinib would be associated with additional improved efficacy compared to pemigatinib that is not captured in the QALY calculation. However, the fact that the company referred to in vitro results indicates that there is probably too much uncertainty at this moment regarding this potential uncaptured benefit.

4.2.9 Resources and costs

The cost categories included in the model were treatment acquisition costs, drug administration costs, adverse event costs, end of life and disease management costs. Unit prices were based on the British National Formulary (BNF) and NHS reference prices.[38, 39]

4.2.9.1 Resource use and costs data identified in the review

According to the CS, the SLR identified no relevant studies reporting UK relevant health care resource use and cost information in line with the SLR eligibility criteria. The methods and results are reported in Appendix G and I of the CS.[9]

4.2.9.2 Treatment costs (with PAS)

Futibatinib is provided as a PAS discount of [redacted] on the list price of [redacted] per pack. The drug acquisition costs for pemigatinib are based on the list prices presented in the BNF. Table 4.12 shows the drug acquisition costs included in the CEA.

Table 4.12: Drug acquisition costs for futibatinib (PAS price) and pemigatinib (list price)

Treatment	Form	Strength/unit	Pack size	Cost per pack (list)	Cost per pack (PAS)	Source
Futibatinib (PAS price)						
Futibatinib	Tablet	4 mg	35	[redacted]	[redacted]	Taiho Oncology. Data on file
Futibatinib	Tablet	4 mg	28	[redacted]	[redacted]	Taiho Oncology. Data on file
Futibatinib	Tablet	4 mg	21	[redacted]	[redacted]	Taiho Oncology. Data on file
Pemigatinib (list price)						
Pemigatinib	Tablet	4.5 mg	14	£7,159	NR	BNF[40]
Pemigatinib	Tablet	9 mg	14	£7,159	NR	BNF[40]
Pemigatinib	Tablet	13.5 mg	14	£7,159	NR	BNF[40]

Based on Table 38 in CS.[5]
BNF = British National Formulary; CS = company submission; NR = not reported; PAS = Patient Access Scheme

EAG comment: The EAG noticed that the cost per futibatinib [redacted].

4.2.9.3 Dosage

The dose for futibatinib in this indication is 20 mg to be taken orally QD as a continuous therapy. Pemigatinib is administered 13.5 mg QD on a 14 day-on, 7 day-off schedule.[5] This recommended dosing intensity (RDI) of 100% was applied in the model for both treatments. The company justified this assumption based on the argument that the safety profile of futibatinib and pemigatinib was found to be similar, as confirmed by trial data and clinical experts.[24, 29] As both futibatinib and pemigatinib are associated with a flat price per pack, dose reductions do not result in a reduced cost per pack.

4.2.9.4 Drug wastages

Half a pack of futibatinib or pemigatinib per patient was included as drug wastage in the company's base-case analysis. The CS stated that this was based on the assumption that, on average, patients discontinue treatment halfway through a pack, which was validated by UK clinical experts.[24] The company explored the effect of excluding drug wastages costs in a scenario analysis (Section 5.2.3). A summary of the treatment costs per cycle included in the model are summarised in Table 4.13.

Table 4.13: Treatment costs included in CE model

Treatment	Cycle length, days	Costs per treatment cycle	Source
Futibatinib 20 mg daily (PAS price)	21 (continuous)	[redacted]	Taiho Oncology. Data on file.
Pemigatinib 13.5 mg daily	21 (14 on, 7 off)	£7,159.00	BNF[40]
Based on table 39 in CS.[5] [redacted]			

BNF = British National Formulary; CE = cost effectiveness; CS = company submission; PAS = Patient Access Scheme

EAG comment:

- [redacted] and that the recommended dose of 20 mg QD is used. This gives the cost per treatment cycle as presented in Table 4.13. However, Table 39 in the CS,[5] also presented the costs based on 16 mg and 12 mg; [redacted]
- In the clarification letter response,[7] the company indicated that patients may discontinue treatment upon either toxicity or disease progression at any point during a model cycle. As a consequence, patients will not make the full cost for that treatment cycle. Because of this, in the economic model it is assumed that patients would on average discontinue treatment halfway through a treatment cycle (3 weeks). This assumption was validated by UK clinical experts[24, 29] and makes sense to the EAG.

4.2.9.5 Treatment duration

Treatment costs were modelled based on ToT data, which was assumed to be equal to PFS in the originally submitted model. After clarification, there was an option to model these separately, as explained in Section 4.2.6.

EAG comment: The EAG is concerned that ToT might not be equal to PFS. Based on the results from TA722,[22] the EAG is concerned that PFS >ToT and that, therefore, the company's base-case might be overestimating pemigatinib acquisition costs. In response to clarification question B9,[7] the company provided an update of the model and a scenario analysis where they demonstrated that when they modelled ToT independently from PFS, incremental QALYs did not change and cost savings decreased by 29%.

4.2.9.6 Administration costs

No administration costs were applied because both futibatinib and pemigatinib are oral treatments.

4.2.9.7 Subsequent treatments

Subsequent treatments have been excluded from the model. This simplifying assumption follows from the reasoning that PFS and OS between futibatinib and pemigatinib are expected to be very similar and that, therefore, the subsequent treatments are expected to be identical in terms of expected treatment regimes, time of drug administration and duration of treatment in both arms. The most likely subsequent

treatment according to the company would be mFOLFOX chemotherapy for those patients who are able to tolerate it or BSC otherwise.

4.2.9.8 Health state costs

In Table 4.14 the type of resources and estimated frequency per 21-day cycle for both the PF and PD health states are presented. The company indicated that these were based on TA722 and further verified with UK clinical experts in CCA.[22, 24] Unit costs were sourced from the 2021/2022 NHS reference cost.[39]

The company also reported that UK clinical experts indicated that the use of phosphate binders (daily as a continuous treatment) would also be expected for patient in the PFS state. The company explored this is a scenario analysis, however, the EAG was not able to find these results.[24]

Table 4.14: Resource use estimates per 21-day cycle by health state: base-case

Health state	Unit costs (£)	Resource use per 3 weeks in PF	Resource use per 3 weeks in the PD state	Source
Clinical examination	221.48	0.23	0.23	NHS reference costs 2021/22: WF01A, Consultant led, medical oncology, non-admitted face-to-face attendance, follow-up
CT scan	181.82	0.23	0.06	NHS reference costs 2021/22: RD22Z, Outpatient imaging; CT scan of one area, with pre- and post-contrast
OCT (retinal scan)	158.18	0.25	0	NHS reference costs 2021/22: BZ88A, outpatient procedures, retinal tomography 19 years and over
Blood test	2.96	0.23	0.23	NHS reference costs 2021/22: DAPS05, haematology
Pain medication	0.46	0	20.97	eMIT, 2022/23 (30 mg/1 ml solution for injection, pack of 10). Dose: BNF, 2023 (30 mg dose daily for opioid-naïve patients in palliative care)

Based on Table 40 CS and response to clarification question B11.[5, 7]
BNF = British National Formulary; CS = company submission; CT = computed tomography; eMIT = electronic market information tool; NHS = National Health Service; OCT = optical coherence tomography; PD = progressed disease; PF = progression-free

EAG comment: The EAG noticed that the reported resource use per 21-days in the CS was much lower compared to the resource use estimates provided by clinical experts presented in Table 1 of the Advisory Board Report.[24] The EAG decided to explore the effect of the resource use inputs in an scenario analysis. Details of these frequencies are reported in Section 6.1.2.3.

4.2.9.9 Adverse event costs

In the economic model, AE costs were applied using the mean cost per AE as presented in Table 4.15, using the incidences presented in Section 4.2.7.

Table 4.15: Costs per AE applied in the economic model

AE	Mean cost (£)	Reference
AST increased	0	Watchful waiting (and thus no cost) assumed
Fatigue	770.29	NHS reference costs 2021/22: SA01G-K, acquired pure red cell aplasia or other aplastic anaemia, non-elective short stay weighted average
Hyperphosphataemia (grade 2+)	19.75	BNF, 2023. One pack of phosphate binders - calcium acetate, Renacet 950 mg tablets
Hypophosphataemia	19.39	BNF, 2023. One pack of oral phosphate supplements - Phosphate Sandoz effervescent tablet
Stomatitis	827.18	NHS reference costs 2021/22: FD10E-H, non-malignant gastrointestinal tract disorders with single intervention, non-elective short stay weighted average

Based on Table 41 in CS.[5]
AE = adverse event; AST = aspartate aminotransferase; BNF = British national Formulary; CS = company submission; NHS = National Health Service

4.2.9.10 Miscellaneous unit costs and resource use

A one-off terminal care costs of £6,870.13 was applied in the economic model upon death to account for the costs associated with the intensive months of disease management prior to death.[41] In the CS it is reported that the reference for this cost was aligned with the pemigatinib NICE appraisal, inflated to the latest cost year.[22]

Costs of genetic testing for FGFR2 were not incorporated in the company's base-case, but it was explored in a scenario analysis, which did not have a substantial impact on the results. No additional genetic testing cost are anticipated by the introduction of futibatinib by the company, since genetic testing is already part of routing clinical practice for CCA in the UK, as well as FGFR2 rearrangement fluorescent in situ hybridisation (FISH) is included in the 2024/2025 National Genomic Test Directory for patient with CCA.[24, 42]

EAG comment:

- The addition of genetic testing does indeed not have an effect at all on the incremental costs since the cost will increase in both arms with the same amount. However, the EAG noticed that in the CS, the company reports the genetic testing costs to be £34, however the economic model uses £340 (factor 10 difference). In the economic model, the company seems to have weighted this cost to a cost per person, using a prevalence of FGFR2 fusion or rearrangement to be 10%, however, since the cost in both arms increased with the same amount this change did not influence the results.
- Although the impact of including genetic testing on the CE results is minor, the EAG decided to include them in the EAG base-case analysis. This decision was based on the response from the clinical expert of the EAG team that stated that although "*FGFR fusion testing is routing clinical practices, this is not always performed*".[28] This assumption is also in line with TA722 committee's preferences.[2, 3]

4.2.10 Disease severity

The NICE reference case stipulates that the committee will regard all QALYs as being of equal weight. The committee may also consider the severity of the condition, as determined by the absolute and proportional QALY shortfall (including discounting at the reference case rate), as decision modifier.

Severity can be then taken into account quantitatively in CEAs through QALY weighting, based on the absolute and proportional shortfall, as shown in Table 4.16. Whichever implies the greater severity level will be considered, and if either the proportional or absolute QALY shortfall falls exactly on the cut-off between two severity levels, the higher level will apply.[43]

Table 4.16: QALY weightings for disease severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1.0	Less than 0.85	Less than 12
1.2	From 0.85 to 0.95	From 12 to 18
1.7	At least 0.95	At least 18
QALY = quality adjusted life year		

The results of the QALY shortfall analysis are shown in Table 4.17, where the total lifetime QALYs associated with pemigatinib were obtained from the base-case analysis results, and the estimated total QALYs for the general population reflecting the baseline characteristics of the FOENIX-CCA2 trial (56.3% female and 55.7 years). These results suggest that a QALY weight of 1.2 can be applied.

Table 4.17: Summary of company QALY shortfall analysis

Expected total QALYs for the general population	Total expected QALYs for people with pemigatinib	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
14.13	[redacted]	[redacted]	[redacted]	1.2
Based on Table 43 in CS.[5] CS = company submission; QALY = quality-adjusted life year				

EAG comment: The QALY shortfall results presented in Table 4.17 were validated by the EAG. In addition, the disease burden calculator (iDBC) tool also estimates the likelihood of the applicable QALY weight based on the probabilistic sensitivity analysis (PSA) results provided in the company's model, which can be used to estimate the severity adjusted probability of being cost-effective.[44] The QALY shortfall calculations conducted by the EAG were broadly in line with those presented by the company. The uncertainty around the QALY weights shows that even though a weighted point estimate is 1.2, there is a 23% that the applicable QALY weight is 1.0, and a 3.7% that the applicable QALY weight is 1.7, which may have an impact on the severity adjusted results.

5. Cost effectiveness results

5.1 Company's cost effectiveness results

In Section B.3.10 of the CS,[5] the company presented their CE results by reporting both the ICER and incremental NHB, using both futibatinib list and Patient Access Scheme (PAS) prices. To make this Section more concise, the EAG only presents ICERs based on futibatinib PAS prices. Results including comparator Patient Access Scheme (cPAS) prices for pemigatinib will be presented in a separated Appendix to the EAG report.

Table 5.1 shows the company's base-case deterministic CE results for futibatinib compared to pemigatinib. All results are discounted. Results indicated that futibatinib was less costly and more effective than pemigatinib, accruing [redacted] incremental QALYs and saving [redacted] in total costs. Therefore, futibatinib dominates pemigatinib in the company's base-case scenario. When accounting for disease severity, considering a QALY weight of 1.2, incremental QALYs were now [redacted] and futibatinib was still dominant compared to pemigatinib. Disaggregated discounted QALYs and costs are shown in Tables 5.2 and 5.3, respectively.

Table 5.1: Company base-case deterministic CE results (futibatinib PAS price, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Futibatinib	[redacted]	2.36	[redacted]	[redacted]	0.11	[redacted]	Futibatinib dominates
Pemigatinib	140,130	2.25	[redacted]				

Based on Table 47 in the CS.[5]
CE = cost effectiveness; CS = company submission; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; PAS = Patient Access Acheme; QALY = quality-adjusted life year

Table 5.2: Disaggregated QALYs results (discounted)

Health state	QALY futibatinib	QALY pemigatinib	Increment	Absolute increment	(%) Absolute increment
PF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 39 in Appendix J of the CS.[9]
AEs = adverse events; CS = company submission; PF = progression free; PD = progressive disease; QALY = quality-adjusted life year

Table 5.3: Disaggregated cost results (futibatinib PAS price, discounted)

Cost item	Cost futibatinib (£)	Cost pemigatinib (£)	Increment (£)	Absolute increment (£)	(%) Absolute increment
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring and resource use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of life costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cost item	Cost futibatinib (£)	Cost pemigatinib (£)	Increment (£)	Absolute increment (£)	(%) Absolute increment
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Based on Table 40 in Appendix J of the CS.[9] AEs = adverse events; CS = company submission; PAS = Patient Access Scheme					

Overall, based on the company's base-case results, the new technology is modelled to affect QALYs by:

- Decreasing the number of QALYs in PFS, and increasing the number of QALYs in PD, resulting in an overall increase in QALYs.
- Slightly reducing the QALYs lost due to experiencing AEs.

Overall, based on the company's base-case results, the technology is modelled to affect costs by:

- Its lower unit price compared to pemigatinib.
- Slightly decreasing costs associated to AEs and end of life.
- A minor increase in costs due to monitoring.

EAG comment: As explained in Section 5.3.3 below, the EAG identified several errors in the updated model received after clarification. Triggered by this, the EAG noticed that, while most of the errors found in the updated model were related to the changes made by the company in response to the EAG clarification requests, some of them were already present in the original model. The majority of the errors detected by the EAG in the original model were related to the implementation of the PSA and, therefore, these do not impact the base-case results presented in Table 5.3. Because of this and the lack of time, the EAG did not correct these PSA-related errors in the company's original model (but they were corrected in the model used to generate the EAG's base-case). However, the EAG also noticed that the implementation of the half-cycle correction was incorrect in both the original and updated models. Since this error does impact the model results, it was corrected by the EAG and the company's base-case results after this correction are presented in Table 5.4. Total costs, life years and QALYs are smaller for both arms, but incrementally, results are similar to those presented by the company in Table 5.1.

