Single Technology Appraisal

Ivosidenib for treating advanced cholangiocarcinoma with an IDH1 mutation after at least 1 therapy [ID6164]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ivosidenib for treating advanced cholangiocarcinoma with an IDH1 mutation after at least 1 therapy [ID6164]

Contents:

The following documents are made available to stakeholders:

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

Pre-technical engagement documents

1. **Company submission** from Servier Laboratories Ltd
2. **Company summary of information for patients (SIP)** from Servier Laboratories Ltd
3. **Clarification questions and company responses**
4. **Patient group, professional group and NHS organisation submissions** from:
   a. AMMF
   b. Cholangiocarcinoma UK
   c. RCP-ACP-RCR
5. **External Assessment Report** prepared by University of Aberdeen
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Post-technical engagement documents

7. **Technical engagement response from company**
   a. Company technical engagement response
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8. **Technical engagement responses and statements from experts:**
   a. Chiara Braconi – clinical expert, nominated by Servier Laboratories Ltd
   b. John Bridgewater – clinical expert, nominated by Cholangiocarcinoma UK
   c. Helen Morement – patient expert, nominated by Cholangiocarcinoma UK
9. **External Assessment Report critique of company response to technical engagement** prepared by University of Aberdeen**:**
   a. Main critique

b. Further analysis and figures for committee

Post-committee documents

10. Company response to queries from External Assessment Group on indirect treatment comparison (ITC) numbers

11. Updated External Assessment Group cost-effectiveness results

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

Ivosidenib for treating advanced cholangiocarcinoma with an *IDH1* mutation after at least 1 therapy [ID6164]

Document B

Company evidence submission

April 2023

File name	Version	Contains confidential information	Date
Ivosidenib for treating advanced cholangiocarcinoma with an IDH1 mutation after at least 1 therapy ID6164-doc B	1.0	Yes	21st April 2023

Contents

Tables and figures

Abbreviations

2-HG	2-hydroxyglutarate
5-FU	5-fluorouracil
α-KG	alpha- ketoglutarate
AE	Adverse event
AIC	Akaike information criterion
ASC	Active symptom control
BIC	Bayesian information criterion
BNF	British National Formulary
BOR	Best overall response
BSA	Body surface area
BSC	Best supportive care
BSG	British Society for Gastroenterology
BTC	Biliary tract cancer
C1D1	Cycle 1 day 1
CCA	Cholangiocarcinoma
CI	Confidence interval
CMPH	Committee for Medicinal Products for Human Use
CoS	Crossover Set
CR	Complete response
CT	Computed tomography
dCCA	Distal cholangiocarcinoma
DCR	Disease control rate
DNA	deoxyribonucleic acid
DoR	Duration of response
DSU	Decision Support Unit
EASL	European Association for the Study of the Liver
eCCA	Extrahepatic cholangiocarcinoma
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMIT	Electronic market information tool
ENS-CCA	European Network for the Study of Cholangiocarcinoma
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-BIL21	European Organisation for Research and Treatment of Cancer quality of life questionnaire cholangiocarcinoma and gallbladder cancer module
EOT	End of treatment
ESCAT	ESMO scale for clinical actionability of molecular targets
ESMO	European Society of Medical Oncology
ESMO-MCBS	ESMO magnitude of clinical benefit scale
EU	European union
FGFR	Fibroblast growth factor receptor
GBC	Gall bladder cancer
GI	Gastrointestinal
GLH	genomic laboratory hub
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCRU	health-care resource use
HR	Hazard ratio
HRQoL	Health related quality of life
HST	Highly specialised technology
iCCA	Intrahepatic cholangiocarcinoma
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ICR	independent central review
IDH1	isocitrate dehydrogenase 1

IDH2	isocitrate dehydrogenase 2
IDHM	isocitrate dehydrogenase mutation
INMB	incremental net-monetary benefit
IPCW	inverse-probability-of-censoring weighting
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
LVEF	Left ventricular ejection fraction
LYs	Life years
LYG	Life years gained
mFOLFOX	Modified folinic acid + fluorouracil + oxaliplatin
mGC	Metastatic gastric cancer
MMR	Mismatch repair
MMRM	Mixed Model for Repeated Measures
MRI	Magnetic resonance imagining
MSI	Micro-satellite instability
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not estimable
NGS	Next-generation-sequencing
NHB	Net health benefit
NHS	National Health service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute of Care and Excellence
NICE TA	NICE technology appraisal
NTRK	Neurotrophic tyrosine receptor kinase gene fusion
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PartSA	Partitioned survival analysis
pCCA	Perhilar cholangiocarcinoma
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PGI-C	Patient Global Impressions of Change
PGI-S	Patient Global Impressions of Severity
PK	Pharmacokinetic
PLD	Patient level data
PPS	Per-Protocol Set
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALYs	Quality-adjusted life years
QD	Once daily.
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors.
RMST	Restricted mean survival time
RPSFT	Rank preserving structural failure time model
SAE	Serious adverse events
SAS	Safety Analysis Set
SD	Stable disease

SE	Standard error
SLR	Systematic literature review
SoC	Standard of care
ToT	Time on treatment
TRAE	Treatment related adverse events
TSD	Technical Support Document
TTR	Time to recurrence
WTP	Willingness-to-pay

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

Cholangiocarcinoma (CCA) is a rare cancer, and within that, CCA with an IDH1 mutation, our population of interest for this appraisal, is especially rare, with less than 1 in 50,000 patients (as defined by the HST criteria).

Most cases are diagnosed at an advanced stage, when the cancer has already spread locally (stage III) or to other parts of the body (metastatic, stage IV). The prognosis is dismal, with an estimated 5-year survival of <10%. There are no licensed treatments for CCA patients with an IDH1 mutation and current standard of care is limited to BSC or FOLFOX. The efficacy of FOLFOX in IDH1 mutation, however, has not been studied. In patients with biliary tract cancer, there appears to be only a modest increase in overall survival of 0.9 months with FOLFOX compared to BSC. This comes with a high incidence of adverse events as cytotoxic chemotherapy is associated with a range of AEs, including neutropenia, dyspnoea, fatigue, anaemia, diarrhoea, stomatitis, nausea and vomiting, that can lead to hospitalisation and severely compromise quality of life. Consequently, both clinical outcomes and QoL are very poor in CCA patients with IDH1 mutation.

Ivosidenib is the first targeted therapy (with designated EU orphan status) indicated for the treatment of patients with CCA and IDH1 mutation who have progressed after ≥1 prior line of systemic therapy. For the first time, patients now have an opportunity to benefit from a targeted therapy that is highly effective (Ivosidenib doubled median OS compared to BSC) with a favourable safety profile and a positive QoL impact. The ESMO-Magnitude of Clinical Benefit Scale assigns the highest score of 3 (in the second-line setting) for Ivosidenib, 2 levels above FOLFOX. In addition to the compelling clinical case, the confidential discount on Ivosidenib ensures it is value for money for the NHS. Additionally with around 150 patients eligible for treatment with Ivosidenib, the overall budget impact is anticipated to be small.

Ivosidenib also has the important advantage of being an oral treatment, keeping patient care at home, especially relevant in the post pandemic world with the need to build resilient healthcare systems. As a targeted oral therapy, Ivosidenib is not only aligned to the NHS Long-Term Plan of care closer to home but also to the NHS goal of advancing precision medicine and enabling patient access to personalised treatments based on tumour genetics.

In 2021, NICE approved Pemigatinib, a targeted treatment option for CCA patients with FGFR2 fusion or rearrangement. In contrast, CCA patients with IDH1 mutation currently have no option other than unlicensed cytotoxic chemotherapy. The unmet need is significant and the case is strong for a quick decision making process to approve Ivosidenib and bring about a step change to the care pathway for CCA patients with IDH1 mutation.

B.1.1 Decision problem

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

Table 1: The Decision Problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation, who were previously treated by at least one prior line of systemic therapy	**People with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation, who were previously treated by at least one prior line of systemic therapy**	R132 included to align with license
Intervention	Ivosidenib	Ivosidenib	
Comparator(s)	• Chemotherapy (including fluorouracil and oxaliplatin) • Best supportive care (active symptom control, including stent insertion)	• Chemotherapy (including fluorouracil and oxaliplatin) • Best supportive care (active symptom control)	Servier do not consider stent insertion to be a relevant component of BSC at this line of therapy. In line with NICE TA722, stent insertion was not explicitly considered. As reported in NICE TA722, biliary stents are most likely to be used in patients with hilar or extrahepatic CCAs; however, >90% of patients in ClarIDHy presented with intrahepatic CCA. Furthermore, biliary stent insertion is primarily a treatment option in the earlier stages of disease and, although maintenance or replacement of stents may be required, insertion of a new stent is less likely to be considered after failure of previous lines of chemotherapy.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	

Economic analysis	The use of ivosidenib is conditional on the presence of IDH1 gene mutation. The economic modelling should include the costs associated with diagnostic testing for IDH1 gene mutation in people with advanced cholangiocarcinoma who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.	The scope states that the economic modelling should include the costs associated with diagnostic testing for IDH1 gene mutation in people with advanced cholangiocarcinoma who would not otherwise have been tested and a sensitivity analysis should be provided without the cost of the diagnostic test. However, IDH1 testing is already part of the genetic test directory so funding should be in place. Therefore, Servier believes the base case should not include cost of testing	

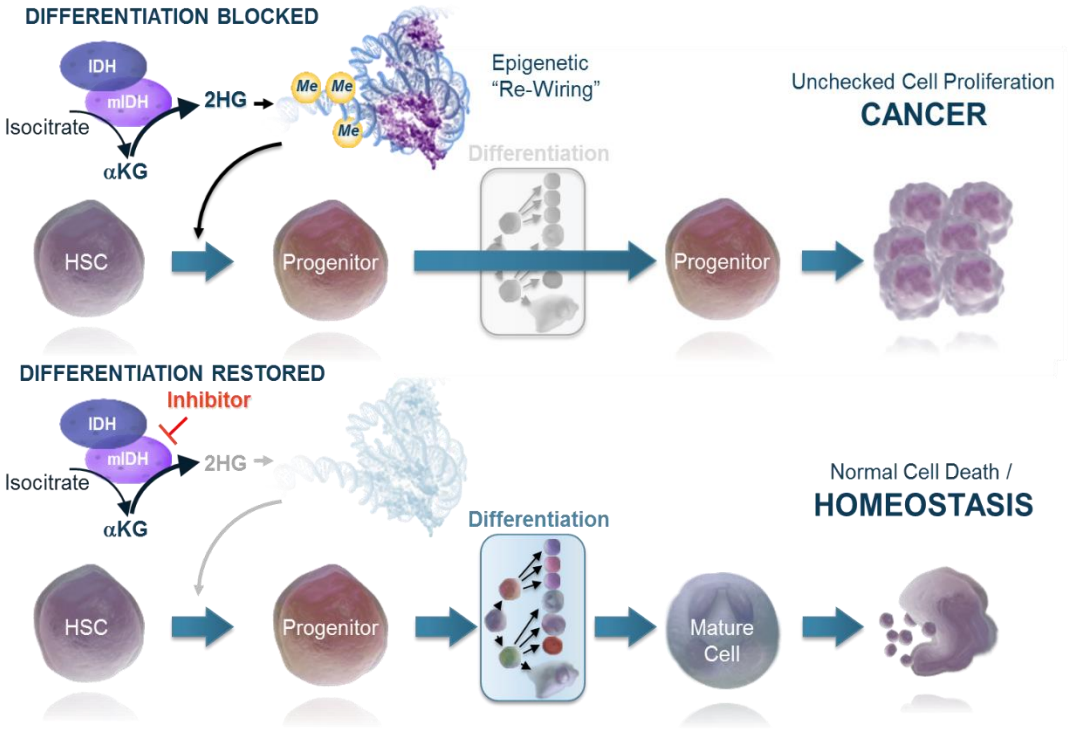
B.1.2 Description of the technology being evaluated

In appendix C include the summary of product characteristics or information for use, and the UK public assessment report, scientific discussion or drafts.