Table 5.4: Company base-case deterministic CE results after correcting the half-cycle correction implementation (futibatinib PAS price, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Futibatinib	[redacted]	2.31	[redacted]	[redacted]	0.11	[redacted]	Futibatinib dominates
Pemigatinib	133,156	2.20	[redacted]				
Based on economic model.[45] CE = cost effectiveness; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; PAS = Patient Access Scheme; QALY = quality-adjusted life year							

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analysis

The company conducted a PSA in which all relevant input parameters were sampled simultaneously from their corresponding probability distributions over 1,000 iterations. The input parameters can be

found in Table 44 of the CS,[5] and the probability distributions used in the PSA in the "Model parameters" sheet of the economic model.[45] The average PSA results are summarised in Table 5.4 and are overall in line with the deterministic ones shown in Table 5.1. When accounting for disease severity, a QALY weight of 1.2 applies; the incremental QALYs were now [redacted] and futibatinib was still dominant compared to pemigatinib.

Table 5.5: Company base-case probabilistic CE results (futibatinib PAS price, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Futibatinib	[redacted]	2.49	[redacted]	[redacted]	0.07	[redacted]	Futibatinib dominates
Pemigatinib	144,860	2.43	[redacted]				

Based on economic model.[45]
CE = cost effectiveness; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; PAS = Patient Access Acheme; QALY = quality-adjusted life year

The company also plotted the PSA outcomes on a CE-plane. These are shown in Figure 5.1. It can be seen that [redacted] From the PSA results, a cost effectiveness acceptability curve (CEAC) was also calculated and shown in Figure 5.2. The CEAC plot indicates that at the common thresholds of £20,000 and £30,000 per QALY gained, the estimated probability that futibatinib is a cost-effective alternative to pemigatinib was [redacted].

Figure 5.1: PSA CE-plane (futibatinib PAS price, discounted)

[redacted]

Based on economic model.[45]
CE = cost effectiveness; ICER = incremental cost-effectiveness ratio; Inc. – incremental; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 5.2: PSA CEAC (futibatinib PAS price, discounted)

Based on economic model.[45]
CEAC = cost effectiveness acceptability curve; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; WTP = willingness-to-pay

EAG comment:

- As mentioned above, and explained in Section 5.3.3, the EAG identified several errors in the original model, most of them related to the implementation of the PSA. The errors identified in the PSA implementation in the original model are the following:
  - Incorrect implementation of half-cycle correction on the "Patient flow" sheet.
  - Incorrect referral on the "PSA iteration" sheet (cells C8:O8 refer to incorrect cells from the "Cost_cals" and "Outcome_calcs" sheets) for the PSA results of futibatinib when using the MAIC-adjusted survival option for futibatinib.
  - Incorrect calculation of the estimation of the standard errors on the "datastore_survival" sheet.
  - Incorrect application of the normal distribution that was applied to the HR rather than the log-HR on the "Model parameters" sheet.
  - Incorrect application of the INDEX and MATCH functions to select the parameters that define the parametric survival functions on the "Model parameters" sheet, as a (-1) value was used in the formula forcing the indexing to be shifted one place to the left.
  - Incorrect setting for the PSA regarding the pemigatinib OS and PFS parameters, as they were set to "No" on the "Model parameters" sheet, and therefore not varied in the PSA results.
  - Parameters for the AEs durations were linked to wrong cells and the assumed gamma distribution would return a value of 0 on the "Model parameters" sheet, effectively not including these parameters in the PSA.
  - Parameters for the AEs disutilities, the disutility attached to PD and parameters for healthcare resource use were not included in the PSA as they were set to "No" on the "Model parameters" sheet.
  - Resource use and unit costs of optical coherence tomography (OCT) (retinal scan) were not considered in the PSA, since these parameters were not included at all in the "Model parameters" sheet of the model.
  - Incorrect specification of Cholesky matrices used in "Datastore_DoT" sheet. The EAG was not able to solve this error for the EAG base-case as the EAG did not have access to these data.

- Given the lack of time, the EAG was unable to correct these PSA-related errors in the company's original model. Therefore, the EAG would like to stress that the PSA results presented above are based on the company's submitted model including at least all the described errors. For the EAG base-case and PSA results, the EAG corrected these errors.
- Finally, the EAG would like to express its concerns regarding the numerous errors identified in the company's model after the clarification phase. Because of this, the EAG is concerned that additional errors may still be present in the company's model.

5.2.2 Deterministic sensitivity analysis

The company also conducted DSAs where all input parameters, for which there were only a point estimate value in the model (these can be found in column N in "Model parameters" sheet), were varied by ±20% of their mean value. Since the base-case scenario resulted in dominance (negative ICER), tornado diagrams for futibatinib versus pemigatinib showing the 10 parameters with the largest influence on the results are presented separately for incremental costs and incremental QALYs. This can be seen in Figure 5.3 and 5.4, respectively. Overall, most input parameters have a minor impact on the model results, except for the HRs for OS and PFS.

Figure 5.3: DSA tornado diagram for incremental costs (futibatinib PAS price, discounted)

Based on economic model.[45]
DSA = deterministic sensitivity analysis; HR = hazard ratio; OS = overall survival; PAS = Patient Access Scheme; PD = progressed disease; PF = progression free; PFS = progression-free survival

Figure 5.4: DSA tornado diagram for incremental QALYs (futibatinib PAS price, discounted)

Based on economic model.[45]
DSA = deterministic sensitivity analysis; HR = hazard ratio; OS = overall survival; PAS = Patient Access Scheme; PFS = progression-free survival; QALYs = quality-adjusted life years

EAG comment: The DSA results presented above are also based on the company's model including the errors identified by the EAG.

5.2.3 Scenario analysis

The company presented 13 scenario analyses to assess the robustness of the model results to changes in some modelling assumptions. A summary of the results of these scenarios is provided in Table 5.5. These included exploring alternative OS and PFS extrapolations and HRs for the effect between futibatinib and pemigatinib, a cost comparison scenario and cost scenarios excluding drug wastage costs and include genetic testing costs. In conclusion, the modelling assumptions explored by the company had little effect on the results. The only scenario where futibatinib was not dominant was under the assumption that the OS HR was equal to 1. In that scenario the resulting ICER was in the SW (more costs, lower incremental QALYs) quadrant of the CE-plane.

EAG comment:

- In general, the scenarios explored by the company did not change the main conclusions from the base-case. However, as explained in Section 4.2.6, the EAG considers that independent modelling of survival curves, and modelling ToT separately from PFS, should have been explored by the company as well. These options were incorporated by the company in the model received with the responses to the clarification questions.
- The EAG would like to stress again that the results and conclusions form the scenario analyses were also based on the model including the errors identified by the EAG. The EAG did not rerun the company scenarios due to lack of time.

Table 5.6: Summary of company scenario analyses (futibatinib PAS price, discounted)

Scenario	Description (base-case)	Description (scenario)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Base-case	-	-	[redacted]	[redacted]	**Futibatinib dominates**
1. Cost comparison	PFS HR = 0.93 OS HR = 1.05 AE rates as in Table 4.12	Futibatinib versus pemigatinib OS and PFS HR = 1 Equal rate of AEs in both arms	[redacted]	[redacted]	Futibatinib cost saving
2. Futibatinib PFS (I)	Futibatinib PFS lognormal	Futibatinib PFS log-logistic	[redacted]	[redacted]	Futibatinib dominates
3. Futibatinib PFS (II)	Futibatinib PFS lognormal	Futibatinib PFS Weibull	[redacted]	[redacted]	Futibatinib dominates
4. Futibatinib versus pemigatinib PFS HR (I)	HR = 0.93	Futibatinib versus pemigatinib PFS HR = 1	[redacted]	[redacted]	Futibatinib dominates
5. Futibatinib versus pemigatinib PFS HR (II)	HR = 0.93	Unadjusted HR = [redacted](FOENIX-CCA2 and FIGHT-202)	[redacted]	[redacted]	Futibatinib dominates
6. Futibatinib versus pemigatinib PFS HR (III)	HR = 0.93	MAIC HR = [redacted]	[redacted]	[redacted]	Futibatinib dominates
7. Futibatinib OS (I)	Futibatinib OS lognormal	Futibatinib OS log-logistic	[redacted]	[redacted]	Futibatinib dominates
8. Futibatinib OS (II)	Futibatinib OS lognormal	Futibatinib OS Weibull	[redacted]	[redacted]	Futibatinib dominates
9. Futibatinib versus pemigatinib OS HR (I)	HR = 1.05	Futibatinib versus pemigatinib OS HR = 1	[redacted]	[redacted]	10,974,473 (in SW quadrant)
10. Futibatinib versus pemigatinib OS HR (II)	HR = 1.05	Unadjusted HR = [redacted] (FOENIX-CCA2 and FIGHT-202)	[redacted]	[redacted]	Futibatinib dominates
11. PFS and OS HR	PFS HR = 0.93 OS HR = 1.05	PFS and OS HR = 1	[redacted]	[redacted]	Futibatinib dominates
12. Wastage costs	Included	Excluded	[redacted]	[redacted]	Futibatinib dominates
13. Genetic testing cost	Excluded	Included	[redacted]	[redacted]	Futibatinib dominates

Scenarios 1-13 are based on Table 51 in the CS.[5]

AEs =adverse events; CS = company submission; ICER = incremental cost-effectiveness ratio; Inc. = incremental; QALY = quality-adjusted life year; HR = hazard ratio; OS = overall survival; PAS = Patient Access Scheme; PFS; progression-free survival

5.3 Model validation and face validity check

The validation efforts conducted on the economic model were briefly discussed in the validation Section of the CS (B.3.14).[5] The company indicated that guidance from the report of the ISPOR-SMDM Modelling Good Research Practices Task Force-7 was followed.[46] The validation efforts discussed in Section B.3.14 of the CS referred to technical verification and the implementation of feedback from UK economic and clinical experts. Other validation aspects, such as the validation of some input parameters or how experts' feedback was used to validate other modelling features are scattered over Document B of the CS.[5] In addition, more details about model validation were provided by the company in response to some clarification questions.[7] In the remaining of this Section, the validation efforts performed on the model, as presented by the company, are categorised according to the types of validation used in the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool.[47]

5.3.1 Validation of the conceptual model

5.3.1.1 Face validity testing (conceptual model)

The company indicated that the model structure and key assumptions were reviewed by UK clinical and health economic experts in an Advisory Board.[24, 29]

5.3.1.2 Cross-validity testing (conceptual model)

The previous pemigatinib NICE appraisal TA722 was used for cross-validation. The main difference with respect to the company's model was that in TA722 a distinction was made between PFS and ToT. While originally the company assumed PFS to model ToT for this submission, an option to specify these separately was included after clarification.

5.3.2 Input data validation

5.3.2.1 Face validity testing (input data)

Input parameters were also reviewed by UK clinical and health economic experts in an Advisory Board.[24, 29] These included survival curves extrapolations, utility values or assumptions about drug wastage, subsequent treatments and frequency of resource use.

5.3.2.2 Model fit testing

The company highlighted that, given the relatively immature OS data available from the FOENIX-CCA2 trial, a thorough clinical validation process was conducted with the purpose to inform the most robust PFS and OS extrapolations for both futibatinib and pemigatinib. However, as explained throughout Section 4.2.6, the EAG did not agree with some of the choices made by the company.

In clarification question B17,[7] the EAG questioned the expert rankings of futibatinib OS and PFS extrapolations since these do not seem to be in line with the presented evidence. For example, the EAG pointed out that, even if the number of patients at risk are low after 15 months for PFS, which could indicate uncertainty around the long-term extrapolations, the experts selected as preferred extrapolations the models that provided the highest long-term survival probabilities. However, according to the EAG, these choices are hard to justify based on goodness of fit to the data. The company referred to NICE TSD 14, to indicate that statistical fit to the observed KM data is one of a number of factors which should be used to inform the selection of the most appropriate extrapolations

to include in a CE model.[25] The EAG understands and agrees with this statement, but it considers that the final selection should be based on a combination of these "number of factors". The company's choices seem to be greatly driven by expert opinion, giving less weight to these other factors, such as model fit, which would make for example exponential extrapolations inappropriate according to the EAG.

5.3.3 Validation of the computerised model (technical verification)

The company explained that the model underwent two independent quality control and technical validation processes after full development. Despite this, the EAG found some (minor) errors in the model that were corrected during the clarification phase. Details are provided below.

5.3.3.1 External review

Verification of model implementation (and input data) were performed by health economists not involved in the model development. This was done in accordance with a pre-specified test plan. Details of this plan were not reported by the company. Input data verification was documented in the relevant worksheets of the model, however, the EAG is unclear where exactly in the model this can be found. Discrepancies were discussed and resolved by updating the input data where required.

Despite the verification efforts reported by the company, the EAG identify numerous errors in the model submitted by the company after clarification, which led to the identification of errors in the model originally submitted by the company. A list with the errors identified by the EAG can be found in Section 6.1.2. The EAG corrected as many of these errors as possible before running the EAG base-case and PSA. However, given the large number of errors identified, the EAG cannot be certain that there are no more remaining errors in the company's model.

5.3.3.2 Extreme value testing

The implementation of the sensitivity and scenario analyses was reviewed with the help of two checklists (for technical and stress test checks) based on the published TECH-VER checklist.[48] The results of these tests were provided by the company in Table 17 in response to clarification question B15 (not shown here).[7] According to the company, all tests resulted in the expected outcome.

5.3.3.3 Testing of traces

Markov traces can be found in the "Patient flow" sheet of the model. A plot of the traces to facilitate visual inspection was included in the model submitted together with the responses to the clarification letter ("Results" sheet).

5.3.3.4 Unit testing

The company indicated that technical verification included assessing the validity of the model results, calculations, data references, model interface, and VBA code.

5.3.4 Operational validation (validation of model outcomes)

5.3.4.1 Face validity testing (model outcomes)

Although it is not explicitly mentioned in the CS, the EAG assumed that model results were presented to experts who provided some sort of validation.

5.3.4.2 Cross validation testing (model outcomes)

5.3.4.2.1 Comparisons with other technology appraisals and other models (not *necessarily technology appraisals)*

In response to clarification question B15,[7] the company compared the total QALYs and life years gained (LYG) obtained for pemigatinib with those reported in TA722,[22] a previous CADTH submission,[49] and the study by Shi et al. 2023.[18] This is summarised in Table 5.6. The company concluded that the model results were closely aligned to those reported in TA722 and the previous CADTH submission. However, in TA722 the estimated QALYs are redacted so only LYG can be compared. It can be seen that the company's model estimated 0.19 less LYG for pemigatinib compared to TA722. This might imply that the current submission also estimates less QALYs for pemigatinib compared to TA722. Since in the company's base-case the incremental QALYs are small ([redacted]), a small difference in QALYs for pemigatinib could have substantial impact on the model results ([redacted]). The company also explained that the lower total QALYs and LYG reported by Chen et al. (2023) are due to the model using a 5-year time horizon. Therefore, it could be argued that this study is not the most appropriate to validate model results.

Table 5.7: Total QALY and LY results for pemigatinib from TA722 and previous studies

Source	Total QALYs	Total LYG
CS	[redacted]	2.25
TA722[22]	NR	2.44
Shi et al. (2023)[18]	1.15	1.61
CADTH, (2022)[49]	1.65	2.56
Based on Table 16 in clarification letter response.[7] CS = company submission; LYG = life years gained; NR = not reported; QALY = quality-adjusted life year		

It is unclear why a similar exercise was not attempted to validate the total costs estimated by the model. As highlighted in Sections 4.2.6 and 4.2.9 of this report, it is likely that in the company's base-case, the total costs for pemigatinib are higher than those obtained in TA722, since ToT was modelled as equal to PFS and from TA722 it is known that ToT is lower than or equal to PFS. After clarification, the company included in the model the option to model ToT separately. However, since in TA722 costs are redacted, it is not possible to know if and to what extent, pemigatinib costs in this submission are higher than those reported in TA722.

5.3.4.3 Validation against outcomes using alternative input data

This type of validation was not explicitly reported by the company unless it was considered part of the scenario analyses.

5.3.4.4 Validation against empirical data

5.3.4.4.1 *Comparison with empirical data used to develop the economic model (dependent validation)*

This type of validation was not reported by the company.

5.3.4.4.2 Comparison with empirical data not used to develop the economic model (independent validation)

This type of validation was not reported by the company.