Table 2 Technology being evaluated

UK approved name and brand name	Ivosidenib (Tibsovo)
Mechanism of action	Ivosidenib is an inhibitor of mutated IDH1 enzyme. Mutated IDH1 converts alpha- ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG) which blocks cellular differentiation and promotes tumourigenesis in both haematologic and non-haematologic malignancies. The mechanism of action of ivosidenib beyond its ability to suppress 2-HG and impair cellular differentiation is not fully understood across indications. In an IDH1-mutant intra-hepatic cholangiocarcinoma patient-derived xenograft mouse model, ivosidenib reduced 2-HG levels.
Marketing authorisation/CE mark status	[redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Ivosidenib monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy. Include the (draft) SmPC for pharmaceuticals or information for use (IFU) for devices in appendix C. Provide the (draft) UK Public Assessment Report for pharmaceuticals or a (draft) technical manual for devices in appendix C.]
Method of administration and dosage	500mg once daily (2x 250mg tablets) to be taken orally. Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient
Additional tests or investigations	The use of ivosidenib is conditional on the presence of IDH1 gene mutation. Therefore, diagnostic testing for IDH1 gene mutation in people with advanced cholangiocarcinoma should be carried out through an NGS panel, which is already commissioned by NHS England
List price and average cost of a course of treatment	£12,500 list price
Patient access scheme (if applicable)	PAS simple discount

Figure 1. Mechanism of action of ivosidenib



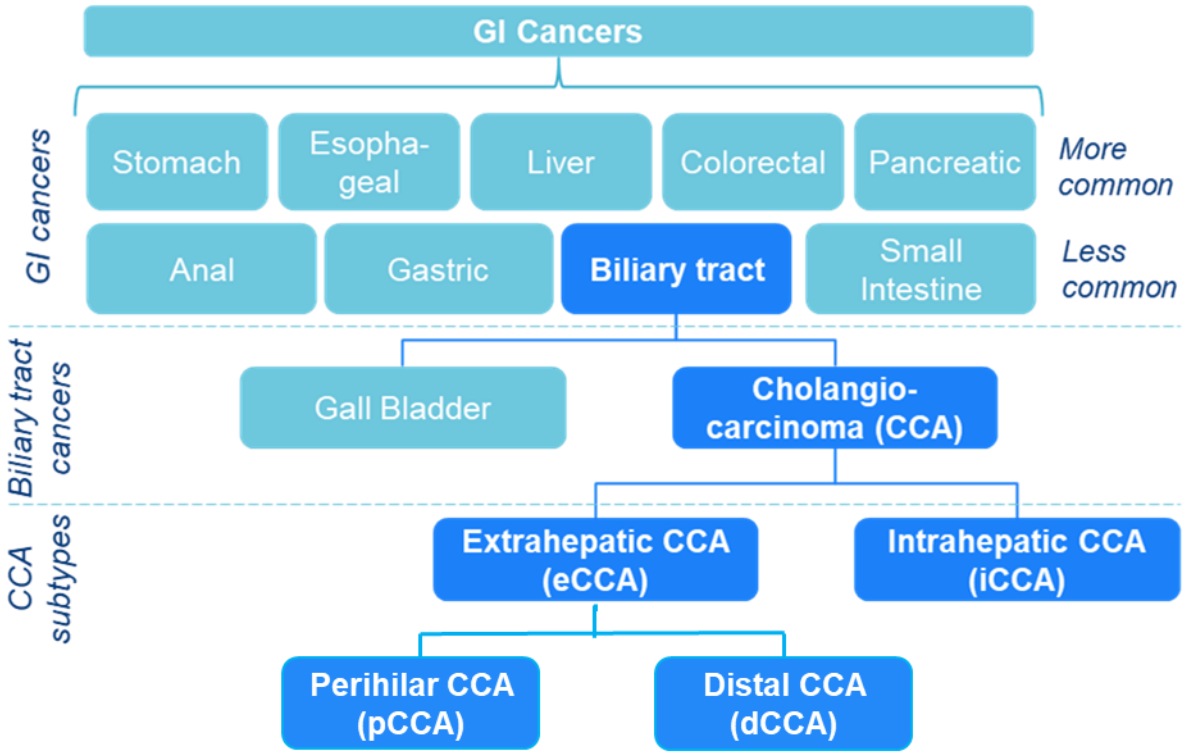
Source: Cairns, 2013 (1)
Abbreviations: 2-HG, 2-hydroxyglutarate; αKG, alpha-ketoglutarate; HSC, hematopoietic stem cells; IDH, isocitrate dehydrogenase; mIDH, mutant isocitrate dehydrogenase.

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

B.1.3.1 Disease overview

Gastrointestinal (GI) cancers refers to malignant conditions of the GI tract and accessory organs of digestion, including the oesophagus, stomach, biliary system, pancreas, small intestine, large intestine, rectum and anus (2). Among the GI cancers, biliary tract cancers (BTC) are very infrequent (3). BTCs are malignancies that arise from the epithelium of the biliary system and include the following malignancies: cholangiocarcinoma (CCA), gall bladder cancer (GBC), and ampulla of vater cancer (4). A breakdown of GI malignancies is provided in Figure 2.

Figure 2: Overview of GI malignancies



Source: Adapted from Banales et al. 2020 (57).
Abbreviations: GI, gastrointestinal; CCA, cholangiocarcinoma.

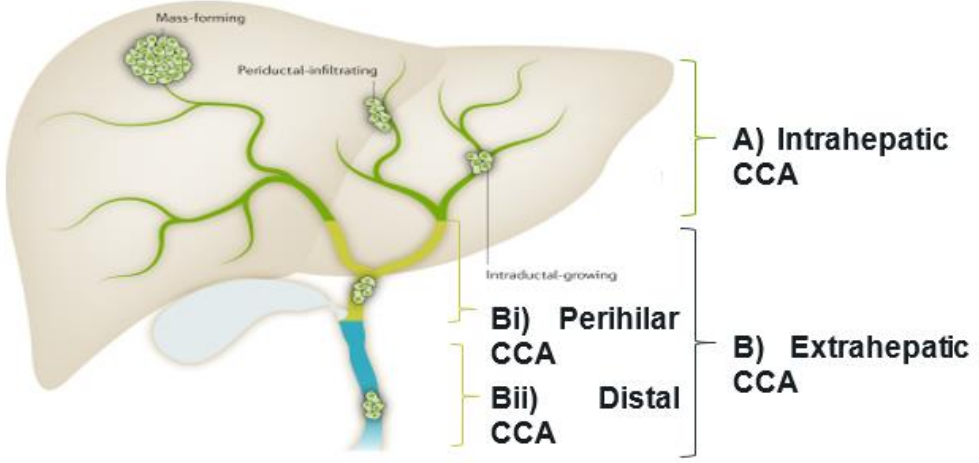
More than 90% of CCAs are adenocarcinomas and are broadly divided into three histological types based on their growth patterns: mass-forming, periductal-infiltrating, and intraductal-growing (5) and arise from the intrahepatic or extrahepatic epithelial cells (6). The main types of CCA include (7) (8):

- **iCCA tumours:** originating from the biliary tree within the liver.

- **eCCA tumours:** originating outside the liver parenchyma and further subdivided based on their site of origin
- **Perihilar (pCCA):** also called Klatskin tumours and arising from the hilum region where the hepatic ducts exit the liver and join to form the common hepatic duct.
- **Distal (dCCA):** arising from the bile duct region that includes the common bile duct and insets into the small intestine.

The different subtypes of CCA are illustrated in Figure 3.

Figure 3. CCA subtypes



Source: Adapted from Banales et al. 2020 (3)
Abbreviations: CCA, cholangiocarcinoma.

The overall incidence of CCA is increasing with currently around 2,800 people diagnosed each year in the UK, although it is not always clear which subtype the cancer is (9). Coding issues within the UK make differentiation between subtypes difficult, but each subtype has distinct risk factors, molecular pathogenesis, therapeutic options, and prognosis.

IDH mutations in CCA

CCAs vary across individuals at histological, genomic, epigenetic, and molecular levels. Mutations can arise across classifications, where small bile duct iCCA can be attributed to *IDH1*, isocitrate dehydrogenase 2 (*IDH2*) mutations or *FGFR2* fusions (10). These genetic alterations allow for personalised /precision medicine in CCA where the mutation can be treated specifically with a targeted therapy.

The IDH proteins are critical metabolic enzymes involved in hypermethylating deoxyribonucleic acid (DNA) and histones, which can result in altered gene expression that can activate oncogenes and inactivate tumour-suppressor genes (11). IDH proteins play a role in several types of tumours, and exist as three isoforms: *IDH1*, *IDH2*, and *IDH3* (12). IDH1 mutations are rare, occurring in 16.5% of iCCA patients and 1% of eCCA patients (13). Five mutations (i.e., p.R132H, p.R132C, p.R132G, p.R132S, and p.R132L) have been described in *IDH1*-mutated cancers, but R132C is the most frequent in iCCA (14). *IDH1* is found in the cytoplasm and peroxisomes (15, 16) and the gene encoding *IDH1* is located on chromosome 2q33.3 (17). IDH proteins catalyze the oxidative decarboxylation of isocitrate to produce carbon dioxide and alpha-ketoglutarate (α-KG) (12).