6. Evidence Assessment Group's Additional Analyses

6.1 Exploratory and sensitivity analyses undertaken by the EAG

6.1.1 Explanation of the company adjustments after the request for clarification

In their response to the request for clarification, the company made the following corrections to the originally submitted model:

- Under PH, the hazard rates for OS and PFS are assumed to be equal between futibatinib and pemigatinib when all patients have discontinued treatment, i.e., at 24 months (clarification question B5).[7] Otherwise, a PH implies a continued treatment effect, even when patients are no longer on treatment.
- The wastage options were incorrectly switched in the original model (clarification question B10).[7]
- The probability of futibatinib being cost-effective at different WTP thresholds was estimated incorrectly.[7]

The updated company base-case results (discounted and including PAS price for futibatinib) indicated that futibatinib was still less costly and more effective than pemigatinib, accruing [redacted] incremental QALYs and saving [redacted] in total costs. Therefore, futibatinib dominates pemigatinib in the company's updated base-case scenario. It should be noted though that, compared to the original base-case, the incremental costs remained almost identical, however, the incremental QALYs were reduced by approximately [redacted]%, illustrating the effect of assuming equal hazard rates after treatment discontinuation. When accounting for disease severity, considering a QALY weight of 1.2, incremental QALYs were now [redacted] and futibatinib was still dominant compared to pemigatinib. The EAG considers these changes appropriate and used this version of the model as the starting point for building the EAG base-case described below.

Please note that after the EAG report was finished, the company noticed that the EAG implementation of the half-cycle correction (see Sections 6.1.2 and 6.1.3.1 for details) did not include the first model cycle. This means that the results after fixing this error were slightly different. For practical reasons (minor impact), and due to time constraints, the EAG did not repeat all the analyses again after fixing this error.

6.1.2 Explanation of the EAG adjustments

Table 6.1 summarises the CE key issues categorised according to the sources of uncertainty as defined by Grimm et al. 2020:[50]

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide CIs, small sample sizes, or immaturity of data)
- Bias & indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight)

Identifying the uncertainty sources can help determine the course of action to be taken (i.e., whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Table 6.1 also

lists suggested alternative approaches, expected effects on the CE, whether it is reflected in the EAG exploratory analyses, and if additional evidence or analyses might help to resolve the identified key issues.

The changes that the EAG made (to the model received with the response to the clarification letter) can be subdivided into the following three categories (according to Kaltenthaler et al. 2016):[51]

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

After the proposed changes were implemented in the company's model, additional scenario analyses were also explored by the EAG in order to assess the impact of alternative assumptions on the CE results.

6.1.3 EAG base-case

The adjustments made by the EAG, to define the EAG base-case (using the base-case after clarification as starting point) are listed below.

6.1.3.1 Fixing errors

As explained in Section 5.1, in Section 5.2.1 and Section 5.3.3, the EAG identified several errors related to the calculations of the half-cycle corrected values, the implementation of the PSA analysis and the PSA calculations of the disease management cost in PF disease as the costs attributed to OCT (retinal scan) were not included in the PSA calculations. The EAG identified, and corrected where possible, the following errors in the model, with specifics highlighted in the model prepared by the EAG, before running the EAG analyses presented in this chapter:

1. Incorrect implementation of half-cycle correction on the "Patient flow" sheet. After the EAG report was finished, the company noticed that the EAG implementation of the half-cycle correction did not include the first model cycle. For practical reasons (minor impact), and due to time constraints, the EAG did not repeat all the analyses again after fixing this error.
2. Incorrect referral on the "PSA iteration" sheet (cells C8:O8 refer to incorrect cells from the "Cost_cals" and "Outcome_calcs" sheets) for the PSA results of futibatinib when using the MAIC-adjusted survival option for futibatinib.
3. Incorrect calculation of the estimation of the standard errors on the "datastore_survival" sheet.
4. Incorrect application of the normal distribution that was applied to the HR rather than the log-HR on the "Model parameters" sheet.
5. Incorrect application of the INDEX and MATCH functions to select the parameters that define the parametric survival functions on the "Model parameters" sheet, as a (-1) value was used in the formula forcing the indexing to be shifted one place to the left.
6. Incorrect setting for the PSA regarding the pemigatinib OS and PFS parameters, as they were set to "No" on the "Model parameters" sheet, and therefore not varied in the PSA results.
7. Parameters for the AEs durations were linked to wrong cells and the assumed gamma distribution would return a value of 0 on the "Model parameters" sheet, effectively not including these parameters in the PSA.

8. Parameters for the AEs disutilities, the disutility attached to PD and parameters for healthcare resource use were not included in the PSA as they were set to "No" on the "Model parameters" sheet.
9. Resource use and unit costs of OCT (retinal scan) were not considered in the PSA, since these parameters were not included at all in the "Model parameters" sheet of the model.
10. Incorrect specification of Cholesky matrices used in "Datastore_DoT" sheet. The EAG was not able to solve this error for the EAG base-case as the EAG did not have access to these data.

6.1.3.2 Fixing violations

No violations were found by the EAG in the model provided in response to the clarification letter.

6.1.3.3 Matters of judgement

11. Independent modelling of OS (Weibull) and PFS (log-normal) curves (Section 4.2.6). In their base-case, the company assumed a PH model for both OS and PFS. The EAG considered that the PH is likely invalid. Therefore, an independent modelling approach was preferred by the EAG (sheet "Settings" – row 56). OS was extrapolated using a Weibull distribution (Section 4.2.6). Using the adjusted data and based on the models' statistical fit, the visual inspection and the clinical plausibility, the EAG selected the Weibull distribution as the preferred option to model OS for futibatinib and pemigatinib (sheet "Survival" – cell AA43 and AA175). PFS was extrapolated using a lognormal distribution (Section 4.2.6). Using the adjusted data, and based on the models' statistical fit, the visual inspection and the clinical plausibility, the EAG selected the lognormal distribution as the preferred option to model PFS for futibatinib and pemigatinib (sheet "Survival" – cell L43 and L175).
12. The assumption that hazard rates for OS and PFS are equal between futibatinib and pemigatinib when all patients have discontinued treatment does not apply under independent modelling. In their base-case, PH for OS and PFS were assumed. The company included in the model the option to use the same hazard rates for both OS and PFS after all patients have discontinued treatment (after 24 months). Otherwise, under PH, this would imply a continued treatment effect. When independent modelling is assumed, this option is no longer needed since PFS and OS are directly defined by the selected extrapolations (sheet "Settings" – row 53).
13. OS and PFS extrapolations should be based on (MAIC) adjusted data (Section 4.2.6). In their base-case, the company used unadjusted futibatinib data to select their preferred extrapolations for both OS and PFS. The EAG considered that using (MAIC) adjusted data would make futibatinib and pemigatinib populations more comparable. Therefore, this approach was preferred by the EAG (sheet "Settings" – row 56).
14. ToT should be modelled independently of PFS (assuming ToT <= PFS) (Section 4.2.6). In their base-case, the company assumed ToT = PFS. The EAG considered that this assumption is likely to be invalid. Therefore, modelling separately ToT and PFS was preferred by the EAG. ToT was extrapolated using a Weibull (Section 4.2.6). Based on the futibatinib ToT data provided by the company, the EAG selected the Weibull distribution as the preferred option to model ToT for futibatinib (sheet "Survival" – cell L147).
15. When modelling ToT in their scenario analyses (following the clarification phase), the company presented one scenario in which ToT was completely independent of PFS and one scenario in which ToT was assumed to be restricted by PFS in the upper bound. The EAG base-case assumed that ToT cannot be greater than PFS (sheet "Settings" – row 57 and sheet "Survival" – cell H144).
16. The company omitted costs of genetic testing for FGFR2 were not in their base-case. Although the EAG expects the incremental impact of adding these costs to base-case would be negligible on the

CE calculations, based on the feedback provided by a clinical expert to the EAG, it was considered appropriate to add these costs in the EAG base-case analysis (sheet "Settings" – row 44). This was also preferred by the TA722 committee.

6.1.4 EAG exploratory scenario analyses

The EAG conducted a series of scenario analyses to explore the impact of key assumptions and uncertainties within the CE analyses. While the main focus was on the key issues described in Table 6.1, other uncertainties were also explored by the EAG. A description of scenario analyses conducted by the EAG is provided below.

6.1.4.1 Scenario analyses set 1: OS, PFS and ToT

The EAG explored the impact of using alternative parametric models to fit OS, PFS and ToT data for futibatinib and pemigatinib treatment arms. Alternative extrapolation options for OS included the log-logistic, generalised gamma, and log-normal models. Alternative extrapolation options for PFS included the Weibull, generalised gamma, and log-logistic models. Alternative extrapolation options for ToT included the Gompertz and generalised gamma models. Regarding ToT, a scenario was also explored in which the restriction of ToT smaller than or equal to PFS was removed.

The EAG also run a scenario analysis using dependent models for OS and PFS as per company's base-case approach. In their base-case, the company assumed the PH assumption was valid. However, to address the expectation that there should be no survival difference expected between futibatinib and pemigatinib treatments when patients stop receiving treatment, the company updated their model by assuming that the hazard rates for OS and PFS for pemigatinib are set equal to those of futibatinib after 24 months (see Section 4.2.6). The EAG run scenario analyses in which the 24 months cut-off point was also incorporated into this EAG's scenario analysis.

6.1.4.2 Scenario analyses set 2: cost comparison

In Section 3.4 of this report, the EAG concluded that there seems to be little difference in PFS and OS between futibatinib and pemigatinib. This means that an assumption of equal effectiveness seems reasonable, at least in terms of these two outcomes. Based on this, the EAG conducted a cost-comparison scenario, where it is assumed equal efficacy between futibatinib and pemigatinib, and that AEs for pemigatinib are the same as those for futibatinib.

6.1.4.3 Scenario analyses set 3: alternative resource use and costs assumptions

The EAG also run a scenario analysis excluding genetic testing (3a) and assuming no drug wastage (3b). As these changes influenced both treatment arms, and based on the results presented by the company, the EAG did not expect a large difference in the incremental effects. In addition, scenario analyses using the resource use estimates as provided by clinical experts in the Advisory Board Report were also explored by the EAG.[24] Table 6.1 shows the resource use per 3 weeks values per health state for both the company base-case and the scenario analysis. The Advisory Board reported that pain medication is given continuous. Therefore, the EAG used a frequency of 21, equal to the number of days in the cycle. There is no information about the OCT retinal scan in the Advisory Board Table, therefore the EAG assumed the same frequency as the company for the retinal scan use.

Table 6.1: Resource use estimates per 21-day cycle by health state as per company's base-case analysis and EAG scenario analysis

Health state	Resource use per 3 weeks in PF state		Resource use per 3 weeks in PD state	
	Company base-case	Scenario analysis	Company base-case	Scenario analysis
Clinical examination	0.23	1	0.23	1.5
CT scan	0.23	1	0.06	0.25
OCT (retinal scan)	0.25	0.25	0	0
Blood test	0.23	0.25	0.23	1.5
Pain medication	0	21	20.97	21

Based on Table 40 CS and Table 1 of the Advisory Board Report.[7, 24]
CS = company submission; CT = computed tomography; EAG = External Assessment Group; OCT = optical coherence tomography; PD = progressed disease; PF = progression free

6.1.5 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 6.2: Overview of key issues related to the CE (conditional on FEs highlighted in Section 6.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
The EAG disagrees with the company's approach of modelling OS and PFS assuming PH	4.2.6	Methods Transparency	Independent modelling, as it considers the PH assumption is likely to be invalid. Extrapolation model selection should be based on MAIC-adjusted data for both futibatinib and pemigatinib. OS curve selection: Weibull. PFS curve selection: log-normal.	-	Yes	No
The EAG disagrees with the company's approach of assuming ToT equal to PFS	4.2.6	Methods Transparency Unavailability	Modelling ToT and PFS independently, as ToT is smaller than or equal to PFS. Extrapolation model selection for ToT should be based on adjusted data for both futibatinib and pemigatinib. However, ToT data for pemigatinib are not available. ToT curve selection for futibatinib: Weibull. ToT curve selection for pemigatinib: same PFS HR estimated from the MAIC.	+/-	Partial	ToT data for pemigatinib.
The EAG is uncertain about the number of remaining errors in the company's model	4, 5, 6	Methods	Model errors identified and corrected by the EAG.	+/-	Partial	A new model where extensive technical verification has been conducted, preferably by an external party.

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator; [b] Explored

CE = cost effectiveness; EAG = External Assessment Group; FEs = fixing errors; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; PH= proportional hazards; ToT = time on treatment

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

6.2.1 Results of the EAG preferred base-case scenario

Table 6.3 shows the results of the deterministic EAG's base-case (discounted and assuming futibatinib PAS price). These indicated that futibatinib was less costly but also less effective than pemigatinib, accruing [redacted] incremental QALYs and saving [redacted] in total costs. Note that in the EAG's base-case scenario the ICER is in the SW quadrant of the CE-plane. In this situation, large ICERs are favoured when compared to common thresholds, as opposed to what happens when the ICER is in the NE quadrant of the CE-plane. When accounting for disease severity, considering a QALY weight of 1.2, incremental QALYs were now [redacted], which keeps the ICER in the SW quadrant.

Compared to the company's base-case after clarification shown at the beginning of Section 6.1.1, the incremental costs were reduced by approximately [redacted], whereas the incremental QALYs became negative (pemigatinib results in more QALYs than futibatinib). Disaggregated discounted QALYs and costs are shown in Tables 6.4 and 6.5, respectively.

Table 6.3: EAG base-case deterministic CE results (futibatinib PAS price, discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Futibatinib	[redacted]	1.81	[redacted]	[redacted]	-0.277	[redacted]	352,788*
Pemigatinib	128,216	2.08	[redacted]				

Based on electronic model after clarification,[1] with errors fixed by the EAG as described above.
* ICER in SW quadrant of the CE-plane.
CE = cost effectiveness; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; PAS = Patient Access Scheme; QALY = quality-adjusted life year

Table 6.4: Disaggregated QALYs results (EAG base-case, discounted)

Health state	QALY futibatinib	QALY pemigatinib	Increment	Absolute increment	(%) Absolute increment
PF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on electronic model after clarification, with errors fixed by the EAG as described above.[1]
AEs = adverse events; EAG = External Assessment Group; PD = progressive disease; PF = progression free; QALY = quality-adjusted life year

Table 6.5: Disaggregated cost results (EAG base-case, futibatinib PAS price, discounted)

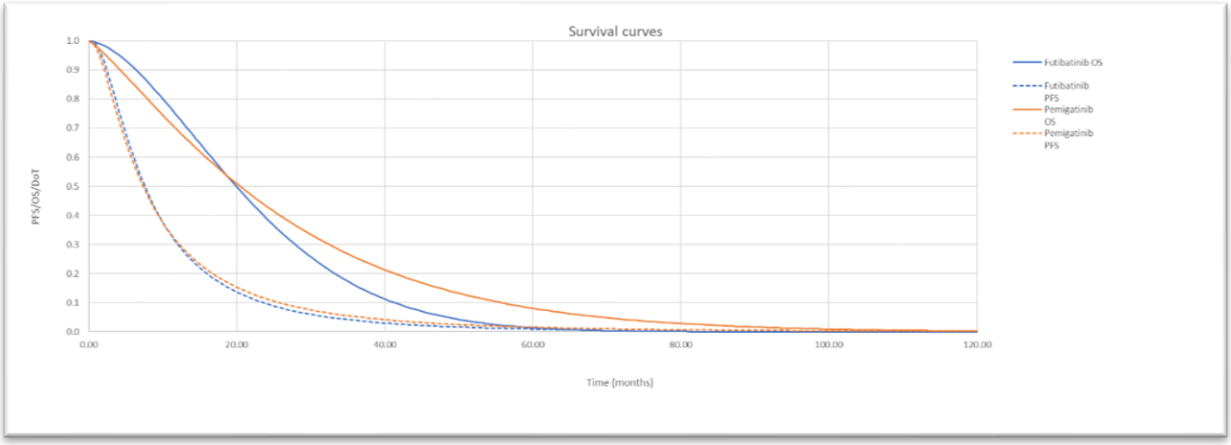
Cost item	Cost futibatinib (£)	Cost pemigatinib (£)	Increment (£)	Absolute increment (£)	(%) Absolute increment
Drug acquisition	[redacted]	£117,617	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	£0	[redacted]	[redacted]	[redacted]