Mutations in IDH proteins leads to production of high levels of 2-hydroxyglutarate (2-HG), which inhibits α-KG dependent dioxygenases including histone and deoxyribonucleotide demethylases, which play a key role in regulating the epigenetic state of cells (see **Error! Reference source not found.**) (18–20). Other studies have demonstrated that patients with IDH mutations display a cytosine-guanine dinucleotide island methylator phenotype, which is associated with extensive, coordinated hypermethylation; and that overexpression of mutated IDH1 can induce histone and DNA hypermethylation, and impair normal cellular differentiation (21–23). Thus, the cancer-associated IDH mutations block normal cellular differentiation and promote tumourigenesis via the abnormal overproduction of 2-HG (12). Inhibition of mutant IDH1 is expected to reduce 2-HG levels and restore cellular differentiation, thereby act as relevant therapeutic targets in CCA (24–26).

The complexity of CCAs' molecular genomics has opened avenues for improving the outcome for this therapeutically challenging rare disease and the new approaches have been reflected in the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines.

Testing

The use of ivosidenib is conditional on the presence of *IDH1* gene mutation. Therefore, diagnostic testing for IDH1 gene mutation in people with advanced CCA should be carried out through a next-generation-sequencing (NGS) panel.

The ESMO Precision Medicine Working Group recommends routine NGS in all CCA patients, stating that molecular testing is recommended for metastatic disease from diagnosis and that IDH testing should be part of the gene panel.

Given the background that NGS molecular profiling is available through England via the genomic laboratory hubs, clarification questions were covered during an advisory board held by Servier in June 2022, as to it's availability and application (27). Feedback from clinicians was that inclusion on the national directory does not always mean it is routinely carried out in NHS practice, and that this is still dependent upon the willingness and ability to deliver the result. FGFRs have led the way and now genomic laboratory hubs (GLHs) have some experience of profiling the tissue specimens, but there is regional variation and postcode issues. There is still notable heterogeneity, variability and reliability of the outputs, although the main point is that it is available and commissioned.

Risk factors

CCA is associated with multiple risk factors such as cirrhosis, choledocholithiasis Caroli's disease, hepatitis B virus (HBV), hepatitis C virus and bile duct cysts (28, 29). The risk factors for CCA are mostly similar across CCA subtypes (30, 31).

Khan *et al.*, (2019) summarised a more comprehensive list of suspected risk factors for iCCA and/or eCCA. (32) Risk factors found to have a strong association with CCA include bile duct cysts, Caroli's disease, cholangitis, choledocholithiasis and cirrhosis. However, risk factors such as smoking and type II diabetes were found to have a weak association with CCA.

B.1.3.2 Burden to patients, carers, and society

Epidemiology

CCA is frequently diagnosed at an advanced stage, which can make it difficult or impossible to determine the anatomical origin and histological subtype and the late diagnosis can lead to disease misclassification (33). Challenges in the diagnosis and classification of CCA have historically made it difficult to quantify the true incidence. The incidence of iCCA has changed over the past two decades with a rising incidence of iCCA, whilst the incidence of eCCA has remained relatively stable or decreased. The reason for this change is unclear; however, it could be due to an

increase in the accuracy. and availability of diagnostic tools or the evolving International Classification of Diseases (ICD) coding system (34).

There were 29,653 CCAs diagnosed between 2001–2017, 51.6% were female, and the median age of diagnosis was 75 years (IQR 66–82). The incidence rate increased on average by 0.8 per million per year from 2.9 per 100,000 in 2001 to 4.4 in 2017 whilst the mortality rate increased by 1.3 per million. In 2001, the age-standardised incidence rate for CCAs was 2.7 per 100,000 (95% confidence interval [CI]: 2.5, 2.8). In 2010–2013, the incidence rate per 100,000 in England had risen to 3.58.12 In 2017, the reported incidence was 4.3 per 100,000, with 4.0 in females (95% CI: 3.7, 4.2) and 4.6 in males (95% CI: 4.3, 4.9). In 2017, there were 2,187 persons diagnosed with CCA in England (1,069 males and 1,118 females). Over the same time period, the age-standardised mortality rate rose from 2.6 (95% CI: 2.4, 2.8) in 2001 to 4.7 per 100,000 in 2017, with 4.5 in females (95% CI: 4.3, 4.8) and 4.9 in males (95% CI: 4.6, 5.2). (35)

No more than 300 people in England will be eligible for the technology in its licensed indication. As Ivosidenib is only for patients with advanced/metastatic disease and also for only for those reaching second-line therapy, 164 people per year are thought to be eligible, as seen in table 3.

Prognosis

The prognosis of CCA is dismal owing to its silent clinical character, difficulties in early diagnosis and limited therapeutic approaches (17). Advanced stage diagnosis results in 30% of CCA patients being eligible for tumour resection (36) and poor survival outcomes among patients with CCA have been reported across multiple analyses covering various patient subgroups and clinical settings (37). The prognostic factors and the therapeutic approaches to CCA differ depending upon their location along the biliary tree (38).

All stage one year survival in 2015 for bile duct cancer was around 30% and 25% for men and women respectively.5 Year survival was 5% for both sexes. Most cases are diagnosed at the advanced stage where the cancer has already spread beyond the bile duct. (9)

Approximately 70% of patients are diagnosed late with unresectable, locally advanced, or metastatic disease—these patients have an estimated 5-year survival rate of ≤10% (39–41). In patients with BTC who have progressed on first-line (1L) treatment, median OS is 6.2 months when treated with systemic chemotherapy (i.e., mFOLFOX + active symptom control [ASC]) (17).

The role of IDH1 mutation as a prognostic factor in CCA is still a matter of debate with retrospective studies showing opposite results. In a meta-analysis of 104 CCA patients, although there was a trend for longer OS and lower levels of Ca 19.9 in mIDH patients, this was not statistically significant. There was neither an association with other factors such as sex, histologic grade, age nor pattern of metastases (14, 42).

Diagnosis

No specific screening methods are available to reliably detect CCA in its early stages, as most CCA cases are found only after the cancer has advanced to an incurable stage (as noted previously) (43). Most patients (~70%) are diagnosed at late stages of disease progression due to lack of specific symptoms (5).

Additionally, CCA is frequently misdiagnosed as cancer of unknown primary origin (8, 33, 44) as the diagnosis requires a high level of suspicion in the appropriate clinical setting and a confirmatory constellation of clinical, laboratory, endoscopic and radiologic data (10).

Histologically advanced CCA often resembles metastatic disease to the liver which makes it challenging to diagnose (2). If the cancer is unresectable or metastatic, then micro-satellite instability (MSI) or DNA mismatch repair (MMR) testing and other biomarker testing will be performed (38). For accurate diagnosis, it is important to distinguish between the tumour subtypes (iCCA, pCCA, dCCA or GBC) (43).

B.1.3.2.1 Diagnosis of iCCA

Due to often late presentation of iCCA and nonspecific symptoms, iCCA may be detected incidentally as an isolated intrahepatic mass on imaging. Several imaging modalities are used in the evaluation of primary hepatic masses (45). Computed tomography (CT) and magnetic resonance imagining (MRI) are both helpful for the detection of the primary tumour in the first instance (46). ICCA in patients with

cirrhosis is difficult to diagnose radiographically (47, 48), requiring histopathology for definitive diagnosis (17). Mass-forming iCCA of >1 cm diameter can be diagnosed using a positron emission tomography (PET); however, PET was found to be more useful for staging or confirmation (46). Nevertheless, imaging techniques are not always reliable for diagnosing iCCA (48).

B.1.3.3 Unmet need in the treatment of CCA

CCA often presents signs or symptoms at a later stage of disease (49). Management of CCA includes multiple treatment modalities such as chemotherapy, radiation therapy, targeted therapy, immunotherapy and surgery; however, complete resection is the only potentially curative treatment, although most patients are not candidates for surgery (and this is no longer an option once patients progress to advanced stage disease). In patients with unresectable locally advanced or metastatic CCA, palliative chemotherapy is the primary treatment option (38). As a result of the delayed presentation, patients are frequently diagnosed at an advanced/metastatic stage when the disease is incurable (14, 43) with ~70% being ineligible for tumour resection (5). Furthermore, during the course of the disease, patients experience aggravating and non-specific symptoms (e.g., jaundice, weight loss and abdominal pain) (43) and the impact of CCA symptoms on the daily lives, work productivity, QoL, mental health and sexual function of patients suffering from the disease is immense (50).

In addition, patients potentially face the harmful side effects of systemic chemotherapy, which can be avoided with an oral targeted treatment. These harmful effects also extend beyond the physiological effects as during the last months of a patients life they have to attend hospital for administration of a systemic treatment, which places a burden on the patient and their carers/family. The effect of a hospital visit especially during the post COVID-19 era can cause extreme anxiety especially for those already suffering with a weakened immune system due to the effects of chemotherapy. Therefore, where there is a targeted treatment against an actionable mutation, this should always be preferred. This was further emphasised by an advisory board held by Servier in June 2022, where clinicians reaffirmed the need to consider the patient perspective, and not just clinical outcomes. The fact that a patient is worked up with biopsy to establish mutational status emphasises that if an alteration is found the expectation is to treat with the targeted agent (27).

For advanced/metastatic CCA, treatment options are very limited in 2nd line, and as a result there is no consistent or clearly defined SoC (32, 51). mFOLFOX is recommended as a 2nd line of therapy in some guidelines despite limited efficacy and a high toxicity burden (17). The ABC-06 study investigated 2nd line mFOLFOX chemotherapy vs. ASC in advanced BTC. Whilst there were small increases in OS in the mFOLFOX arm, there was also a high incidence of adverse events (AEs) in this patient group. OS was longer in the ASC plus mFOLFOX group than in the ASC alone group, with a median OS of 6.2 months in the ASC plus mFOLFOX group vs. 5.3 months in the ASC alone group (adjusted HR, 0.69, p-value: 0.031) (24). Grade 3–5 AEs were reported in 56 (69%) of 81 patients in the ASC plus mFOLFOX group and 42 (52%) of 81 patients in the ASC alone group. Therefore, there is an unmet need in advanced/metastatic CCA patients who require a 2nd line of treatment due to a limited survival benefit from FOLFOX and an unfavourable safety profile (17) There are no other satisfactory treatment options, and Ivosidenib offers significant additional benefit over existing treatment options. FOLFOX has a ph3 study in Biliary Tract Cancer (BTC), not cholangiocarcinoma with an R132 mutation, and the incremental benefit over best supportive care is <1mth, hence its clinical value is limited. Its use/recommendation in clinical guidelines (as of today) illustrates the lack of other satisfactory options. In recent years, there has been a paradigm shift towards targeted therapies for diseases with mutations. This shift is articulated through updates of international and local clinical guidelines, recommending to use targeted treatments over FOLFOX if mutations are confirmed

Furthermore, some patients with CCA are treated with BSC and have a median survival time of approximately 3-6 months (although this may be underestimated due to the characteristics of patients receiving BSC in practice being likely older and more unwell versus those enrolled in clinical trials, such as the ABC-06 study) (52). Half of all untreated patients do not survive beyond three to four months from presentation of symptoms (53). Consequently, the goal of treatment is to increase OS and PFS, while balancing this against potential toxicities (14).

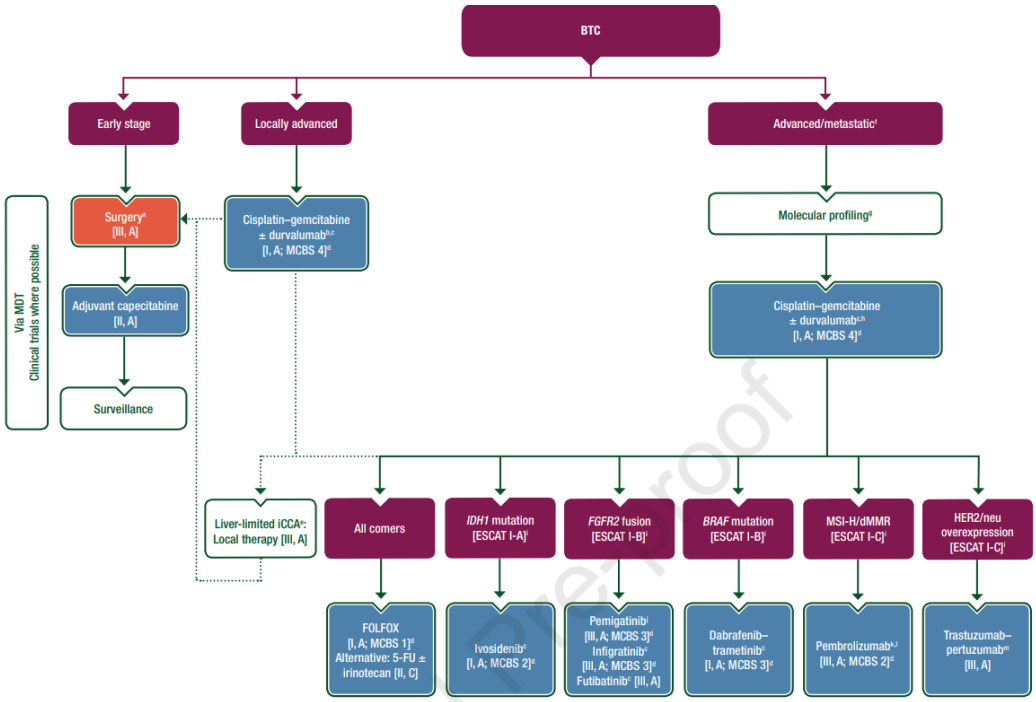
B.1.3.4 Clinical pathway of care

Guidelines on the treatment of CCA have been published by three European organizations; the ESMO, the European Association for the Study of the Liver (EASL) and the European Network for the Study of Cholangiocarcinoma (ENS-CCA)

(51, 5, 33, 54)) The ESMO guidelines and the ENS-CCA consensus statement both recommend cisplatin-gemcitabine 1st line (51, 5, 54). The EASL guidelines suggest that there is no SoC in the 1st line of therapy for unresectable CCA (33). However, the EASL guidelines have not been updated since 2014 to reflect the latest treatment options (81). In addition, The British Society for Gastroenterology (BSG) published guidelines on the management of CCA for the UK (55)

The ESMO guidelines were updated in November 2022. Figure 4 shows the ESMO 2022 algorithm for BTC treatment. These guidelines now recommend the combination of cisplatin–gemcitabine with durvalumab should be considered in the 1st line setting, although this regimen does not currently have a marketing authorisation for use in the UK. These guidelines reflect the latest treatment options available, particularly in the form of targeted treatments. Of these, pemigatinib was approved by NICE in August 2021 for treating relapsed or refractory advanced CCA with *FGFR2* fusion or rearrangement (TA722).

Figure 4. European (ESMO) BTC treatment guidelines



Source: Adapted Vogel et al (2023) (54).
Abbreviations: 1st LOT, 1st line of therapy; 2nd LOT, 2nd line of therapy; BTC, biliary tract cancer; FOLFOX, folinic acid, fluorouracil and oxaliplatin; SoC, standard of care.

The guidelines position mFOLFOX as the SoC in the 2nd line setting after cisplatin–gemcitabine although there is no specific licensed indication in BTC. Ivosidenib is

recommended for the treatment of patients with CCA and *IDH1* mutations who have progressed after ≥1 prior line of systemic therapy [I, A; ESMO-MCBS score: **3**; ESCAT score: I-A]. This ESMO score of 3 puts ivosidenib on the same level as pemigatinib and 2 levels above mFOLFOX (54), and this positioning of ivosidenib is aligned with the proposed positioning of ivosidenib in the treatment pathway in UK practice, presented in this submission. In addition, these guidelines also state that molecular testing is recommended for metastatic disease from diagnosis, and that IDH testing should be part of the gene panel.

The ENS-CCA consensus statement recommends FOLFOX as 2nd LOT but there are no further options recommended (5). The EASL guidelines suggest that there is no SoC in the 2nd LOTs for unresectable CCA (33). However, as previously mentioned the EASL guideline has not been updated since 2014**.** BSG published guidelines on the management of CCA, which are summarised in Table 3. (55)

Table 3: BSG guidelines

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

Abbreviations: CCA, cholangiocarcinoma.

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

Source: Khan *et al.*, (2012). (55)

B.1.4 Equality considerations

No equality issues to be considered.

B.1.5 NICE HST criteria

Servier acknowledges NICE's decision to deny HST criteria as it took into account the disease as a whole rather than the real world number of patients with IDH1 mutation and CCA.

However Servier believes that ivosidenib qualifies for the HST criteria, and an ICER threshold of £100,000, for the reasons outlined below.

The acceptance of the HST has a significant impact on how Ivosidenib is considered and which ICER threshold it will be judged against. This highlights the difficulties of using the ICER as a hard decision making rule given the intricacies in this case. We believe there is a strong case for NICE to use the ICER as a sense of location weighing up the different considerations in arriving at the right decisions for patients and the NHS.

Criterion 1 states that the disease is very rare defined by 1:50,000 in England. Ivosidenib is licensed for the treatment of locally advanced or metastatic CCA with an *IDH1* R132 mutation, and has an incidence rate of 0.8:50,000 as described in **Error! Reference source not found.**. It is very difficult to group this into a disease defined as CCA as a whole as the disease here is characterised by the *IDH1* R132 mutation, and with the evolution of targeted treatments, treatment pathways differ greatly, dependent on the disease.

Table 4: Epidemiology inputs

Inputs	Value	Source
Total population in England, 2023	57,600,000	ONS Principle Projection (56)
CCA incidence rate	4.41 per 100,000 persons	Genus et al. 2020 (35)
% of CCA patients with *IDH1* mutation	16.5%	Boscoe 2019 (14)
Total incidence rate with disease	419 (0.8 per 50,000)	ONS Principle Projection (56) (calculated from)
%(number) of patients with advanced/metastatic CCA	65% (272)	Valle et al. 2017 (39)
% (number)of patients receiving second-line therapy	60.40% (164)	Chamberlain et al. 2021 (57)

Abbreviations: CCA, cholangiocarcinoma; ONS, Office for National Statistics.

Criterion 2 states that no more than 300 people in England will be eligible for the technology in its licensed indication and no more than 500 people will be treated across all its indications. As Ivosidenib is only for patients with advanced/metastatic disease and also for only for those reaching second-line therapy, 164 people per year are thought to be eligible.

Criterion 3 states the very rare condition significantly shortens life or severely impairs its quality. All stage one year survival in 2015 for bile duct cancer was around 30% and 25% for men and women respectively.5 Year survival was 5% for both sexes. Most cases are diagnosed at the advanced stage where the cancer has already spread beyond the bile duct. (9)

Criterion 4 states there are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options. FOLFOX has a ph3 study in Biliary Tract Cancer (BTC), not cholangiocarcinoma with an R132 mutation, and the incremental benefit over best supportive care is <1mth, hence its clinical value is limited. Its use/recommendation in clinical guidelines (as of today) illustrates the lack of other satisfactory options. In recent years, there has been a paradigm shift towards targeted therapies for diseases with mutations. This shift is articulated through updates of international and local clinical guidelines, recommending to use targeted treatments over FOLFOX if mutations are confirmed

In addition to this, on 21 March 2018, orphan designation (EU/3/18/1994) was granted by the European Commission for ivosidenib for the treatment of biliary tract cancer (58).

Opinions on orphan medicinal product designations are based on the following three criteria:

- The seriousness of the condition
- The existence of alternative methods of diagnosis, prevention or treatment
- Either the rarity of the condition (affecting not more than 5 in 10,000 people in the EU) or insufficient returns on investment

B.2 Clinical effectiveness

The only RCT in IDH1m population, ClarIDHy was a multicentre, randomized, double-blind, placebo-controlled phase III study to evaluate ivosidenib in patients with unresectable, locally advanced or metastatic CCA and an IDH1 mutation previously treated with a GEM- or 5-FU containing regimen, and provides the relevant efficacy and safety data in this population.

ClarIDHy is reflective of and generalisable to patients in UK clinical practice. Ivosidenib demonstrated a 63% reduction in risk of disease progression vs. placebo, corresponding to a higher median PFS of 2.7 months for patients who received ivosidenib vs. 1.4 months for patients who received placebo (HR, 0.37; 95% CI, 0.25 to 0.54; $p < 0.0001$). After adjusting for crossover using the RPSFT method, the median OS in the placebo arm was 5.1 months vs 10.3 months in the ivosidenib arm (HR, 0.49; 95% CI, 0.34 to 0.70; $p < 0.0001$).

At an advisory board held by Servier, the initial reaction from one advisor was that efficacy signal in terms of progression free survival (PFS) is very clear with one of the clearest hazard ratios with a biologically targeted agent, and also the 12-month PFS at 22% is very strong, that is a lot of people alive for the patient population under investigation.