Cost item	Cost futibatinib (£)	Cost pemigatinib (£)	Increment (£)	Absolute increment (£)	(%) Absolute increment
Monitoring and resource use	[redacted]	£3,624	[redacted]	[redacted]	[redacted]
AEs	[redacted]	£143	[redacted]	[redacted]	[redacted]
End of life costs	[redacted]	£6,492	[redacted]	[redacted]	[redacted]
Total	[redacted]	**£127,876**	[redacted]	[redacted]	[redacted]

Based on electronic model after clarification, with errors fixed by the EAG as described above.[1]
AEs = adverse events; EAG = External Assessment Group; PAS = Patient Access Scheme

The EAG considers that the results of its base-case are more in line with the survival data presented by the company compared to those of the company's base-case for the reasons explained next. In Figure 6.1, the survival curves selected for the EAG base-case are shown. It can be seen that both OS and PFS curves cross after some time, which is what was observed in the KM data shown in Figures 3.9 and 3.10. In the company's base-case, because PH were assumed for both OS and PFS, this did not happen. The OS curve for futibatinib was always higher than or equal to the pemigatinib OS curve and the opposite occurred for PFS. It might be argued that based on Figures 3.9 and 3.10, the number of patients at risk is relatively small when the curves cross, and therefore, there is uncertainty as to whether this will happen or not. However, the plots of the hazard functions in Figures 4.6 and 4.11, show that the hazard functions for futibatinib and pemigatinib cross well before the end of the KM curves follow-up time, which could be an indication that crossing survival functions is plausible. The EAG believes thus that the curves shown in Figure 6.1 are an appropriate representation of the current evidence on survival data. The uncertainty around the long-term behaviour of the futibatinib survival curves could be resolved if more data become available. In addition, Figure 6.2 shows a plot of the OS and PFS HRs over time based on the extrapolations selected for the EAG base-case. These plots show that both HRs are changing over time, which supports the EAG's choice of independent modelling (i.e., the PH assumption is violated since the HR is not constant), and both start below 1 (favouring futibatinib) but after some time they seem to converge to [redacted] (favouring pemigatinib), which is in line with crossing survival curves.

Figure 6.1: Survival curves selected in EAG's base-case



Based on electronic model after clarification, with errors fixed by the EAG as described above.[1]
DoT = duration of treatment; EAG = External Assessment Group; OS = overall survival; PFS = progression-free survival

Figure 6.2: HRs over time in EAG's base-case

Based on electronic model after clarification, with errors fixed by the EAG as described above.[1]
EAG = External Assessment Group; GP = general population; HRs = hazard ratios; OS = overall survival; PFS = progression-free survival

6.2.2 Results of the EAG PSA

Table 6.6 shows the results of the probabilistic EAG's base-case (discounted and assuming futibatinib PAS price). These indicated that futibatinib was less costly but also less effective than pemigatinib, accruing [redacted] incremental QALYs and saving [redacted] in total costs. These EAG's PSA results are comparable with the EAG base-case results. As in the EAG's base-case scenario, the expected ICER of the PSA results are also in the SW quadrant of the CE-plane. The CE-plane presented in Figure 6.3 shows that [redacted]. This indicates that futibatinib is [redacted] compared to pemigatinib. Based on the CEAC shown in Figure 6.4, the probability that futibatinib is cost effective at thresholds of £20,000 and £30,000 per QALY gained is [redacted].

Table 6.6: EAG base-case deterministic and EAG base-case PSA results (futibatinib PAS price, discounted)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
EAG base-case (futibatinib PAS price, discounted)					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	352,788*
Pemigatinib	128,216	[redacted]			
EAG PSA (futibatinib PAS price, discounted)					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	306,144*
Pemigatinib	121,087	[redacted]			

Based on electronic model after clarification, with errors fixed by the EAG as described above.[1]
* ICER in SW quadrant of the CE-plane.
CE = cost effectiveness; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 6.3: EAG probabilistic CE-plane

[redacted]

Based on electronic model after clarification, with errors fixed by the EAG as described above.[1]
CE = cost effectiveness; EAG = External Assessment Group; ICER = incremental cost-effectiveness; QALY = quality-adjusted life year

Figure 6.4: EAG probabilistic CEAC

[redacted]

Based on electronic model after clarification, with errors fixed by the EAG as described above.[1]
CEAC = cost effectiveness acceptability curve; EAG = External Assessment Group; WTP = willingness-to-pay

6.2.3 Results of the EAG additional exploratory scenario analyses

The results of the scenario analyses are provided in Table 6.7. These results are all conditional on the EAG base-case settings. The scenario analyses conducted by the EAG indicated that the results were reasonably stable for the alternative assumptions explored. In general, futibatinib seems to be less costly, and depending on the assumptions regarding the extrapolations of the survival curves, the incremental QALYs can be either positive or negative, but in any case, not far from 0.

Table 6.7: Results of exploratory scenario analyses by the EAG

Scenario	Assumption	Incr. costs	Incr. QALYs	ICER per QALY
EAG base-case		[redacted]	[redacted]	352,788*
OS alternative extrapolation options	Log-logistic	[redacted]	[redacted]	Dominant
	Generalised gamma	[redacted]	[redacted]	332,658*
	Log-normal	[redacted]	[redacted]	Dominant
PFS alternative extrapolation options	Weibull	[redacted]	[redacted]	241,442*
	Generalised gamma	[redacted]	[redacted]	258,241*
	Log-logistic	[redacted]	[redacted]	365,249*
HR-based approach of OS and PFS using unadjusted trial data	Dependent modelling of OS and PFS as per company's base-case (Log-normal)	[redacted]	[redacted]	Dominant
ToT alternative extrapolation options	Gompertz	[redacted]	[redacted]	356,467*
	Generalised gamma	[redacted]	[redacted]	355,470*
ToT independent of PFS	Remove restriction ToT<PFS	[redacted]	[redacted]	352,417*
Cost comparison	Futibatinib versus pemigatinib OS and PFS HR = 1 Equal rate of adverse events in both arms	[redacted]	[redacted]	Cost saving
Wastage costs	Exclude	[redacted]	[redacted]	343,732*
Genetic testing costs	Exclude	[redacted]	[redacted]	352,788*
Resource use frequency	Same frequency as reported by clinical experts in the Advisory Board Report	[redacted]	[redacted]	361,096*

Based on electronic model after clarification, with errors fixed by the EAG as described above.[1]
* ICER in SW quadrant of the CE-plane.
EAG = External Assessment Group; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; Inc. = incremental; OS = overall survival; PFS = progression free survival; ToT = time on treatment; QALY = quality-adjusted life year

6.3 EAG's preferred assumptions

The step-by-step changes made by the EAG to derive its base-case, using the CS base-case and the model submitted after clarification as starting point, can be seen in Table 6.8. The change with the largest impact on the results was the independent modelling of OS and PFS combined with removing the restriction on equal OS and PFS hazard rates after 24 months. Changing to independent modelling alone may result in invalid survival curves for pemigatinib. Therefore, independent modelling has to be used in combination without restricting the hazard rates after 24 months. This change led to a decrease in the incremental costs and to negative incremental QALYs. Independent modelling of ToT had also a substantial impact on the incremental costs, by reducing the difference between futibatinib and pemigatinib treatments. The impact of the other changes made by the EAG was minor.

Table 6.8: Individual impact of EAG preferred assumptions

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CS base-case					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	140,130	[redacted]			
CS base-case after the clarification					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	142,163	[redacted]			
Correction of the half-cycle correction implementation					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	135,191	[redacted]			
Independent modelling of OS (Weibull) and PFS (log-normal)*					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	117,775	[redacted]			
Remove restriction on equal OS and PFS hazard rates after 24 months					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	143,638	[redacted]			
Independent modelling of OS (Weibull) and PFS (log-normal) & remove restriction on equal OS and PFS hazard rates after 24 months					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	336,212**
Pemigatinib	136,821	[redacted]			
OS and PFS extrapolations based on (MAIC) adjusted data					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	138,497	[redacted]			
ToT modelled independent of PFS					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	124,703	[redacted]			
ToT modelled independent of PFS and restricted by PFS					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	116,671	[redacted]			

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Include costs of genetic testing					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Pemigatinib	142,503	[redacted]			
EAG's base-case					
Futibatinib	[redacted]	[redacted]	[redacted]	[redacted]	352,788**
Pemigatinib	128,216	[redacted]			

Based on the model submitted following the clarification phase.[1]

* This change (independent modelling) may result in invalid survival curves for pemigatinib since it has to be used together with the assumption "Remove restriction on equal OS and PFS hazard rates after 24 months". Therefore, looking at this change alone can be misleading.

** ICER in SW quadrant of the CE-plane.

CE = cost effectiveness; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; Inc. = incremental; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; ToT = time on treatment

6.4 Conclusions of the CE section

The CS[5] and response to clarification[7] provided sufficient details for the EAG to appraise the literature searches conducted to identify economic, HRQoL and cost data on adult patients treated with futibatinib and pemigatinib. Searches were conducted in October 2023. Searches were transparent and reproducible, and comprehensive strategies were used. Databases, conference proceedings and HTA resources were searched. Overall, the EAG has no major concerns about the literature searches conducted, although searches could have been more sensitive in order to minimise the risk of relevant records being missed.

The company's base-case complied with the NICE reference case. PROs were collected in the FOENIX-CCA2 trial, including EQ-5D-3L data. The utility values derived from these data used the UK tariff.

The key issues highlighted by the EAG throughout this report (and summarised in Table 6.1) were the following:

1) The EAG disagrees with the company's approach for modelling OS and PFS.
2) The EAG disagrees with the company's approach for modelling ToT.
3) The EAG is uncertain about the number of remaining errors in the company's model.

The first concern of the EAG in this submission regarding the CE evidence was related to the model structure. The company argued that the model structure in the current submission was in line with the model structure used in TA722. However, in TA722 the PSM employed five health states instead of three that were assumed in the current submission, because in TA722 ToT was modelled independently of PFS. The EAG considered that incorporating actual ToT data in the model could sufficiently impact the estimated treatment costs. Therefore, the EAG asked the company to add to the model a functionality to allow for independent modelling of ToT and PFS, which was included in the model version submitted with the clarification letter response.

Another EAG concern is related to the exclusion of mFOLFOX as comparator in the economic model. As explained in the clinical effectiveness sections of this report, the EAG does not concur with the company's rationale to disregard mFOLFOX from the relevant comparators claiming superiority of

pemigatinib over mFOLFOX based on the unanchored and improperly adjusted MAIC analyses in TA722.[22] According to the EAG, the company did not present any new evidence that would support the inferiority of mFOLFOX as compared to pemigatinib, while clinical opinion, although valued by the EAG, it should be used as a complementary to objective evidence. Therefore, since the economic analyses presented by the company in this submission did not include mFOLFOX as comparator, their results should be reassessed should mFOLFOX be considered a relevant comparator for this appraisal.

As mentioned above, the EAG main concerns are related to the implementation of treatment effectiveness (OS, PFS and ToT) in the economic model. The main points of concern are summarised below:

- The EAG questions the plausibility of the PH assumption for both OS and PFS, given that crossing survival curves and hazard functions were reported. Therefore, the EAG prefers to employ an independent modelling approach to extrapolate OS and PFS for both futibatinib and pemigatinib.
- The company selected the OS and PFS extrapolation models for futibatinib based on unadjusted survival data (FOENIX-CCA2 data not matched to the FIGHT-202 trial), while the HR as estimated from the MAIC analysis was used for the pemigatinib OS and PFS curves. However, the EAG is unclear why the company used the unadjusted curves for futibatinib while implementing an HR based on the MAIC analysis for pemigatinib. The appropriate methodology of a MAIC requires balanced populations in terms of treatment effect modifiers (and prognostic factors in unanchored MAICs), so using unadjusted curves while implementing an adjusted MAIC-derived HR does not seem to meet this requirement. The EAG preferred thus extrapolation options based on adjusted survival data for both OS and PFS.
- To support the selection of extrapolation models, the company used clinical feedback based on futibatinib only (but not on pemigatinib). However, clinical experts provided feedback on extrapolations of both futibatinib and pemigatinib treatments. The EAG is also unclear why this approach was chosen since clinicians would be expected to have more experience from using pemigatinib treatment and hence their feedback on the validation of the pemigatinib extrapolations should have been considered.
- As mentioned above, the EAG's preferred approach to extrapolate OS and PFS would be independent modelling for both futibatinib and pemigatinib. When the company explored this scenario, different types of extrapolations were selected for pemigatinib and futibatinib. However, this approach (selecting different parametric extrapolations for different treatment arms) is not recommended by TSD14,[25] given the similar mechanism of action of futibatinib and pemigatinib treatments. Therefore, the EAG prefers using the same type of distribution for both arms when selecting independent models.
- The EAG base-case analysis employed an independent modelling approach for OS and PFS based on the adjusted data for the futibatinib arm (FOENIX-CCA2 data matched to the FIGHT-202 trial data). A Weibull distribution was chosen for OS and a log-normal distribution for PFS.
- The EAG was unclear why the company did not include ToT data for futibatinib from the FOENIX-CCA2 trial given their availability, instead of assuming that ToT would be equal to PFS. As requested by the EAG, in the model submitted after clarification, ToT and PFS curves were allowed to be modelled independently, with the additional restriction that ToT ≤ PFS. The EAG preferred this approach. For pemigatinib, the PFS HR estimated from the MAIC would be the best approach considering the lack of the pemigatinib data (even though there is uncertainty as to whether the same HR observed for PFS would be observed for ToT). The EAG also agreed with the company's choice to use a Weibull model for extrapolating ToT.

Regarding AEs, the company noted that not all AEs included in TA722 meet the inclusion criteria for either the FOENIX-CCA2 or the FIGHT-202 trials or were not reported in the latest data cut for FIGHT-202,[14] and for that reason were not included in the model. In addition, the company explained that grade 2+ hyperphosphatemia was additionally included in the model, given the high proportion of patients experiencing it in the FOENIX-CCA2 trial. In any case, the impact of AE-related assumptions on the CE results is expected to be minor seeing how the AEs contribute to both the cost and QALY calculations.

In terms of HRQoL, the company indicated that a MMRM with progression status as covariate was used to derive the utilities included in the base-case analysis. However, the results of such analyses were not reported in the CS. Therefore, the EAG is unable to comment on the validity of such analyses and, therefore, on the utilities derived from them. Regarding the (face) validity of the EQ-5D values presented by the company, UK clinical experts considered the value assumed for the PD heath state slightly higher than expected. This was based on the hypothesis that this may have been caused by most HRQoL assessments being completed early after disease progression, and highly symptomatic patients not completing the questionnaire regularly after that. However, the company considered that the PD utility value has a minor impact on the model results since both PFS and OS are similar between futibatinib and pemigatinib, and the same utility value is applied to both treatments. The company did vary the PF and PD utilities by ±20% in their DSA and the change in results was indeed minimal.

The EAG agreed in general with the company in the approach taken to model resource use and costs. There were several minor issues detected which are not expected to have a significant influence on the model results. The EAG noticed that the cost per futibatinib [redacted]. In the economic model the company is calculating [redacted]. The company also explained that patients may discontinue treatment (upon either toxicity or disease progression) at any point during a model cycle, and as a consequence patients will not make the full cost for that treatment cycle. In the economic model it is assumed that patients would on average discontinue treatment halfway through a treatment cycle (3 weeks). Drug wastage was also included as an option in the model, but the calculations use PFS to identify patients (still) on treatment, and ToT to account for those who stop treatment. However, the EAG considers that only ToT should be used in the calculations. Finally, the addition of genetic testing does not have an impact on the incremental costs since these costs are equally applied to both arms. However, the EAG noticed that in the CS, the company reported the genetic testing costs to be £34, whereas the economic model uses £340. In the economic model, the company seems to have weighted this cost for to a cost per person, using a prevalence of FGFR2 fusion or rearrangement to be 10%. However, since the cost in both arms increased with the same amount this change did not influence the results.

The company's base-case deterministic CE (discounted) results for futibatinib (assuming PAS price) compared to pemigatinib indicated that futibatinib was less costly and more effective than pemigatinib, accruing [redacted] incremental QALYs and saving [redacted] in total costs. Therefore, futibatinib dominates pemigatinib in the company's base-case scenario. When accounting for disease severity, considering a QALY weight of 1.2, incremental QALYs were now [redacted] and futibatinib was still dominant compared to pemigatinib. These results were obtained after the EAG corrected the implementation of the half-cycle correction in the original model. Total costs, life years and QALYs were smaller for both arms, but incrementally, results were similar to those presented originally by the company. The average PSA results were overall in line with the deterministic, even though PSA incremental costs were larger (more

negative) and PSA incremental QALYs smaller. The plot of the PSA outcomes on the CE-plane indicated that [redacted]. From the CEAC, it could be seen that at the common thresholds of £20,000 and £30,000 per QALY gained, the estimated probability that futibatinib is a cost-effective alternative to pemigatinib was [redacted]. However, it should be noted that the EAG identified many errors in the company's original model, most of them related to the implementation of the PSA. Given the lack of time, the EAG did not correct these PSA-related errors in the company's original model. Therefore, the company's PSA results presented in this report are based on the model including the errors. For the EAG base-case and PSA, the EAG corrected the model as much as possible. However, given the numerous errors encountered and the lack of time to continue technically validating the company's model, the EAG is concerned that additional errors may still be present in the model. The company's DSAs and scenario analyses showed that most assumptions on input parameters had a minor impact on the model results, except for the HRs for OS and PFS, when PH models are assumed for survival data extrapolation. In general, these analyses did not change the main conclusions from the base-case. However, the EAG considers that independent modelling of survival curves, and modelling ToT separately from PFS, should have been explored by the company as well. The EAG would like to stress again that these results and conclusions are based on the model with uncorrected errors. The EAG did not rerun the company scenarios given the lack of time. The EAG expects that the effect of correcting these errors (such as the half-cycle correction) on the scenario analysis results would be comparable to what was observed after correcting the company's base-case.

The EAG defined a new preferred base-case by first correcting the errors listed in Section 6.1.3, and then:

1. Assuming independent modelling of OS (Weibull) and PFS (log-normal) curves.
2. Removing the assumption that hazard rates for OS and PFS are equal between futibatinib and pemigatinib when all patients have discontinued treatment (this does not apply under independent modelling, only under PH).
3. Fitting OS and PFS extrapolations on (MAIC) adjusted data.
4. Modelling ToT independently of PFS (assuming ToT <= PFS) and assuming a Weibull distribution.
5. Including the costs of genetic testing for FGFR2.

The results of the EAG's base-case analysis indicated that futibatinib was less costly but also less effective than pemigatinib, accruing [redacted] incremental QALYs and saving [redacted] in total costs, with an ICER in the SW quadrant of the CE-plane. In this situation, large ICERs are favoured when compared to common thresholds. When accounting for disease severity, considering a QALY weight of 1.2, incremental QALYs were now [redacted], which keeps the ICER in the SW quadrant. Compared to the company's base-case after clarification, the incremental costs were reduced by approximately [redacted], whereas the incremental QALYs became negative. The EAG's average PSA results were comparable with the EAG base-case results. The PSA ICER was also in the SW quadrant of the CE-plane. The plot of the PSA outcomes on the CE-plane showed that [redacted]. This indicates that futibatinib is [redacted] compared to pemigatinib. The CEAC estimated the probability that futibatinib is cost effective at thresholds of £20,000 and £30,000 per QALY gained at [redacted]. The scenario analyses conducted by the EAG indicated that the results were reasonably stable for the alternative assumptions explored. In general, futibatinib seems to be less costly, and depending on

the assumptions regarding the extrapolations of the survival curves, the incremental QALYs can be either positive or negative, but in any case, not far from 0.

7. References

[1] Taiho Pharma Europe Limited. *Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [ID6302]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Taiho CE model v1.0 14032024* Taiho Pharma Europe Ltd, 2024

[2] National Institute for Health and Care Excellence. *Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement. Technology appraisal guidance [TA722]. Recommendations [Internet]*, 2021 [accessed 11.5.23] Available from: https://www.nice.org.uk/guidance/ta722/chapter/1-Recommendations

[3] National Institute for Health and Care Excellence. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement. Technology appraisal guidance [TA722]. Committee discussion. 2021 [accessed 11.5.23];

[4] National Institute for Health and Care Excellence. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement. Technology appraisal guidance [TA722] [Internet]. 2021 [accessed 4.5.23].

[5] Taiho Pharma Europe Limited. *Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [ID6302]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Document B - Company evidence submission*: Taiho Pharma Europe Ltd, 2024. 120p.

[6] National Institute for Health and Care Excellence. *Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [ID6302]: Clarification questions*. London: NICE, 2024. 16p.

[7] National Institute for Health and Care Excellence. *Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [ID6302]: Response to request for clarification from the EAG*: Taiho Pharma Europe Limited, 2024. 71p.

[8] National Institute for Health and Care Excellence. *Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [ID6302]: Final scope [Internet]*. London: NICE, 2023 [accessed 6.2.24]. 4p. Available from: https://www.nice.org.uk/guidance/gid-ta11371/documents/final-scope

[9] Taiho Pharma Europe Limited. *Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [ID6302]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Appendices*: Taiho Pharma Europe Ltd, 2024. 101p.

[10] McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline statement. J Clin Epidemiol 2016; 75:40-6

[11] Canadian Agency for Drugs and Technologies in Health. *PRESS - Peer Review of Electronic Search Strategies: 2015 Guideline Explanation and Elaboration (PRESS E&E) [Internet]*. Ottawa: CADTH, 2016 [accessed 16.11.20] Available from: https://www.cadth.ca/resources/finding-evidence/press

[12] Taiho Oncology. *FOENIX-CCA2 Clinical Study Report. DCO 29 May 2021 [PDF provided by Company]*, 2021

[13] Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol 2020; 21(5):671-684

[14] Vogel A, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, et al. Pemigatinib for previously treated locally advanced or metastatic cholangiocarcinoma: final results from FIGHT-202. Ann Oncol 2022; 33:S379

[15] Valle JW, Bibeau K, Cho Y, Ren H, Féliz L, Lihou CF, et al. Longitudinal evaluation of quality of life (QoL) in patients (Pts) with FGFR2-driven cholangiocarcinoma (CCA) treated with pemigatinib. J Clin Oncol 2021; 39(3):S276

[16] Subbiah V, Iannotti NO, Gutierrez M, Smith DC, Feliz L, Lihou CF, et al. FIGHT-101, a first-in-human study of potent and selective FGFR 1-3 inhibitor pemigatinib in pan-cancer patients with FGF/FGFR alterations and advanced malignancies. Ann Oncol 2022; 33(5):522-533

[17] Rodon J, Damian S, Furqan M, Garcia-Donas J, Imai H, Italiano A, et al. Abstract CT016: Clinical and translational findings of pemigatinib in previously treated solid tumors with activating FGFR1-3 alterations in the FIGHT-207 study. Cancer Res 2023; 82(S8):CT016

[18] Shi GM, Huang XY, Wen TF, Song TQ, Kuang M, Mou HB, et al. Pemigatinib in previously treated Chinese patients with locally advanced or metastatic cholangiocarcinoma carrying FGFR2 fusions or rearrangements: a phase II study. Cancer Med 2023; 12(4):4137-4146

[19] Shi G, Huang X, Wen T, Song T, Kuang M, Mou H, et al. Pemigatinib in Chinese patients with advanced/metastatic or surgically unresectable cholangiocarcinoma including FGFR2 fusion or rearrangement: Updated data from an open-label, single-arm, multicenter phase II study (CIBI375A201 study). J Clin Oncol 2022; 40(16_suppl):e16183-e16183

[20] Barraclough H, Govindan R. Biostatistics primer: what a clinician ought to know: subgroup analyses. J Thorac Oncol 2010; 5(5):741-6

[21] Welton NJ, Phillippo DM, Owen R, Jones HJ, Dias S, Bujkiewicz S, et al. *NICE DSU Report. CHTE2020 sources and synthesis of evidence; update to evidence synthesis methods*. Sheffield: Decision Support Unit, ScHARR, 2020. 98p. Available from: https://www.sheffield.ac.uk/media/34043/download?attachment

[22] National Institute for Health and Care Excellence. *Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations [ID3740]. Committee papers [Internet]*. London: NICE, 2021 [accessed 28.4.23] Available from: https://www.nice.org.uk/guidance/ta722/documents/committee-papers

[23] MHRA. Lytgobi. Summary of product characteristics [Internet]. [accessed 17.11.23]. Available from: https://mhraproducts4853.blob.core.windows.net/docs/fb49eac7d9ca87a7e57a0df17095e2db95a12a55

[24] Taiho Oncology. *FOENIX-CCA2 Advisory Board Report. 22 May 2023 [Data on File]. PDF provided by Company*, 2023

[25] Latimer N. *NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data.* Sheffield: Decision Support Unit, ScHARR, 2011. 52p. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf

[26] Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Med Res Methodol 2011; 11:61

[27] Royston P, Altman DG. Regression using fractional polynomials of continuous covariates: parsimonious parametric modelling. J R Stat Soc Ser C Appl Stat 1994; 43(3):429-453

[28] Arkenau T. Arkenau NDA. Email to R. Wolff, 12 April 2024. 2024.

[29] Taiho. *Advisory Board Report [Data on file]. PDF provided by Company*, 2023. 35p.

[30] Taiho Oncology. *FOENIX-CCA2 Clinical Study Protocol Amendment 10 [Data on File]. PDF provided by Company*

[31] Dolan P. Modeling valuations for EuroQol health states. Med Care 1997; 35(11):1095–1108

[32] Lamarca A, Palmer D, Wasan HS, Ross P, Ma YT, Arora A, et al. Quality of life (QoL) and value of health (V-He) in advanced biliary cancers (ABC) treated with second-line active-symptom-control (ASC) alone or ASC with oxaliplatin/5-FU chemotherapy (ASC+FOLFOX) in the randomised phase III, multi-centre, open-label ABC-06 trial. Ann Oncol 2022; 33(7_suppl):S564–S565

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

[34] University of Sheffield, NICE Decision Support Unit. *Estimating EQ-5D by age and sex for the UK [Internet]*, [accessed 14.8.23] Available from: https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d

[35] Taiho Oncology. *FOENIX-CCA2 Clinical Study Protocol [Data on File]. PDF provided by Company*

[36] National Institute for Health and Care Excellence. *Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel. Technology appraisal guidance [TA391] [Internet]*. London: NICE, 2016 [accessed 2.8.23] Available from: https://www.nice.org.uk/guidance/ta391

[37] National Institute for Health and Care Excellence. *Cetuximab and panitumumab for previously untreated metastatic colorectal cancer. Technology appraisal guidance [TA439] [Internet]*. London: NICE, 2017 [accessed 2.8.23] Available from: https://www.nice.org.uk/guidance/ta439

[38] British National Formulary (BNF) [Internet]. London: BNF Publications, [accessed 3.8.23]. Available from: https://bnf.nice.org.uk/

[39] NHS Improvement. National schedule of reference costs 2017/18 [Internet]. London: Department of Health, 2018 [accessed 6.11.19]. Available from: https://webarchive.nationalarchives.gov.uk/ukgwa/20200501111106/https://improvement.nhs.uk/resources/reference-costs/

[40] British National Formulary. Pemigatinib [Specialist drug]. Medicinal forms [Internet]. [accessed 3.8.23]. Available from: https://bnf.nice.org.uk/drugs/pemigatinib-specialist-drug/medicinal-forms/

[41] Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: a modelling study. Palliat Med 2015; 29(10):899-907

[42] NHS England. National genomic test directory [Internet]. [accessed 17.5.23]. Available from: https://www.england.nhs.uk/publication/national-genomic-test-directories/

[43] National Institute for Health and Care Excellence. *NICE health technology evaluation topic selection: the manual [PMG37] [Internet]*. London: National Institute for Health and Care Excellence, 2022 [accessed 5.3.24] Available from: https://www.nice.org.uk/process/pmg37/chapter/about-this-guide

[44] Versteegh MM, Ramos IC, Buyukkaramikli NC, Ansaripour A, Reckers-Droog VT, Brouwer WBF. Severity-adjusted probability of being cost effective. Pharmacoeconomics 2019; 37(9):1155-1163

[45] Taiho Pharma Europe Limited. *Futibatinib for previously treated advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [ID6302]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Taiho CE model v2.0 23022024*: Taiho Pharma Europe Ltd, 2024

[46] Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. Med Decis Making 2012; 32(5):733-43

[47] Vemer P, Corro Ramos I, van Voorn GA, Al MJ, Feenstra TL. AdViSHE: a validation-assessment tool of health-economic models for decision makers and model users. Pharmacoeconomics 2016; 34(4):349-61

[48] Büyükkaramikli NC, Rutten-van Mölken MPMH, Severens JL, Al MC, C. N, Büyükkaramikli MPMH, et al. TECH-VER: a verification checklist to reduce errors in models and improve their credibility. Pharmacoeconomics 2019; 37(11):1391-1408

[49] CADTH. CADTH Reimbursement Review: Pemigatinib (Pemazyre). Can J Health Technol 2022; 2(6)

[50] Grimm SE, Pouwels X, Ramaekers BLT, Wijnen B, Knies S, Grutters J, et al. Development and Validation of the TRansparent Uncertainty ASsessmenT (TRUST) Tool for assessing uncertainties in health economic decision models. Pharmacoeconomics 2020; 38(2):205-216

[51] Kaltenthaler E, Carroll C, Hill-McManus D, Scope A, Holmes M, Rice S, et al. The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis. Health Technol Assess 2016; 20(26):1-48

Single Technology Appraisal

Futibatinib for Previously Treated Advanced Cholangiocarcinoma with FGFR2 Fusion or Rearrangement [ID6302]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG 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 30 April 2024** 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 information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

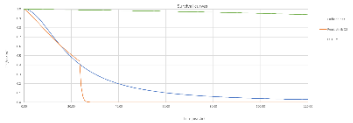
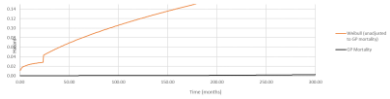
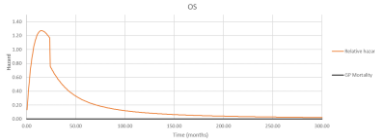
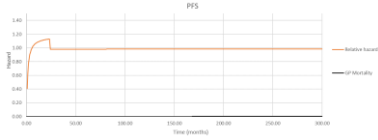
Section 1. Executive summary

Issue 1 Description of the assumption that hazard rates for OS and PFS are equal between futibatinib and pemigatinib when all patients have discontinued treatment under independent modelling