Ivosidenib better maintained the patient's QoL vs. placebo, by limiting decline in mobility, usual activities and anxiety or depression, as measured by the EQ-5D-5L. Clinically meaningful declines in physical and emotional functioning were observed via EORTC QLQ-C30 in the placebo arm compared to the ivosidenib arm, and tiredness symptoms were significantly increased for placebo. The two advisors spoken to during an advisory board meeting held by Servier that had recruited patients into ClarIDHy both stated they had no idea which patients where on active treatment and normally you would have a sense of understanding.

Safety data from ClarIDHy shows ivosidenib to have a favourable safety profile over placebo. Grade ≥3 TEAEs were reported in 89 patients (53.6%) in the ivosidenib arm vs. 22 patients (37.3%) in the placebo arm. Reported toxicities are manageable in patients with advanced CCA. TEAEs leading to discontinuation were less common in the ivosidenib arm when compared to the placebo arm (6.6% vs. 8.5%).

There is a lack of trial data for the relevant comparators specifically in IDH1 mutated CCA, however, indirect treatment comparisons using the most robust data sources and methods possible provide plausible evidence of clinically meaningful improvements in survival outcomes compared with current standard of care (FOLFOX). A Bucher analysis indicates that ivosidenib vs FOLFOX has a HR of [redacted] which is within the commonly associated threshold for a clinically meaningful improvement over SoC.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted in June 2021, subsequently updated on 24 January 2023, designed to answer the following research question:

- What are the clinical efficacy and safety outcomes of current treatment options in adults with unresectable, advanced or metastatic CCA?

A total of 6,023 references were identified from electronic databases searches conducted on 18th June 2021 (MEDLINE®: 1,212; Embase®: 3,860; CENTRAL®: 951). After removing duplicates, title and abstract of 4,634 references were screened

against the eligibility criteria. During screening, 4,260 references were excluded, resulting in 374 publications that were assessed for eligibility at the full text review stage. Out of these, 216 references were excluded based on full-text review which resulted in inclusion of 158 relevant references from databases search. Of these 158 publications, 44 publications (24 full text, 15 conference abstracts and 5 posters) for 28 studies were prioritised for data extraction. These 28 studies are 19 RCTs (as these were considered to provide most robust evidence) and nine non-RCTs on populations of interest (three on *IDH1*, five on *FGFR2* and one on *NTRK* mutations).

Regarding the studies identified via other methods, 30,453 publications were assessed for eligibility. Out of these, 37 additional publications were included: seven from cross-checks of other SLRs and TLR, three from the clinical trial search, 24 from the hand-search of conferences websites from 2016 to 2021 and three from other searches. Data from 18 publications for 8 studies were extracted.

Including the updated search, a total of 47 studies described in 90 publications met the eligibility criteria. The list of all 47included studies is presented in Appendix D. Additional details of the methodology and results are also provided in Appendix D

Notably, the eligibility criteria for the SLR conducted is broader than the population relevant to this appraisal (i.e., the SLR covers a broader CCA population, and not just those patients in second line therapy). This broader population was considered appropriate for the purpose of the SLR to ensure no potentially relevant studies were missed (e.g., a study for a broader CCA population that may report subgroup analyses by *IDH1* mutation) and therefore, a full unedited report can be found in the appendix.D However, aligned with the scope for this submission, the only identified studies considered to be of direct relevance to this appraisal are ClarIDHy and ABC-06 (as listed in Table 14).

Table 5. Included studies identified from clinical SLR

Study name (trial name): NCT	Study phase and centres	Relapsed or refractory CCA 2L+ (N)/ IDH1m identified (N)	Treatment/ comparator	CCA type N (%) Intrahepatic, extrahepatic, Hilar
Abou-Alfa 202055 (ClarIDHy): NCT02989857 (59)	Phase 3 France, Italy, South Korea, Spain, the	185/185	Ivosidenib (AG-120)/ placebo	Ivosidenib (AG-120) •iCCA: 111 (90) • eCCA: 1 (1)

	UK, and the US			•Hilar CCA: 4 (3) Placebo • iCCA: 58 (95) • eCCA: 1 (2) • Hilar CCA: 0
Lamarca 201934 (ABC-06): NCT01926236 (17)	Phase 3 UK	117/NR	mFOLFOX+ASC/ ASC	mFOLFOX+ASC • iCCA: 34 (56.6) • eCCA: 26 (43.3) • Hilar CCA: NR ASC • iCCA: 38 (66.6) • eCCA: 19 (33.3) • Hilar CCA: NR

Abbreviations: Abbreviations: ASC, Active symptom control; CCA, cholangiocarcinoma; mFOLFOX, folinic acid, fluorouracil and oxaliplatin; NR not recorded

B.2.2 List of relevant clinical effectiveness evidence

The relevant clinical effectiveness data for ivosidenib come from the phase 3 ClarIDHy study [NCT02989857]. A brief description of the ClarIDHy study is provided in Table 6.

Table 6: Clinical effectiveness evidence

Study	AG120-C-005 ClarIDHy (Phase III-pivotal) [NCT02989857]
Study design	Multicenter, placebo-controlled, randomized, double-blind study
Population	mIDH1 nonresectable or metastatic CCA previously treated patients
Intervention(s)	Tibsovo® 500 mg QD orally in continuous 28-day cycles
Comparator(s)	Placebo (n = 61) Crossover permitted at radiographic disease progression
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	**PFS (per ICR)** **Safety, PFS (by investigator review), OS**, ORR, **QoL**, PK, pharmacodynamic.
All other reported outcomes	[Please mark in bold the outcomes that are incorporated into the model]

Abbreviations: CCA, cholangiocarcinoma; ICR, independent central review; ORR; objective response rate; N/A, not applicable; OS, overall survival; PFS, progression-free survival; PK pharmacokinetic; QD, once daily.

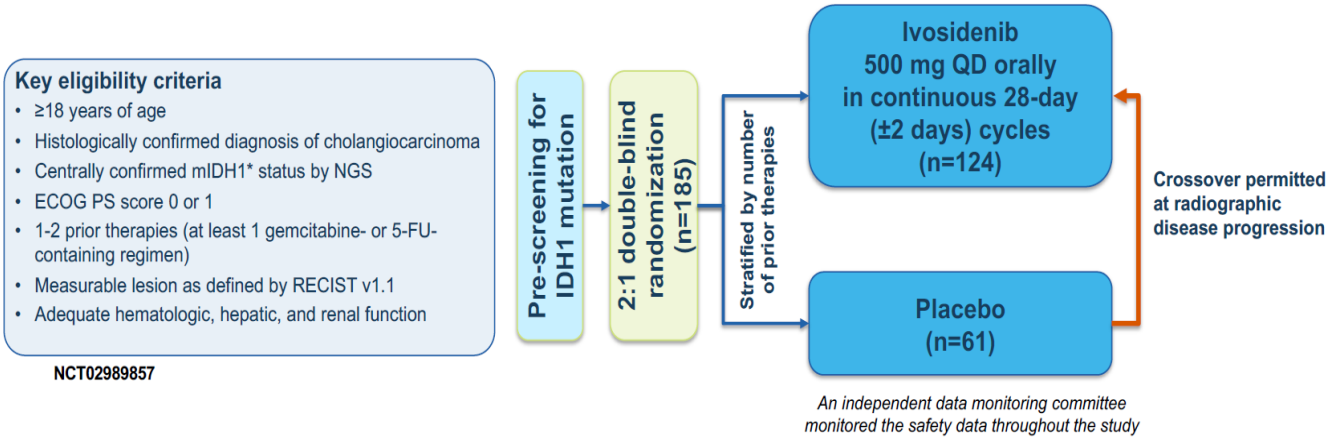
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Study Design

ClarIDHy was a multicentre, randomized, double-blind, placebo-controlled phase III study to evaluate ivosidenib in patients with unresectable, locally advanced or metastatic CCA and an *IDH1* mutation previously treated with a GEM- or 5-FU containing regimen. The patient population in ClarIDHy is representative of the real-world population. ClarIDHy had a patient-centric trial design that included input from the CCA Foundation (patient support association) and aimed to be ethically responsible, with the chosen comparator as placebo, due to no available evidence supporting 2nd line chemotherapy at the time of trial design (13). Patients were randomized in a 2:1 ratio to ivosidenib and placebo arms, and patients in each arm were further stratified by number of prior systemic treatment regimens for advanced disease (1 or 2) (59).

All patients enrolled in the ClarIDHy study continued with their assigned study treatment until withdrawal and/or study completion as per protocol (13). An overview of the ClarIDHy study design is illustrated in Figure 5.

Figure 5. ClarIDHy: study design



Source: Abou-Alfa 2019 (59)
Abbreviations: ECOG, Eastern Cooperative Oncology Group; 5-FU, 5-fluorouracil; mIDH1, mutant isocitrate dehydrogenase 1; NGS, next-generation sequencing; PS, performance status; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

Inclusion and exclusion criteria

Patients aged at least 18 years with a confirmed diagnosis of unresectable or metastatic CCA with documented *mIDH1* gene were eligible for this study. The key inclusion and exclusion criteria are summarized in Table 7.

Table 7. Key inclusion and exclusion criteria for ClarIDHy study

Inclusion criteria	Exclusion criteria
• ≥ 18 years of age • Histopathological diagnosis of unresectable or metastatic CCA and ineligible for curative resection, transplantation, or ablative therapies • Documented *IDH1* gene-mutated disease based on central laboratory testing • ECOG PS 0 or 1 • Expected survival ≥ three months • ≥ One evaluable/measurable lesion (RECIST v1.1) • Documented disease progression following ≥ one and ≤ two prior systemic regimens for advanced disease (must have received ≥ one GEM- or 5-FU-containing regimen for advanced CCA)	• Received a prior IDH inhibitor • Received systemic anticancer therapy or an investigational agent < two weeks prior to day one (four weeks for prior immune based anticancer therapy) • Received radiotherapy to metastatic sites of disease < two weeks prior to day one • Underwent hepatic radiation, chemoembolization, and radiofrequency ablation < four weeks prior to day one • Have known symptomatic brain metastases requiring steroids; patients with previously diagnosed brain metastases were eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for ≥ four weeks and have radiographically standard deviation for ≥ three months prior to study entry

Source: Clinical Study report (60)
Abbreviations: ECOG, Eastern Cooperative Oncology Group; GEM, gemcitabine; 5-FU, 5-fluorouracil; IDH, isocitrate dehydrogenase; *IDH1*, isocitrate dehydrogenase 1; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[1] 'ECOG PS 0 or 1' is a listed inclusion criterion in the study. However, the baseline characteristics show patients with ECOG PS of ≥1. When screened all patients had ECOG PS values of either zero or one. However, baseline characteristics refer to ECOG PS at baseline rather than at screening

Study treatments

Overall, 187 patients were randomized: 126 patients received 500 mg oral ivosidenib once daily (provided as 250 mg strength tablets) and 61 patients received placebo once daily in continuous 28-day cycles (plus or minus two days), starting on cycle 1 day 1 (C1D1). Study visits were done every other week during cycles 1–3 (days one and 15) and on day one of subsequent cycle (59).