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
In Section 1.1 (page 12), the following is stated: "The assumption that hazard rates for OS and PFS are equal between futibatinib and pemigatinib when all patients have discontinued treatment (company) does not apply under independent modelling." In Section 6.1.3.3 (page 130), the following is stated: "The assumption that hazard rates for OS and PFS are equal between futibatinib and pemigatinib when all patients have discontinued treatment does not apply under independent modelling. In their base-case, PH for OS and PFS were assumed. The company included in the model the option to	Please amend any text stating that the assumption that hazard rates for OS and PFS are equal between futibatinib and pemigatinib when all patients have discontinued treatment "does not apply" under independent modelling. Any text suggesting that extrapolations are "invalid" when such an assumption is applied should also be removed or amended. It should also be acknowledged that removing this assumption under independent modelling implicitly assumes differences in hazard rates (i.e. continued treatment effects) post discontinuation, which is in contrast to the EAG's preference under dependent modelling. The company also request that the EAG reconsider their preferred	It is factually inaccurate to state that this assumption "does not apply" in the case where independent models are used; assuming hazards are equalised following treatment discontinuation is an accepted approach regardless of the choice of independent or dependent models, unless there is a clinical rationale for differences in treatment effect post-discontinuation (such as in the case of therapies with different mechanisms of action or differences in subsequent treatments), which has not be adequately acknowledged by the EAG. Equalisation of hazards post-discontinuation under independent modelling has been applied in prior NICE appraisals, for example in the submission for nivolumab with	The EAG would like to clarify several points here: 1. The PH model assumes (and imposes) a lifetime treatment effect that it is not necessarily supported by the data. In that sense, independent modelling is different because the magnitude of the treatment effect, if any, is driven by the data and not by assumptions. 2. In clarification question B5, the EAG asked the company to present the results of a scenario in which when ToT = 0 (i.e., all patients have progressed or stopped due to toxicity, or died) there is no more treatment effect on OS,

use the same hazard rates for both OS and PFS after all patients have discontinued treatment (after 24 months). Otherwise, under PH, this would imply a continued treatment effect. When independent modelling is assumed, this option is no longer needed since PFS and OS are directly defined by the selected extrapolations (sheet "Settings" – row 53)."	assumptions to address this contradiction. If the EAG's preference is to remove this assumption under independent modelling, such that PFS and OS are directly defined by the selected extrapolations, this should be acknowledged as a preference, and a clinical justification provided.	ipilimumab for untreated advanced renal cell carcinoma (TA780).[1] In the case of futibatinib, the EAG have acknowledged that there is no clinical rationale for differences in long-term treatment effect once all patients have discontinued treatment, particularly given futibatinib or pemigatinib share the same mechanism of action. Furthermore, subsequent treatments following both treatments are also expected to be identical (usually consisting of the mFOLFOX chemotherapy regimen for the patients who are able to tolerate it, or BSC) based on UK clinical expert feedback. The EAG state in Table 1.10 that their preference is to assume "OS benefit modelled as long as patients are on treatment", which contradicts the removal of this assumption when independent models are applied. The company agree with the EAG that no continued treatment effect post-discontinuation should be modelled for either	but also to conduct other scenario analyses that are considered relevant to test the assumption of treatment effect waning (the latter were not provided). In their response, the company *"agree that no benefit between futibatinib and pemigatinib is expected beyond the point where no more patients are receiving treatment"*. However, it was never stated in the clarification letter that this was the EAG's preferred approach. In fact, because the EAG considered it uncertain, we asked the company to conduct more scenarios around this assumption. 3. It was the company's choice to update the model such that the hazard rates for OS and PFS for pemigatinib are set equal to those of futibatinib after a selected timepoint, which was set to 24 months, at which ~11% and ~12% of

		futibatinib or pemigatinib, but this remains true regardless of the selected modelling approach.	patients on futibatinib and pemigatinib. It should be noted that this is not the same as the scenario the EAG asked for, and it has several issues associated: for example, the cut-off point of 24 months seems arbitrarily selected and it is unclear why only the pemigatinib curves are changed after this point. 4. The EAG would like to confirm that a combination of model settings can indeed lead to invalid survival curves or hazard functions. To be more specific, the EAG report states *"The change with the largest impact on the results was the independent modelling of OS and PFS combined with removing the restriction on equal OS and PFS hazard rates after 24 months. Changing to independent modelling alone may result in invalid survival curves for pemigatinib"*. The EAG

			considers these extrapolations below invalid (all plots taken from the model) where the survival functions, hazards functions and hazard ratios take invalid forms.     The EAG does not know the cause of this, since we were

			unable to further explore the model due to time constraints. 5. The EAG would like to acknowledge that the sentence *"OS benefit modelled as long as patients are on treatment"* in Tables 1.10 and 6.2 should have been removed. 6. To summarise: the EAG prefers independent modelling. Under PH, the EAG questioned the validity of a lifetime treatment effect. It was the company's choice to implement a cap in the treatment effect at 24 months and, as far as we are concerned, this choice was also based on preference without clinical justification provided. Some justification has been presented now, but not at the time of writing the report. Equalizing hazards after discontinuation is one possible approach to treatment effect waning, but other scenarios should have been

			explored as requested in clarification question B5. Because of this, the arbitrary selection of the time point where hazards are equal and the invalid curves that sometimes are observed in the model, the EAG prefers to stick with their current approach of independent modelling with no further restrictions.

Issue 2 Description of the company's argumentation for including mFOLFOX as a relevant comparator

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 1.3, Table 1.2 (page 13) states the following: "The case made by the company for omitting mFOLFOX from the decision problem is based on one analysis carried out as part of TA722, which has shown that pemigatinib may be more effective than mFOLFOX and symptom control. The conclusion is therefore that it is unnecessary to include mFOLFOX because if pemigatinib is	Please remove or amend the statements regarding the uncertainty of the benefit of pemigatinib over chemotherapy.	These statements are a misrepresentation of the argumentation in the company submission, in particular with regard to the role of expert feedback and clinical guidelines. The clinical expert feedback was not presented to justify a survival benefit for pemigatinib over chemotherapy, which is not a consideration within the scope of this appraisal. However, the clinical feedback reflects the	Not a factual inaccuracy. Table 1.2 correctly refers to Section 2.3 of the EAG report which provides a comprehensive summary of the clarification provided by the company as well as the concerns raised by the EAG regarding omitting mFOLFOX.

superior to mFOLFOX, then any superiority of futibatinib over pemigatinib would automatically imply superiority of futibatinib over mFOLFOX as well. <…> The company suggested that omission of mFOLFOX is also supported by guideline positions and expert clinical opinion, but these guidelines recommend pemigatinib as an option, and mFOLFOX continues to be recommended." This issue is also present in Section 3.6 (page 82): "For mFOLFOX to be justifiably omitted, it would need to be shown to be inferior to pemigatinib in the same population, but the company were unable to provide sufficiently strong evidence that pemigatinib was superior to mFOLFOX. This was a concern because it meant that any demonstration of superiority for futibatinib over pemigatinib would not necessarily indicate futibatinib was better than mFOLFOX."		current UK clinical practice: as stated by the experts, the patient population of relevance to this submission would normally receive pemigatinib in the current practice (any uncertainty in its comparative efficacy notwithstanding).[2] Similarly, the argumentation around clinical practice guidelines has been misrepresented. For clarity, the British Society of Gastroenterology (BSG) 2023 guidelines state that CCA should be subjected to molecular profiling as soon as possible, and treatment options for targetable alterations such as FGFR2 fusions or rearrangements should be considered (i.e. pemigatinib, as the only NICE-recommended treatment targeting FGFR2 fusions or rearrangements in current UK clinical practice).[3] The European Society of Medical Oncology (ESMO) guidelines (2022), which were noted by clinical experts to be relevant to UK practice, present a more specific treatment pathway for patients with FGFR2	

This issue is also present in Section 4.2.4 (page 89): "The main concerns of the EAG relates to the omission of mFOLFOX from the comparators list. Although the EAG accepts the company's decision to omit BSC from the current analyses (see EAG comments in Section 2.4), the EAG does not concur with the company's rationale to disregard mFOLFOX from the relevant comparators claiming superiority of pemigatinib over mFOLFOX based on the unanchored and improperly adjusted MAIC analyses in TA722.[22] As explained in the EAG comments in Section 2.4, the company did not present any new evidence that would support the inferiority of mFOLFOX as compared to pemigatinib, while clinical opinion, although valued by the EAG, it should be used as a complementary to objective evidence." This issue is also present in Section 6.4 (page 141):		fusions or rearrangements, and they preferentially recommend pemigatinib over chemotherapy alternatives.[4] Therefore, although clinical guidelines cannot and were not used by the company to suggest that mFOLFOX is not a treatment option for patients with CCA, they do support the clinical opinion on current UK clinical practice for using pemigatinib over chemotherapy in eligible patients with FGFR2 fusions or rearrangements. Consequently, futibatinib is positioned as a direct alternative to pemigatinib for eligible patients, and not as an alternative to mFOLFOX. This was also acknowledged by NHS England in their budget impact submission for this appraisal. As such, any uncertainty regarding the benefit of pemigatinib over chemotherapy is not a relevant consideration for this appraisal, nor is it something the company in this appraisal should be reasonably expected to comment on. For this reason, related statements should be	

"As explained in the clinical effectiveness sections of this report, the EAG does not concur with the company's rationale to disregard mFOLFOX from the relevant comparators claiming superiority of pemigatinib over mFOLFOX based on the unanchored and improperly adjusted MAIC analyses in TA722.[22] According to the EAG, the company did not present any new evidence that would support the inferiority of mFOLFOX as compared to pemigatinib, while clinical opinion, although valued by the EAG, it should be used as a complementary to objective evidence."		either amended to correctly reflect the argumentation in the company submission or completely removed from the EAG report.	

Issue 3 Omission of response rates from the MAIC analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 1.4, Table 1.9 (page 17) states that in order to resolve some uncertainty around the MAIC analyses, it might help to "Perform ITCs for **response rates and** HRQoL."	Please amend to "Perform ITCs for HRQoL."	A MAIC analysis for response rates has already been presented by the company in the response to the clarification question number A.20.	Amended accordingly.

Issue 4 Contradiction in EAG preferences for the preferred modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
In Section 1.5, Table 1.10 (page 18) states: "Because survival and hazard curves for futibatinib and pemigatinib cross after some time futibatinib may no longer be dominant (ICER in SW quadrant of the CE-plane)."	Please reconsider this text in the context of the stated EAG preference, provided in the same table, for "OS benefit to be modelled as long as patients are on treatment", i.e. there should be no OS benefit following discontinuation.	Crossing of survival and hazard curves post-discontinuation is not clinically plausible, as acknowledged by the EAG in their preference for OS benefit to be modelled as long as patients are on treatment.	Please refer to the response to issue 1 in this section.

Issue 5 Clarification of follow-up duration

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 1.6 (page 20) states: "The single-study trial data of 103 patients in the specified population demonstrated futibatinib was associated with an OS at 12 months of 73.1%, a PFS of 35.4% at 12 months, complete response (CR) in 1% and partial response (PR) in 42% at the final data cut-off (DCO) (median 25 months), and a	Please amend to: "The single-study trial data of 103 patients in the specified population demonstrated futibatinib was associated with an OS at 12 months of 73.1%, a PFS of 35.4% at 12 months, complete response (CR) in 1% and partial response (PR) in 42% at the final data cut-off (DCO) (median **follow-up** 25	To avoid possible misunderstandings of the meaning of "25 months".	Amended accordingly.

mean improvement of EuroQoL visual analogue scale (EQ VAS) of 4.76 points at 9 months.”	months), and a mean improvement of EuroQoL visual analogue scale (EQ VAS) of 4.76 points at 9 months.”		

Section 2. Critique of company’s definition of decision problem

Issue 1 Formatting of outcomes in the decision problem

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment

In Section 2, Table 2.1 (page 24), the outcomes addressed in the company submission are listed as follows:
 	
• Efficacy data
• ORR
• DOR
• PFS
• OS
• DCR
• HRQoL data
• EORTC QLQ-C30
• EQ-5D-3L
• EQ VAS
• AE data
	Please adjust the hierarchy of the list:
	
	• Efficacy data
	  ○ ORR
	  ○ DOR
	  ○ PFS
	  ○ OS
	  ○ DCR
	• HRQoL data
	  ○ EORTC QLQ-C30
	  ○ EQ-5D-3L
	  ○ EQ VAS
	• AE data
		To clarify the classification of the outcomes presented in the company submission, to avoid any confusion.	Formatting updated accordingly.

Section 3. Clinical effectiveness

Issue 1 Formatting of outcomes in the decision problem

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 3.2.1 (page 37) states: "Ninety-six (**93.25**) patients had discontinued treatment by the time of the data cut off (DCO)."	Please amend to: "Ninety-six (**93.2**) patients had discontinued treatment by the time of the data cut off (DCO)."	The percentage is 93.20%.	Amended accordingly.

Issue 2 Sources of figures

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The source for Figure 3.1 in Section 3.2.5.1 is stated as: "Based on Figure **9**, CS" Source of Figure 3.3 (Section 3.2.5.3, page 56) is not provided	Please amend source of Figure 3.1 to: "Based on Figure **10**, CS" Please add the source for Figure 3.3: "**Based on Figure 7, CS**"	Figure 10 and Figure 7 of the company submission present the data reproduced in Figures 3.1 and 3.3, respectively	Amended accordingly.

Issue 3 Typographic error

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 3.2.5.4 (page 58) states: "Several measures of HRQoL were reported to be measured - EORTC QLQ-C30, EQ-5D-3L, EQ VAS. **QQ-VAS.**"	Please amend to: "Several measures of HRQoL were reported to be measured - EORTC QLQ-C30, EQ-5D-3L, EQ VAS."	Typographic error	Amended accordingly.

Issue 4 Clinically meaningful change in EORTC QLQ-C30

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
In Section 3.2.5.4, Table 3.17 (page 59), the scale value change for constipation at Cycle 4 is not bolded: "+10.0 (34.9)"	Please **bold** this value.	In line with the footnote provided in this table, a 10-point change from baseline for EORTC QLQ-C30 scores was predefined as the minimally important difference to designate a change as clinically meaningful (shown in bold).	Amended accordingly.

Issue 5 Clinical effectiveness values

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 3.6 (page 82) states: "This demonstrated futibatinib was associated with an OS at 12 months of 73.1%, a PFS of 35.4% at 12 months, CR in 1% and PR in 42% at the final DCO (median 25 months."	Please amend to: "This demonstrated futibatinib was associated with an OS at 12 months of 73.1%, a PFS of 35.4% at 12 months, CR in 1% and PR in **40.8%** at the final DCO (median **follow-up** 25 months)."	In line with Table 13 and page 42 of Document B of the company submission.	Amended accordingly.

Section 4. Cost effectiveness

Issue 1 EAG implementation of half cycle correction

Description of problem	Description of the amendment	Justification for amendment	EAG comment
Section 5.2.1 (page 119) states: "Incorrect implementation of half-cycle correction on the 'Patient flow' sheet"	The company acknowledges the error in the implementation of half-cycle correction in the submission model, and apologise for this oversight. However, the company would note that the amendment of the error by the EAG was not applied in cycle 0 of the model (Patient flow tab: N8:P8, Z8:AB8	To ensure accuracy of presented model results.	The EAG would like to thank the company for correcting this error. Given the minor impact on the model results, the EAG prefers to keep the report as it is now, otherwise, all analyses reported in Chapter 6 need to be repeated, which is unfeasible at this moment. We

	and AL8:AN8). The company have updated this in the model to ensure half cycle correction has been applied in every cycle. Results for the company base case (after the response to clarification questions) is provided in the appendix. Whilst this had a very small impact on the results, the EAG results may also need updating to account for this.		have added a sentence to Section 6.1.3.1 of the EAG report to explain this issue.

Issue 2 Acknowledgement of NICE reference case

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.1, Table 4.2 (page 86) states: "PROs collected in FOENIX-CCA2 included EQ-5D-3L data. The utility values derived from these data used the UK tariff"	Please amend to: "PROs collected in FOENIX-CCA2 included EQ-5D-3L data. **As per the reference case,** the utility values derived from these data used the UK tariff"	The UK tariff used in the valuation of the utility values was based on a representative sample of the UK population, as per NICE preferences. Thus this approach is aligned to the NICE reference case, and this should be acknowledged in the NICE reference case checklist.	Amended accordingly.