Crossover

Crossover was allowed for patients in the placebo arm who experienced radiographic disease progression. Placebo patients who continued to meet eligibility criteria established during the end of treatment (EOT) visit were permitted to cross

over to the active treatment group. Placebo was not considered a prior line of therapy for the purpose of eligibility. Of the 61 patients randomized to placebo, 43 patients (70.5%) experienced progressed disease (PD) and crossed over to the ivosidenib arm, and these patients started again with study procedures as at C1D1 and continued to be evaluated for tumour response by the investigator (59).

Inclusion of crossover from the placebo arm to active treatment at disease progression ensured that the trial was patient relevant and ethical, as it allowed all patients to undergo exploratory treatment in absence of any approved treatment options (13). The use of placebo as a comparator and allowance of crossover from placebo to active treatment at the time of progression was considered acceptable by the Committee for Medicinal Products for Human Use (CMPH), as there were no approved drugs in CCA after first line and second-line therapy is ill-defined (61).

Dose modifications and delays

Dose modifications of ivosidenib or placebo from 500 mg to 250 mg were permitted in the study for management of AEs. If more than one AE occurred that required a dose modification, on resolution of all AEs to baseline or grade 1, Ivosidenib or placebo dose was reduced to 250 mg. Re-escalation was allowed with approval from the medical monitor (59).

B.2.3.2 Study Endpoints

Primary endpoint

The primary endpoint was PFS, defined as the time from date of randomization to date of first documented disease progression (as assessed by the independent radiology centre (IRC) per response evaluation criteria in solid tumours (RECIST) v1.1 (62), or date of death due to any cause.

Secondary endpoints

The secondary endpoints included:

- OS, defined as the time from date of randomization to date of death.
- ORR, defined as the proportion of patients with a best overall response (defined as CR or PR) as assessed by the investigator and by the IRC per RECIST v1.1 (62).

- Duration of response (DOR), defined as the time from date of first documented CR or PR to date of first documented disease progression or death due to any cause, as assessed by the investigator and by the IRC per RECIST v1.1.
- Time to recurrence (TTR), defined as the time from date of randomization to date of first documented CR or PR for responders, as assessed by the investigator and by the IRC per RECIST v1.1 (62)
- PFS as determined by the investigator.
- Safety and tolerability:
  - AE, serious adverse events (SAEs), AEs leading to discontinuation or death. The severity of AEs was assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03 (63)
  - Safety laboratory parameters, vital signs, 12-lead ECGs, evaluation of left ventricular ejection fraction (LVEF), ECOG PS, and concomitant medications
- Health-related quality of life (HRQoL) as assessed by validated instruments:
  - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30).
  - EORTC QLQ-BIL21.
  - Patient Global Impressions of Change (PGI-C)/ Patient Global Impressions of Severity (PGI-S).
  - Health economic outcomes as assessed by the EQ-5D-5L.
- Other:
  - PK, defined as serial or sparse blood sampling at specified time points for determination of plasma concentration-time profiles and PK parameters of ivosidenib
  - Pharmacodynamics, defined as blood sampling at specified time points for determination of 2-HG levels to characterize the pharmacodynamic effects of ivosidenib

Exploratory endpoints

The exploratory endpoints included (59):

- Baseline molecular and protein profiling using banked or fresh tumour samples.
- Evaluation of mutant *IDH1* levels and other genes in circulating tumour DNA using serial plasma samples.
- Serial blood and/or plasma samples for morphologic, functional, epigenetic, biologic, and metabolic profiling.
- Correlation of germline DNA drug metabolism, clearance related gene polymorphisms with PK variance, safety, and/or efficacy using buccal swab germline DNA samples, if the data are warranted.

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

B.2.4.1 Statistical analysis

The hypothesis objective states that in patients with unresectable, locally advanced or metastatic CCA and an *IDH1* mutation previously treated with a GEM- or 5-FU containing regimen, ivosidenib improves PFS compared to placebo.

The following patient populations (i.e., analysis sets) were evaluated and used for presentation of the data.

- (60) Intent-To-Treat Set (ITT): All patients who were randomized, with the treatment group designated according to the randomization. The ITT was the primary analysis set for all analyses except for safety.
- Safety Analysis Set (SAS): All patients who received at least one dose of study drug (ivosidenib or placebo). Patients were analyzed according to the actual treatment received. The SAS was the primary analysis set for all safety analyses.
- Per-Protocol Set (PPS): All patients in ITT who did not violate the terms of the protocol in a way that would significantly affect the study outcome, with treatment group designated according to the randomization.
- Crossover Set (COS): A subset of placebo patients who crossed over and received ivosidenib upon the radiographic PD. The COS was the analysis set for analyzing post-crossover data.

Assuming a HR of 0.5 for PFS, a total of 131 PFS events would be required to provide 96% power at a one-sided α level of significance of 0.025 to reject the null hypothesis. A hierarchical testing procedure was adopted for OS analyses only if the primary efficacy endpoint PFS was statistically significant. Two analyses were planned for OS: 1) an interim analysis at the projected time of the final analysis for PFS (provided PFS was significant); 2) a final analysis for OS when 150 deaths were observed. Assuming a HR of 0.67 for OS, a total of 150 deaths were calculated to provide 64% power at a one-sided α level of significance of 0.025 (59, 60).

The ITT population, comprising all randomly assigned patients within the designated treatment group, was used for primary efficacy analyses and other analyses unless otherwise specified. The safety analysis population included all patients who received at least one dose of study treatment, with the actual treatment received before crossover as the treatment group unless otherwise specified. The crossover population included a subset of placebo patients who crossed over and received open-label ivosidenib upon radiographic disease progression (59).

ITT is the standard method used in clinical trials; however, the results may be biased due to the clinical benefit attained by patients receiving treatment post switching and could result in the underestimation of the treatment effectiveness or AEs, as the ITT method does not attempt to adjust for treatment switching (64). Consequently, the results from ClarIDHy (and any subsequent analyses making use of the findings from ClarIDHy, such as the cost-effectiveness model) could misrepresent the true benefits of the experimental treatment. Whilst the ITT approach is a useful method of analysis, NICE advises that it is likely inappropriate in the presence of treatment switching (64). In order to mitigate the bias, NICE recommends the use of crossover adjustment methods (65).

For the ClarIDHy study, different crossover adjustment methods were explored (e.g., simple pooling, RPSFT, inverse-probability-of-censoring weighting [IPCW] and propensity score matching) (66). Ultimately, the RPSFT model was used to preserve the trial randomization, especially as the crossover rates were relatively high (i.e., approximately 70% of the placebo patients ultimately crossed over after progression). Findings from a methodological review showed that in instances of a large proportion of crossover in small trials, the RPSFT method is preferable (66). The RPSFT model is a commonly used and accepted method and has been used in

a large number of previous technology appraisals (67–72). The RPSFT method was used to reconstruct the survival curve (prespecified exploratory analysis) for patients receiving placebo, as if crossover had never occurred (73).

The RPSFT method estimates the difference in OS between groups in the trial if crossover had not occurred. It then proportionally adjusts the OS of those that crossed over to reflect what would have occurred if the participants had remained in their originally assigned group in the absence of switching (74). Key assumptions of this method include the 'common treatment effect', which means that counterfactual survival times are independent of treatment group and requires (at least approximately) that the treatment effect ('acceleration factor', or 'time ratio') be equal for all patients no matter when the treatment is received (75). If, for instance, the patient switches after disease progression it is possible that the benefit derived from treatment may not be equivalent to the benefit of patients who were randomly assigned to the experimental treatment group. Hence, there is potential for bias. Secondly, it assumes there is only random variation between treatment groups at baseline, apart from treatment allocation (75).

The major strengths of RPSFT method include that it maintains original randomized group definitions, thus produces randomization-based effect estimators (75), it uses the complete dataset of the trial, and that ranking of the observed time-to-event data is preserved after adjustment (66). The limitations of the RPSFT method include that the "common treatment effect" assumption cannot be tested and may not be clinically plausible if the magnitude of treatment effect is dependent on extent of disease progression, that it does not use information on covariates which may affect the probability of crossover, and the assumption that mortality decreases constantly during the time that the investigational drug is received which may not reflect reality (66).

A Cox regression model stratified by the randomization stratification factor was used to estimate the HR and the 95% CI for the PFS and OS comparison of the ivosidenib and placebo groups as well as the OS analyses. A log-rank test stratified by the randomization stratification factor was used to assess significance. Ninety-five percent (95%) CIs for the survival rate estimates were calculated via log–log transformation. Patients starting treatment with a new anticancer therapy before IRC-assessed progression or death were censored at the last adequate assessment

before the new anticancer therapy. Patients alive without a post-baseline assessment were censored at the randomization date. Patients who did not progress or die by the data cut-off date were censored at the last adequate assessment date. Patients with progression or death following a long gap (≥2 consecutive scheduled assessments missing) were censored at the date of the last adequate assessment before the gap (59). For OS, patients without documentation of death at the time of the data cut-off date were censored at the date the patient was last known to be alive or the data cut-off date, whichever was earlier.

Subgroup analyses by previous line of therapy, sex, extent of disease at screening, CCA type, ECOG PS score, and geographical region were performed on PFS per IRC and OS, and included Kaplan-Meier (KM) summaries, unstratified log-rank test, p values, and HRs from Cox regression models. The proportional hazard assumption was met based on graphic check. Mixed-effect models with repeated measurements (with baseline score, treatment, visit, and treatment-by visit as fixed effects and patient as random effect) were used on change scores from baseline to cycle 2 day 1 for subscales of the EORTC QLQ-C30 and QLQ-BIL21, corresponding to the three domains of interest (physical functioning, pain, and appetite loss) (76, 77). Clinically meaningful change thresholds on these subscales were estimated by means of the respective PGI-C ratings as anchors. The focus was on cycle 2 day 1, considering the availability of QoL data. QoL analyses were exploratory in nature; therefore, type 1 error control for multiplicity was not considered. All time-to-event endpoints were estimated by means of KM methods. Descriptive statistics were used to summarize safety data, response rates, QoL data, PK and pharmacodynamic data. All reported p values are one-sided unless otherwise specified. Statistical analyses were performed via statistical analysis software, version 9.4.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

The quality assessment of ClarIDHy is summarised in Table 8. Quality assessments of the studies identified by the SLR are summarised in Appendix D.

Table 8: Risk of bias

Study / Reference	Study Trial ID (Study Name)	Interventions	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Abou-Alfa et al., 2020 (7)	NCT02989857 (ClarIDHy)	Ivosidenib vs Placebo							

High Unclear Low

B.2.6 Clinical effectiveness results of the relevant studies

B.2.6.1 Study population

B.2.6.1.1 Patient disposition

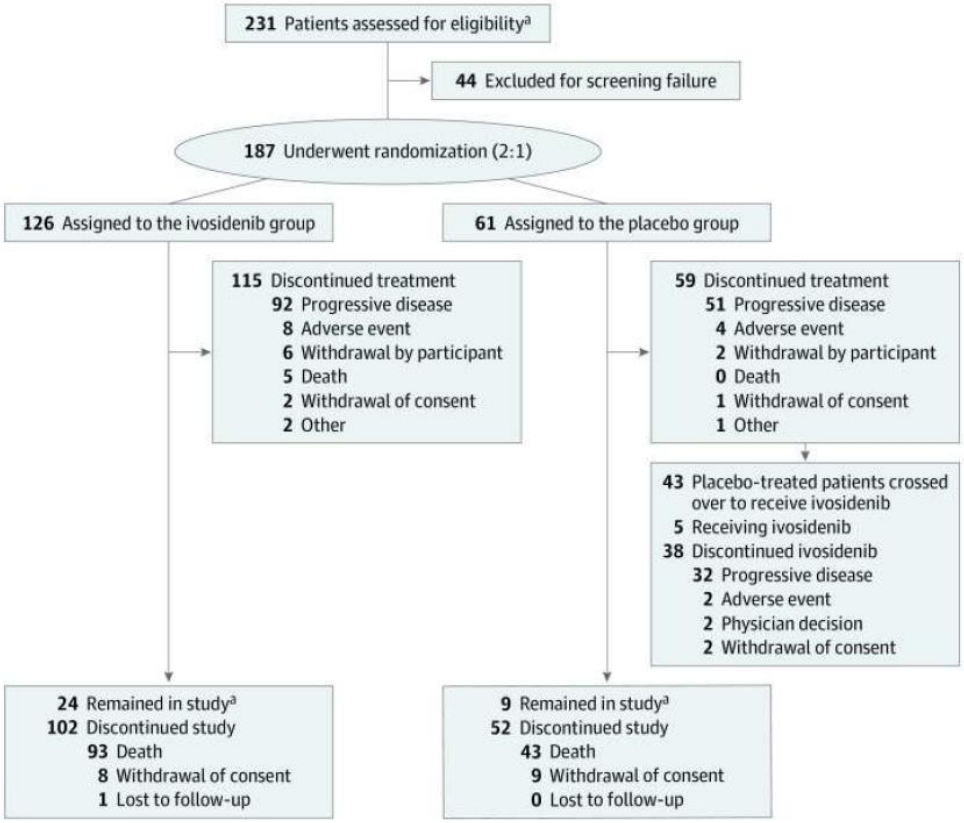
Overall, 231 patients were assessed for eligibility between 20 February 2017 and 1 March 2019. Based on secondary analysis (31 May 2020 data cut-off date), 187 patients have been randomized; 126 patients received ivosidenib and 61 patients received placebo. Enrolment was completed on 1 March 2019, and no additional patients were randomized in the study after this date. The patient population in ClarIDHy was representative of the real-world population for mIDH1 CCA (24).

As of the final database lock date of 21 June 2021, among patients who were randomized to and received ivosidenib or placebo, the most common reason for treatment discontinuation was PD in 98 patients (79.7%) and 51 patients (86.4%), respectively. There were no other clinically meaningful differences between the ivosidenib and placebo arms in terms of reasons for discontinuation.

Of the 61 patients randomized to placebo, 43 patients (70.5%) experienced PD based on investigator assessment and crossed over to receive open-label ivosidenib as per the protocol. At the time of the final database lock date of 21 June 2021, 36 patients (83.7%) had discontinued treatment. The most common (≥ 5%) reasons for

treatment discontinuation among patients who crossed over were progression of disease in 36 patients (83.7%) and withdrawal of consent in three patients (7%). This is described in the CONSORT diagram in Figure 6.

Figure 6. ClarIDHy - CONSORT diagram



Source: Zhu 2021 (78)

Note: As of the cut-off date (31 May 2020).

B.2.6.1.2 Baseline characteristics

Baseline characteristics of patients in the ClarIDHy study are presented in Table 9.

Table 9. ClarIDHy: patient demographics and baseline characteristics (31 May 2020 data cut-off)

Parameter	Ivosidenib (n = 126)	Placebo (n = 61)
Age (years)		
Median (range)	61 (33 to 80)	63 (40 to 83)
Sex, n (%)		
Male	44 (35)	24 (39)
Female	82 (65)	37 (61)
ECOG PS score at baseline, n (%)		
0	50 (40)	19 (31)
1	75 (60)	41 (67)
2	0	1 (2)
3	1 (1)	0
IDH1 mutation, n (%)		
R132C	86 (68)	45 (74)
R132L	21 (17)	7 (11)
R132G	17 (14)	6 (10)
R132S	2 (2)	1 (2)
R132H	0	2 (3)
Cholangiocarcinoma subtype		
Intrahepatic	113 (90)	58 (95)
Extrahepatic/perihilar	5 (4)	1 (2)
Unknown	8 (6)	2 (3)
Extent of disease at screening		
Local/regional	9 (7)	5 (8)
Metastatic	117 (93)	56 (92)

Source: Abou-Alfa (2020) (59)
Abbreviations: ECOG, Eastern Cooperative Oncology Group; IDH1, isocitrate dehydrogenase 1; PS, performance status

B.2.6.2 Primary efficacy outcome

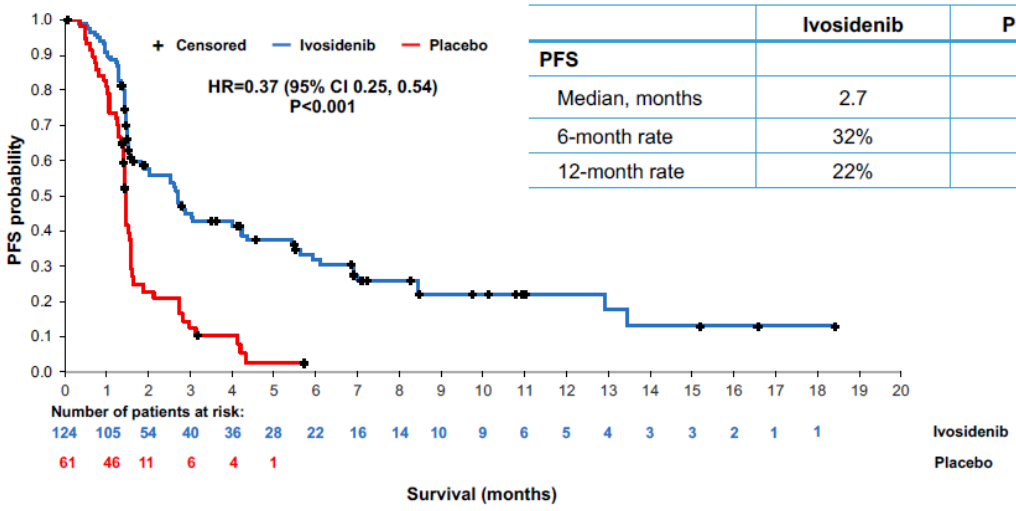
PFS based on IRC review was analyzed at the time of primary analysis (31 January 2019 data cut-off). Ivosidenib demonstrated a 63% reduction in risk of disease progression versus placebo, corresponding to a higher median PFS of 2.7 months

for patients who received ivosidenib versus 1.4 months for patients who received placebo (HR, 0.37; 95% CI, 0.25 to 0.54; p < 0.0001) (59).

No patients in the placebo group were free from progression for ≥6 months (59). The 6-month PFS rate was 32% and the 12-month PFS rate was 22% for the ivosidenib group. 6- and 12-month PFS rates in the placebo group were not estimable (NE) (59). At an advisory board held by Servier, the reaction from one advisor was extremely positive, as it was noted that the efficacy signal in terms of PFS benefit was one of the clearest benefits expressed via HR they had seen for a biologically targeted agent, and also that the 12-month PFS proportion of 22% was notably high, in consideration of the patient population under investigation (27).

Figure 7 presents the KM analysis of PFS for the ivosidenib and placebo arms.

Figure 7. ClarIDHy: ivosidenib vs. placebo – PFS (overall) (31 January 2019 data cut-off)



	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE

Source: Abou-Alfa 2020 (59).
Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival.

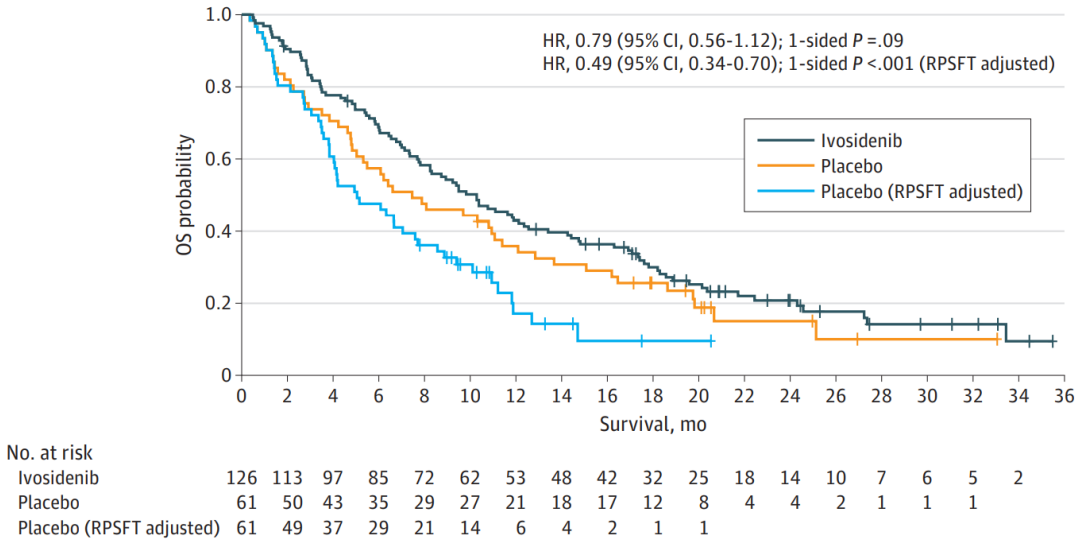
B.2.6.3 Secondary efficacy outcomes

Based on the secondary analysis (31 May 2020 data cut-off), ClarIDHy enrolled 187 patients with *IDH1*-mutant CCA, with 126 patients in the ivosidenib arm and 61 patients in placebo arm (78). Of the 61 patients in the placebo arm, 43 patients (70.5%) crossed over to open-label ivosidenib upon radiographic disease progression and unblinding. Median OS was 10.3 months in the ivosidenib arm and 7.5 months in the placebo arm, demonstrating a numerical improvement of 2.8 months in OS (HR, 0.79; 95% CI, 0.56 to 1.12; p = 0.093) before adjusting for crossover (Figure 8). The 6-month OS rate was 69% for ivosidenib and 57% for

placebo, and the 12-month OS rate was 43% for ivosidenib and 36% for placebo (78)

After adjusting for crossover using the pre-specified RPSFT method, the median OS in the placebo arm was 5.1 months vs 10.3 months in the Ivosidenib arm, demonstrating an improvement in OS of 5.2 months. (HR, 0.49; 95% CI, 0.34 to 0.70; p < 0.0001).