Issue 3 Independent modelling of ToT and PFS

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.2 (page 88) states: "To further elaborate, independent modelling of ToT and PFS curves in TA722 indicated that PF patients on pemigatinib can still remain in PF while not on treatment and can, therefore, have lower treatment costs than the costs that are estimated if ToT is assumed to be equal to PFS. Using the PFS curve as an upper bound of the ToT curve in TA722, as per the company's response above, is not the same as assuming equal ToT and PFS given that the second option may lead to a bias in the estimated costs."	Please amend this wording to acknowledge that the ToT curve does not fall below the PFS curve for the majority of trial follow-up, which substantially limits the impact that this issue may have on costs.	The company accept that this statement is theoretically true, however, only impacts costs if the ToT curve falls below the PFS curve, and this is not the case for the vast majority of the trial follow-up, as shown in Figure 4.13 of the EAG report. This should be acknowledged when considering the impact of this assumption on economic model results.	Not a factual inaccuracy. While this might be the case for futibatinib, for pemigatinib it remains unknown.

Issue 4 Proportion of female trial participants

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.3 (page 89) states:	Please amend to:	In line with Table 29, Document B of the company submission	Amended accordingly.

"Patients included in the economic model were assumed to have an average baseline age of 55.7 years, a mean weight of 73.9 kg, a mean body surface area of 1.83 m2, and consist of a 56.3% **male** population based on the FOENIX-CCA2 trial population characteristics.[12]"	"Patients included in the economic model were assumed to have an average baseline age of 55.7 years, a mean weight of 73.9 kg, a mean body surface area of 1.83 m2, and consist of a 56.3% **female** population based on the FOENIX-CCA2 trial population characteristics.[12]"		

Issue 5 Clarification of figure title

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Title of Figure 4.3 (page 91) states: "Schoenfeld residual plot for futibatinib versus pemigatinib for OS"	Please amend to: "Schoenfeld residual plot for futibatinib **(adjusted)** versus pemigatinib for OS"	In line with Figure 23, Document B of the company submission	Amended accordingly.

Issue 6 Interpretation of log-cumulative hazard plots

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.6.1 (page 94) states: "the company did not comment on the fact the log-cumulative hazards	Please amend to: "the company did not comment on the fact **that, in the opinion of the**	Please acknowledge that this observation is the view of the EAG	Not a factual inaccuracy.

of OS in Figure 4.2 do not seem to be in parallel"	**EAG,** the log-cumulative hazards of OS in Figure 4.2 do not seem to be in parallel"		Lines that cross (as it happens here) cannot be parallel by definition.

Issue 7 Interpretation of log-cumulative hazard plots implications for PH

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.6.1 (page 94) states: "In fact, the log-cumulative hazard OS curves in Figure 4.2 seem to cross at several time points, which is **a clear indication** of non-PHs, despite the non-significant p-value of the Schoenfeld test." Section 4.2.6.1 (page 94) states: "The EAG does not agree with this assessment as the log-cumulative hazard plots for PFS in Figure 4.7 seem to cross at several time points despite the non-significant p-values of the Schoenfeld tests."	Please amend to: "In fact, the log-cumulative hazard OS curves in Figure 4.2 seem to cross at several time points, which **may indicate** non-PHs, despite the non-significant p-value of the Schoenfeld test." Please amend the second statement to reflect this.	The company acknowledge that crossing of proportional hazard plots can be an indication that the proportional hazards assumption does not hold in cases where a HR shows a significant treatment effect (i.e. where the 95% CIs do not cross the null). However, in the case of futibatinib and pemigatinib, where a similar treatment effect is expected and where the HR is close to 1 for OS and PFS (with 95% CIs spanning the null), crossing of log cumulative hazard plots is inevitable. To demonstrate this point, in the case when there is no difference in hazards between treatments, log cumulative hazard plots would lie exactly on top of each other and	Not a factual inaccuracy. The case where the HR = 1 does not apply in this situation. The EAG statement is furthermore supported by the plot of crossing hazards and a non-constant HR over time, also included in the EAG report.

		cross on multiple occasions, but this would not be an indication that the PH assumption does not hold. In such cases, the assessment of PH should be based on a visual inspection of the plots, which, in the company's view, showed that the futibatinib and pemigatinib curves largely ran parallel to each other, and the p-value of the Schoenfeld test. The EAGs statement that the crossing of the log-cumulative hazard plots is a "clear indication of non-PHs" is factually inaccurate and should be removed from the report throughout.	

Issue 8 Interpretation of smoothed hazard plots and the impact of tail ends of survival curves

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.6.1 (page 94) states: "The EAG again disagrees with this interpretation, as this reasoning is dismissing about half of the observed data. Specifically, Figure 4.6 shows that the hazard functions seem to change substantially after	Please amend this statement to correctly reflect the company's statements on the tail ends of curves and numbers at risk.	This is a misrepresentation of the company's statement. As quoted, the company states in their response "that the tail ends of both curves should be interpreted with caution, given the low numbers of patients at risk at later timepoints"; at no point	Not a factual inaccuracy. The company brought the argument of the tails as another argument to justify proportional hazards. The EAG just wanted to point out that the hazards functions cross

~10 months, but this time point represents less than half of the overall follow-up period for the observed data. Therefore, it cannot be argued that the curves after ~10 months represent the 'tail' of the curve and 'should be interpreted with caution'. The EAG's concerns are also confirmed by the number of patients at risk in Figure 3.10, which shows that more than half of the patients remained at risk after ~15 months of follow-up time."		was it stated that there are low numbers of risk after the 10 month timepoint, only that the hazards were similar up to this point. The latter statement was to bring the EAG and committee's attention to low numbers at risk later in the trial follow-up (which are clearly reported in Figure 14 of the company submission) to inform their assessment. For clarity, smoothed hazards are presented up to 25 months, but from 20 months of follow-up only 30/103 (29%) and 42/108 (39%) of patients in the futibatinib unadjusted and pemigatinib arms were still at risk and thus hazards in the later sections of these plots should be interpreted with caution.	well before the tails of the curves.

Issue 9 Contradictions in the approach to hazard rates after 24 months

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.6.1 (page 96) states: "Therefore, the company updated their model by assuming that the	Please amend this statement in light of the EAG preference that there should be no survival difference expected between	As discussed in amendments to Section 1, notwithstanding the EAG's view around the appropriateness of the PH	Please refer to Issue 1 in Section 1.

hazard rates for OS and PFS for pemigatinib are set equal to those of futibatinib after 24 months, at which time point ~11% and ~12% of patients on futibatinib and pemigatinib treatments, respectively, were still on-treatment based on the PFS curve, which informed ToT in the company's original and revised (following the clarification phase) base-case analysis. The EAG considers that although this approach can partially address the issue, there are still concerns if that would be the most appropriate, especially considering the uncertainty around the PH assumption previously discussed. **This approach may still be dismissing and not appropriately aligning with the observed data**." Section 6.2.1 (page 135) states: "These plots show that both HRs are changing over time, which supports the EAG's choice of independent modelling (i.e., the PH assumption is violated since the HR is not constant), and both start	futibatinib and pemigatinib when patients stop receiving treatment, which contradicts with the highlighted statement.	assumption, assuming hazard rates for OS and PFS for pemigatinib are set equal to those of futibatinib after 24 months is not "dismissing and not appropriately aligning with the observed data" as stated here. The EAG's stated preference is that "there should be no survival difference expected between futibatinib and pemigatinib when patients stop receiving treatment", to which the company has agreed, and this is true regardless of the use of dependent or independent models. Please note that there are multiple contradictions across the EAG report with regard to the preferred approach to modelling the hazard rates after 24 months that should be addressed. For instance, please refer to the highlighted statement from Section 6.2.1 in the first column of this table, to Section 6.2.2 (page 136), to Section 6.3 (page 139) and Section 6.4 (page 144), which imply contradicting assumptions with regard to the long-term treatment effect.	

below 1 (favouring futibatinib) but after some time they seem to converge to 1.20 (favouring pemigatinib), which is in line with crossing survival curves." Please also refer to Section 6.2.2 (page 136), Section 6.3 (page 139) and Section 6.4 (page 144).			

Issue 10 Rationale for unadjusted curves for the OS of futibatinib

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.6.1 (page 96) states: "The EAG is **unclear** why the company used the unadjusted curves for the OS of futibatinib while they implemented an HR based on the MAIC analysis for the OS of pemigatinib." This issue is also present in Section 6.4 (page 141):	Please adjust this statement to reflect the fact that clear rationale have been provided by the company in response to clarification questions.	The detailed justification for this approach has been provided by the company in response to clarification question C2. Specifically, it was stated that this approach permitted the use of the adjusted base case MAIC results, which represent the least biased estimates of the relative effects between futibatinib and pemigatinib. It also allowed the futibatinib extrapolations to be based on the maximum sample size; avoiding the reduction in	Not a factual inaccuracy. This remains unclear. The EAG considers that only adjusted data should have been used, as explained in the EAG report.

"However, the EAG is **unclear** why the company used the unadjusted curves for futibatinib while implementing an HR based on the MAIC analysis for pemigatinib."		effective sample size that would be associated with extrapolation of the MAIC-adjusted FOENIX-CCA2 data. Clinical validation of the most plausible survival curves for futibatinib was also performed based on curves generated using unadjusted FOENIX-CCA2 data. Therefore, the statement that the company's justification for this approach is unclear is not factually correct and should be amended.	

Issue 11 Confidentiality of pricing for futibatinib

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.9.2 (page 111) states: "The EAG noticed that [redacted] However, in the most recent electronic market information tool (eMIT) document, updated on 5 April 2024, the list price for futibatinib is not available.41 Therefore, the EAG	Please consider removing these statements.	This cost is correct, as supplied by the company. This cost would not be provided on the eMIT, given that the eMIT does not include branded medicines that are on-patent. Furthermore, the price for futibatinib would not be found on the BNF, given futibatinib has not yet been launched in the UK (given this requires a recommendation from NICE). In addition, the pricing	Amended accordingly.

was unable to verify if this was indeed correct or not." Section 6.4 (page 142) also states: "However, in the most recent eMIT document, the list price for futibatinib is not available.[41]"		arrangement for futibatinib is commercially confidential. Consequently, this statement should be removed in its entirety from the EAG report. In addition, please note that the details of futibatinib pricing are confidential and should be highlighted as commercial in confidence; confidentiality highlighting was therefore added to the EAG statement provided here.	

Issue 12 Futibatinib pack size and pricing arrangements

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.9.2 (page 111) states: [redacted] The results of this	Please remove or amend these statements to correctly reflect the pricing arrangements for futibatinib.	[redacted]	Amended accordingly.

scenario analysis are shown in Section 6.2.3 of this report." Table 4.13 (page 112) states : "Note that costs per treatment cycle are based on a pack-size of 35." Section 4.2.9.4 (page 112) states: "However, Table 39 in the CS,[5] also presented the costs based on 16 mg and 12 mg; [redacted]" Section 6.4 (page 142) also states: [redacted]		[redacted] In addition, no exploratory analysis on pack size was reported in Section 6.2.3 of the EAG report. Please remove the indicated statements, as they are based on an incorrect understanding of the futibatinib pricing arrangement, and adjust this issue throughout the report where relevant. In addition, please note that the details of the futibatinib pricing arrangement are commercial in confidence and should be indicated as such.	

[redacted]			

Issue 13 Identification of the number of patients on treatment

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.9.5 (page 112) states: "The EAG checked the calculations in the economic model and noticed that **PFS was used to identify those patients on treatment, and ToT for those who stop treatment.** However, the EAG considers that ToT should have been used in all calculations."	Please could the EAG clarify the error described here. In the economic model, drug acquisition costs are calculated directly from the selected outcome (PFS or ToT), for example in column L of the "Cost_Calcs" sheet for futibatinib, depending on the selection in cell E57 of the "Settings" sheet.	If ToT is selected to inform duration of treatment at the front end of the model, then ToT is used to calculate drug acquisition costs. Whether drug wastage is applied is independent of the outcome used to inform duration of treatment.	Amended accordingly.

Issue 14 Independent modelling of ToT and PFS

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.9.5 (page 112) states:	Please amend to:	Modelling of ToT does not impact incremental QALYs, and cost savings do not halve. The scenario	Amended accordingly.

"In response to clarification question **B8**,[7] the company provided an update of the model and a scenario analysis where they demonstrated that when they modelled ToT independently from PFS, **both the cost saving and incremental QALYs almost halved**."	"In response to clarification question **B9**,[7] the company provided an update of the model and a scenario analysis where they demonstrated that when they modelled ToT independently from PFS, **incremental QALYs did not change and cost savings decreased by 29%**."	in question is provided as 3b in Table 19 of the clarification questions response and should be compared to the revised company base case (scenario 3) where ToT is set equal to PFS but all other assumptions are equal. There is no change in incremental QALYs, and savings only changed by 29%.	

Issue 15 Cost of phosphate binders

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.9.8 (page 113) states: "The company also reported that UK clinical experts indicated that the use of phosphate binders (daily as a continuous treatment) would also be expected for patient in the PFS state. **The company explored this is a scenario analysis, however, the EAG was not able to find these results**.[24]"	Please remove the statement regarding the scenario analysis.	Please note that this scenario analysis was not performed and it was listed in error in the company submission. Instead, the costs of phosphate binders were assumed to be captured in the adverse event cost of hyperphosphatemia, and therefore are already captured in the base case analysis.	Not a factual inaccuracy. By the time of writing the EAG report, this was unknown.

Issue 16 Cost of hyperphosphataemia

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 4.15 (page 113) states the cost of hyperphosphataemia (grade 2+) as 19.74 (£).	Please amend to **19.75** (£).	In line with Table 41 of Document B of the Company Submission.	Amended accordingly.

Issue 17 Cost of genetic testing

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.9.10 (page 114) states: "Although the impact of including genetic testing on the CE results is minor, the EAG decided to include them in the EAG base-case analysis."	Please amend to: "Although **including genetic testing has no impact** on the CE results, the EAG decided to include them in the EAG base-case analysis."	Since futibatinib and pemigatinib have the same position in the treatment pathway, the use of genetic testing is expected to be exactly the same for these two treatments. Inclusion of genetic testing has therefore no impact on the model results.	Not a factual inaccuracy. It might not have impact on the incremental results, but it has a minor impact on each arm separately.

Section 5. Cost effectiveness results

Issue 18 Presentation of company base case results prior to EAG clarification question response

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Throughout Section 5, the presented company model results are taken from the version of the economic model prior to clarification question responses.	Please amend the company model results to those updated in the clarification question response, such that these reflect the company's latest base case assumptions.	The presented company model results do not represent the most up-to-date base case analysis submitted by the company. In addition, please find the model results with the EAG feedback implemented in the appendix to this response.	Not a factual inaccuracy. The company is correct. However, to meet the deadlines for this project Chapter 5 had to be based on the original submission. Changing all results after clarification was unfeasible. And given that the impact was minor, it was decided to address these in Section 6.1.1.

Issue 19 PSA settings

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 5.2.1 (page 119) states: "Incorrect setting for the PSA regarding the pemigatinib OS and PFS parameters, as they were set	Please remove this statement.	This is not an error in the company model. In the company base case, HRs were used to derive pemigatinib survival curves, and thus pemigatinib OS and PFS	Not a factual inaccuracy. This becomes an error when independent modelling is selected, even if it has no

to “No” on the “Model parameters” sheet, and therefore not varied in the PSA results.”		parameters were not relevant for the PSA.	impact on the company’s base-case.

Issue 20 Disutilities settings

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 5.2.1 (page 119) states: “Parameters for the AEs disutilities, the disutility attached to PD and parameters for healthcare resource use were not included in the PSA as they were set to “No” on the “Model parameters” sheet.”	Please remove or amend this statement.	Disutilities for AEs were set to “Yes” on the “Model parameters” sheet.	Not a factual inaccuracy. In the model version that the EAG received these were set to “No”.

Issue 21 DSA results

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 5.2.2 (page 121) states: “The DSA results presented above are also based on the company’s	Please amend these statements to reflect that, among the highlighted issues, only half-cycle correction	Given that these are deterministic analyses, among the highlighted issues, only half-cycle correction	Not a factual inaccuracy. As mentioned in the EAG report, the EAG cannot be sure that there are other errors in

model including the errors identified by the EAG." Section 5.2.3 (page 121) states: "The EAG would like to stress again that the results and conclusions form the scenario analyses were also based on the model including the errors identified by the EAG."	impacts the results of the deterministic analyses.	impacts the results, and this impact is minimal. Please find company PSA, DSA and scenario results with this error corrected in the appendix to this response.	the model. While it a minor impact on the results is expected, this is still unknown.

Issue 22 PFS HR

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 5.6 (page 122), scenarios 1 and 11: "HR = 0.93"	Please amend: "**PFS** HR = 0.93"	For clarity in comparison with OS HR provided in these scenarios.	Amended accordingly.

Section 6. Evidence Assessment Group's Additional Analyses

Issue 1 Model results in Table 6.5

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 6.5 (page 134) states the following values: Drug acquisition absolute increment: [redacted] Monitoring and resource use (%) absolute increment: [redacted] End of life costs absolute increment: [redacted] Total absolute increment: [redacted]	Please amend to the following values: Drug acquisition absolute increment: [redacted] Monitoring and resource use (%) absolute increment: [redacted] End of life costs absolute increment: [redacted] Total absolute increment: [redacted]	To align with the results of the economic model.	Amended accordingly.

Issue 2 Legend for Figure 6.1

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Legend of Figure 6.1 (page 135) is unclear.	Please clarify the legend and the abbreviations used in this figure.	Currently the abbreviations in the legend are unclear and interpretation of this figure is therefore not clear.	The Figure has been replaced.

Issue 3 Model results in Table 6.6

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 6.6 (page 137) states the following value for incremental QALYs for futibatinib in the EAG base-case: [redacted]	Please adjust to [redacted]	To align with the results of the economic model.	Amended accordingly.

Issue 4 Model results in Table 6.7

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 6.7 (page 138) states the following value for the incremental costs for the log-logistic OS alternative extrapolation option: [redacted]	Please adjust to [redacted]	To align with the results of the economic model.	Amended accordingly.

Issue 5 Impact of model errors on the results of the PSA

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 6.4 (page 143) states:	Please clarify that the identified errors had no impact on the % chance of cost-effectiveness.	None of the identified errors had any impact on the % chance of cost-effectiveness: in the EAG PSA, this	Not a factual inaccuracy. Initially, the EAG PSA in the model received after clarification would not run

“For the EAG base-case and PSA, the EAG corrected the model as much as possible.”		was still 100%, as reported in Section 6.2.2.	without errors. Afterwards, the model would show a large discrepancy between the deterministic and PSA ICERs.

Section 7. Confidentiality highlighting

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG comment
Section 2, Table 2.1 (page 23)	The decision problem addressed in the company submission has confidentiality highlighting	Please remove confidentiality highlighting from the decision problem addressed in the company submission	Amended accordingly.
Section 3.2.3, Table 3.10 (page 48)	The values for best response to prior anticancer therapy and the mean time from the last prior anticancer therapy to the first dose date of futibatinib do not have confidentiality highlighting	Please add confidentiality highlighting to these values, in line with Table 9 of Document B of the company submission	Amended accordingly.
Section 3.2.5.1 (page 52)	The values for the number of patient deaths at the latest DCO and the number of patients censored do not have confidentiality highlighting	Please add confidentiality highlighting to these values, in line with page 48 of Document B of the company submission	Amended accordingly.

Section 3.2.6, Table 3.19 (page 65) Section 3.6 (page 83)	The values for TEAEs (any cause) and SAEs are not highlighted Values for TRAE drug discontinuation and AEs with outcome of death are highlighted	Please add confidentiality highlighting to the values for TEAEs (any cause) and SAEs Please remove the confidentiality highlighting from the values for TRAE drug discontinuation and AEs with outcome of death, in line with Table 24 of Document B of the company submission	Amended accordingly. Amended accordingly.
Section 3.2.6.2 (page 66)	The number of deaths on study treatment or within 30 days of the last dose of futibatinib is not highlighted The number of deaths due to AEs and the specific reasons of deaths throughout the EAG comment are not highlighted	Please add confidentiality highlighting to these values, in line with page 65 of Document B of the company submission and response to clarification question A22	Amended accordingly.
Section 3.4.1 (page 78) Figure 3.9 (page 79) Figure 3.10 (page 81) Section 4.2.6.1 (page 90) Figures 4.2 and 4.3 (page 91)	The HR and RMST values and KM figures derived from the MAIC analysis have confidentiality highlighting	Please remove confidentiality highlighting from the outputs of the MAIC analysis	Amended accordingly.

Section 4.2.6.1 (pages 93, 95) Section 4.2.6.2 (page 100) Section 4.2.6.3 (pages 104, 106) Table 5.6 (page 122)			
Section 3.4.2 (page 80)	OS data have confidentiality highlighting	These values do not require confidentiality highlighting, in line with page 60 and Table 22 of Document B of the company submission	Amended accordingly.
Section 3.6 (page 82)	Mean improvement in EQ VAS lacks confidentiality highlighting	Please add confidentiality highlighting to this value, in line with Table 17 of Document B of the company submission	Amended accordingly.
Figure 4.4 (page 92) Figure 4.5 (page 93) Figure 4.9 (page 100) Figure 4.10 (page 101)	Survival extrapolation curves have confidentiality highlighting	Survival curves obtained for futibatinib and pemigatinib based on publicly available data do not require confidentiality highlighting	Amended accordingly.
Figure 4.6 (page 95) Section 4.2.6.2 (page 98)	Data regarding hazard plots and ratios for futibatinib and pemigatinib and parameters relevant to the validity of proportional hazard	These values do not require confidentiality highlighting	Amended accordingly.

Figure 4.7 (page 98) Figure 4.8 (page 99) Figure 4.11 (page 102)	assumptions such as Schoenfeld residual plot p-values have been highlighted as confidential		
Section 4.2.7, Table 4.9 (page 107)	Frequency of AEs included in the model has been highlighted as confidential	These values do not require confidentiality highlighting, in line with Table 35 of Document B of the company submission	Amended accordingly.
Section 4.2.9.2 (page 111) Section 4.2.9.4 (page 112)	Details of futibatinib pricing arrangements have not been labelled as confidential	Please add confidentiality highlighting to any information on the futibatinib pricing arrangements	Amended accordingly.
Table 5.3 (page 116)	Costs for pemigatinib are not marked as confidential	Disaggregated costs for pemigatinib should be marked as confidential, in line with Table 40 of Appendix J of the company submission	Amended accordingly.

References

1. National Institute for Health and Care Excellence. Nivolumab with ipilimumab for untreated advanced renal cell carcinoma. Available at: https://www.nice.org.uk/guidance/ta780/chapter/3-Committee-discussion [Accessed 26 April 2024].
2. Taiho Oncology. Data on File. FOENIX-CCA2 Advisory Board Report. 22 May 2023.
3. Rushbrook SM, Kendall TJ, Zen Y, et al. British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma. Gut 2023.
4. Vogel A, Bridgewater J, Edeline J, et al. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2023;34:127-140.

Appendix

Company Base Case Deterministic Results (After EAG Clarification)

Company base case results are presented below, reflecting the latest company base case which was revised during the response to EAG clarification to include:

- Correction of wastage implementation
- Hazard rates for OS and PFS set equal between futibatinib and pemigatinib when all patients have discontinued (24 months)

In addition to these changes, the company have implemented the EAG's suggested corrections to the model as outlined in Section B.1.3.1 of the EAG report, including the additional correction to the implementation of half-cycle correction as outlined in the resonse to Issue 1 in Section 4. With the exception of the implementation of half-cycle correction, these errors only impacted the probabilistic sensitivity analysis (PSA), but correction of these errors has very limited impact on the probabilistic cost-effectiveness results, which remain very similar to deterministic results, and thus should not be considered a significant source of uncertainty in this appraisal.

Furthermore, the company made one additional correction on the ReSurv tab of the economic model to ensure that the setting to equalise hazards at a specific timepoint can be applied in combination with independent extrapolation of unadjusted FOENIX-CCA2 data. Please note, this does not impact any company or EAG results; exploring independent models based on unadjusted data represents a naïve comparison, and therefore MAIC-adjusted FOENIX-CCA2 data (matched to the FIGHT-202 trial) have been used in all analyses using independent modelling approaches.

Table 1. Company deterministic base-case results (futibatinib PAS priced, discounted)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental NHB at £30,000
Futibatinib	[redacted]	2.31	[redacted]	[redacted]	0.063	[redacted]	Dominant	[redacted]
Pemigatinib	135,180	2.25	[redacted]					

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; NHB: net health benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year

Table 2. Disaggregated QALY results (discounted)

Intervention	QALY futibatinib	QALY pemigatinib	Increment	Absolute Increment	% Absolute Increment
PF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations QALY: quality-adjusted life year

Table 3. Disaggregated cost results (futibatinib PAS price, discounted)

Intervention	Cost futibatinib (£)	Cost pemigatinib (£)	Increment (£)	Absolute increment (£)	(%) Absolute increment
Drug acquisition	[redacted]	124,710	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	0	[redacted]	[redacted]	[redacted]
Monitoring and resource use	[redacted]	3,869	[redacted]	[redacted]	[redacted]
AEs	[redacted]	143	[redacted]	[redacted]	[redacted]
End of life costs	[redacted]	6,459	[redacted]	[redacted]	[redacted]
Total	[redacted]	135,180	[redacted]	[redacted]	[redacted]

Abbreviations: AE: adverse event; PAS = Patient Access Scheme

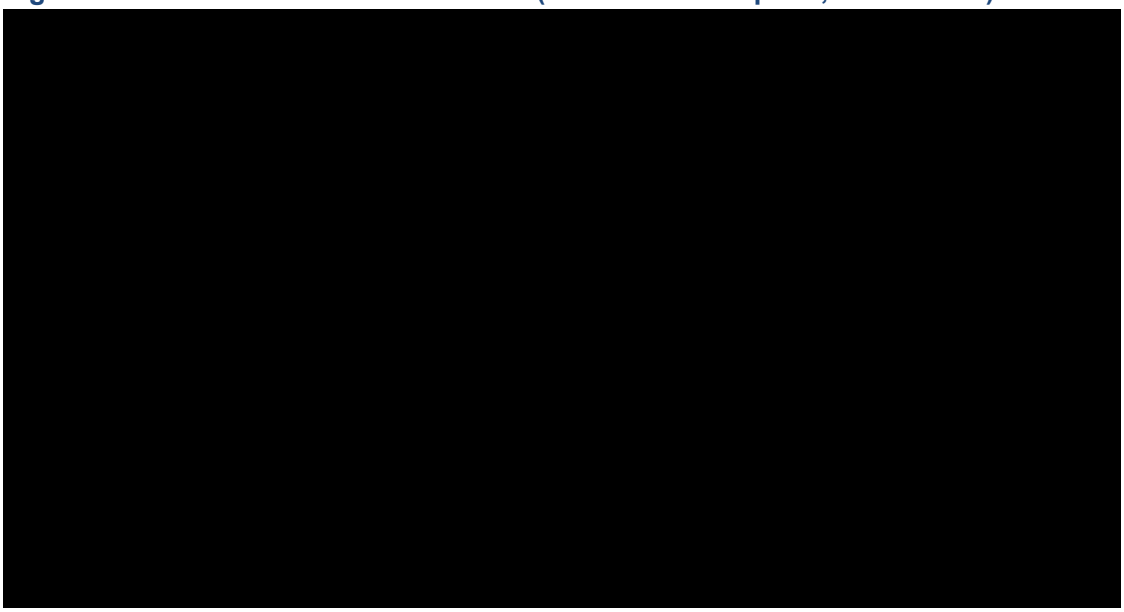
Company Base Case Probabilistic Results

Table 4. Company base-case probabilistic results (futibatinib PAS price, discounted)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. NHB at £30,000
Futibatinib	[redacted]	2.34	[redacted]	[redacted]	0.07	****	Dominant	[redacted]
Pemigatinib	135,857	2.26	[redacted]					

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; NHB: net health benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year

Figure 1. PSA Cost-Effectiveness Plane (futibatinib PAS price, discounted)



Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: Patient Access Scheme; PSA: probabilistic sensitivity analysis

Figure 2. PSA CEAC (futibatinib PAS price, discounted)

Abbreviations: CEAC: cost-effectiveness acceptability curve; ICER: incremental cost-effectiveness ratio; PAS: Patient Access Scheme; WTP: willingness to pay

Company Deterministic Sensitivity Analysis

Figure 3. DSA tornado diagram for incremental NHB (futibatinib PAS price, discounted)

Abbreviations: DSA: deterministic sensitivity analysis; INHB: incremental net health benefit; PAS: Patient Access Scheme

Figure 4. DSA tornado diagram for incremental costs (futibatinib PAS price, discounted)

Abbreviations: DSA: deterministic sensitivity analysis; PAS: Patient Access Scheme

Figure 5.DSA tornado diagram for incremental QALYs (futibatinib PAS price, discounted)

Abbreviations: DSA: deterministic sensitivity analysis; PAS: Patient Access Scheme; QALY: quality-adjusted life year

Company Scenario Analyses

Table 5. Company scenario analyses (futibatinib PAS priced, discounted)

Scenario	Description (base-case)	Description (scenario)	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Base-case	-	-	[redacted]	[redacted]	Dominant
1. Cost comparison	PFS HR = 0.93 OS HR = 1.05 AE rates as in Table 4.12	Futibatinib versus pemigatinib OS and PFS HR = 1 Equal rate of AEs in both arms	[redacted]	[redacted]	Dominant
2. Futibatinib PFS (I)	Futibatinib PFS lognormal	Futibatinib PFS log-logistic	[redacted]	[redacted]	Dominant
3. Futibatinib PFS (II)	Futibatinib PFS lognormal	Futibatinib PFS Weibull	[redacted]	[redacted]	Dominant
4. Futibatinib versus pemigatinib PFS HR (I)	HR = 0.93	Futibatinib versus pemigatinib PFS HR = 1	[redacted]	[redacted]	Dominant
5. Futibatinib versus pemigatinib PFS HR (II)	HR = 0.93	Unadjusted HR = 1.02 (FOENIX-CCA2 and FIGHT-202)	[redacted]	[redacted]	Dominant
6. Futibatinib versus pemigatinib PFS HR (III)	HR = 0.93	Sensitivity analysis MAIC HR = 1.11	[redacted]	[redacted]	Dominant
7. Futibatinib OS (I)	Futibatinib OS lognormal	Futibatinib OS log-logistic	[redacted]	[redacted]	Dominant
8. Futibatinib OS (II)	Futibatinib OS lognormal	Futibatinib OS Weibull	[redacted]	[redacted]	Dominant
9. Futibatinib versus pemigatinib OS HR (I)	HR = 1.05	Futibatinib versus pemigatinib OS HR = 1	[redacted]	[redacted]	12,759,481 (in SW quadrant)
10. Futibatinib versus pemigatinib OS HR (II)	HR = 1.05	Unadjusted HR = 0.96 (FOENIX-CCA2 and FIGHT-202)	[redacted]	[redacted]	Dominant
11. PFS and OS HR	PFS HR = 0.93 OS HR = 1.05	PFS and OS HR = 1	[redacted]	[redacted]	Dominant
12. Wastage costs	Included	Excluded	[redacted]	[redacted]	Dominant
13. Genetic testing cost	Excluded	Included	[redacted]	[redacted]	Dominant

Abbreviations: AEs: adverse events; CS: company submission; ICER: incremental cost-effectiveness ratio; Inc.: incremental; QALY: quality-adjusted life year; HR: hazard ratio; OS: overall survival; PAS: Patient Access Scheme; PFS; progression-free survival.