Figure 8. ClarIDHy: ivosidenib vs. placebo – OS (31 May 2020 data cut-off)



Source: Zhu 2021 (78)
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; RPSFT, rank-preserving structural failure time.

B.2.6.4 Response outcomes

Response outcomes (Table 10) were analyzed at the time of primary analysis (31 January 2019 data cut-off). The ORR (CR or PR) as assessed by IRC was 2.4% in the ivosidenib arm, with three patients who achieved a confirmed PR, and three patients had an unconfirmed response (37). None of the patients in the placebo arm achieved CR or PR.

The treatment duration reported was 11.0, 6.0, and 17.1 months, respectively, in three patients who reported confirmed PR in the ivosidenib arm, thereby providing a clinical benefit and stabilizing the disease vs. placebo. Approximately half (50.8%) of patients in the ivosidenib arm had a best overall response (BOR) of SD, while 17 patients (27.9%) in the placebo arm had a BOR of SD before crossover. More than half (57.4%) of patients in the placebo arm experienced only PD while 41 patients (33.1%) in the ivosidenib arm experienced only PD per RECIST v1.1 (60).

The ORR (CR or PR) assessed by the investigator was similar to that observed with IRC assessment. PR was achieved in four patients (3.2%) in the ivosidenib arm, compared to one patient (1.6%) in the placebo arm. The four patients with PR in the ivosidenib arm had a treatment duration of 22.5, 11.0, 17.1, and 14.1 months, The patient with a PR in the placebo arm had a treatment duration of 5.5 months on placebo and crossed over to ivosidenib subsequently (60).

The DOR for each of these three patients in the ivosidenib arm was 2.79, 2.73, and 11.07 months, respectively. The DOR for each of these four patients in the ivosidenib arm (before crossover) was 7.69, 4.27, 8.08, and 8.77 months, respectively, and 4.30 months for the responder in the placebo arm. None of the patients had a confirmed response after crossover per investigator assessment (60).

The DCR was 53% for ivosidenib arm, with 2% achieving a PR and 51% having SD. In the placebo arm, DCR was 28% (all SDs) (59).

Table 10. Summary of best overall response per independent review committee – before crossover (ITT set)

	Ivosidenib (n=124)	**Placebo (n=61)**
Confirmed BOR, n (%)		
PR	3 (2.4)	0
SD	63 (50.8)	17 (27.9)
PD	41 (33.3)	35 (57.4)
UNK	2 (1.6)	0
NE	1 (0.8)	1 (1.6)
Confirmed ORR (CR or PR), n (%)	3 (2.4)	0
95% CI of response rate[1]	(0.5, 6.9)	(0.0, 5.9)
Odds Ratio (95% CI)[2]	NE (0.29, NE)	
P-value[3]	0.299	
Confirmed + unconfirmed PR, n (%)	6 (4.8)	0

Source: Abou-Alfa et al. 2020 (59)

Abbreviations: BOR, best overall response, CI, confidence interval; n, number; CR, complete response; NE, not estimable; PR, partial response; PD, progressive disease; ORR, objective response rate; SD, stable disease; UNK, unknown.

B.2.6.5 Overview of patient reported outcome measures

QoL was well-maintained in the ivosidenib arm compared to the placebo arm by better preserving physical and emotional functioning and limiting symptom worsening (such as pain, dyspnoea, tiredness), as measured by EORTC metrics (79).

In the ClarIDHy trial, patient HRQoL was assessed prior to dosing on C1D1 and then prior to dosing on day 1 of each subsequent cycle until EOT (79). Ivosidenib was associated with preservation of HRQoL at cycle 2, day 1 compared with placebo, as assessed with mixed-effect models with repeated measurements analyses of the EORTC QLQ-C30 and QLQ-BIL21 instruments (79). There were minimal changes in data between the May 31, 2020 data cut-off and the June 21, 2021 database lock, there was no impact of additional HRQOL data on study results (79).

A clinically meaningful decline in physical functioning was observed via EORTC QLQ-C30 in the placebo arm compared to ivosidenib arm (79):

- Cycle 2 Day 1: Difference of 11.0 points; 95% CI, 4.23 to 17.71; p = 0.001
  - Ivosidenib arm: LS mean [SE]: -2.4 [1.75]
  - Placebo arm: LS mean [SE]: -13.4 [2.95]
- Cycle 3 Day 1: Difference of 12.3 points; 95% CI, 3.88 to 20.76; p = 0.004
  - Ivosidenib arm: LS mean [SE]: -0.3 [1.89]
  - Placebo arm: LS mean [SE]: -12.6 [3.86]

Emotional functioning was significantly worse for placebo vs. ivosidenib based on EORTC QLQ-C30 (79):

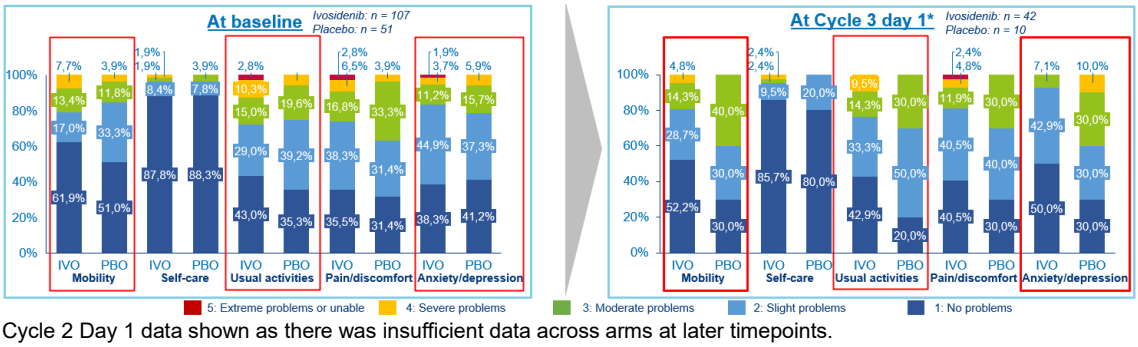
- Cycle 2 Day 1: Difference of 13.8 points; 95% CI, 6.08 to 21.43; p = <0.001
  - Ivosidenib arm: LS mean [SE]: 0.3 [1.96]
  - Placebo arm: LS mean [SE]: -13.5 [3.37]
- Cycle 3 Day 1: Difference of 18.8 points; 95% CI, 8.82 to 28.74; p = <0.001
  - Ivosidenib arm: LS mean [SE]: 1.3 [2.15]
  - Placebo arm: LS mean [SE]: -17.5 [4.59]

Based on the results from EORTC QLQ-BIL21, tiredness symptoms were significantly increased for placebo (79):

- Cycle 2 Day 1: Difference of 13.2 points; 95% CI, -22.67 to -3.77; p = 0.006
  - Ivosidenib arm: LS mean [SE]: 0.0 [2.39]
  - Placebo arm: LS mean [SE]: 13.2 [4.17]
- Cycle 3 Day 1: Difference of 3.9 points; 95% CI, -16.20 to 8.38; p = 0.532
  - Ivosidenib arm: LS mean [SE]: -5.3 [2.65]
  - Placebo arm: LS mean [SE]: -1.4 [5.67]

The trend in emotional functioning was also supported by descriptive results from the EQ-5D-5L; a generic health status instrument. Ivosidenib better maintained the patient's QoL versus placebo, by limiting decline in mobility, usual activities and anxiety or depression, as measured by the EQ-5D-5L (36, 50) (Figure 9). Compared to baseline, ivosidenib increased the proportion of patients that experienced no or slight grade mobility problems (ivosidenib: +3.2%, placebo: -24%), no or slight problems with anxiety or depression (ivosidenib: +9.7%, placebo: -18.5%), and no or slight problems in usual activities (ivosidenib: +4.2%, placebo: -4.5%) at cycle 3 day 1 (57) (Figure 9).

Figure 9. ClarIDHy: EQ-ED-5L responses (January 31, 2019 data cut-off)



Cycle 2 Day 1 data shown as there was insufficient data across arms at later timepoints.
*Each cycle lasts 28 days
Source: Chamberlain 2020 (57)).
Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; QLQ-C30, quality of life questionnaire core 30; QLQ-BIL21, quality of life questionnaire cholangiocarcinoma and gallbladder cancer module; QoL, quality of life.

Furthermore, ivosidenib continued to demonstrate a sustained QoL for 14 cycles (one year). A clinically meaningful physical functional decline was only observed in the placebo arm (59) Patients in the placebo arm reported a larger decline in

physical, cognitive, and emotional functioning from baseline to cycle 2, day 1 compared with those in the ivosidenib arm based on the QLQ-C30 functional subscales (physical, p = 0.002; cognitive, p = 0.029; emotional, p < 0.001) (48). Similar preservation of physical and emotional functioning was also observed for ivosidenib at cycle 3, day 1 (physical, p = 0.004; emotional, p < 0.001). Patients in the placebo arm also reported increased worsening of pain (p = 0.039) and dyspnea (p = 0.026) than patients in the ivosidenib arm based on the EORTC QLQ-C30 symptom subscales from baseline to cycle 2, day 1. Finally, patients in the placebo arm reported higher tiredness (p = 0.006) and anxiety (p = 0.009) by cycle 2, day 1 compared to those in the ivosidenib arm based on the EORTC QLQ-BIL21 (78).

In addition to the patient reported outcome measures reported above, it provides an added advantage to the patients to self-manage their disease since ivosidenib is administered as an oral therapy (two 250 mg tablets, once daily), unlike chemotherapy which requires hospital admission and thereby imposes additional burden to the patients. Hence, ivosidenib helps the patients to maintain a better daily routine and enhance QoL (80).

Two advisors at an advisory board meeting held by Servier had recruited patients into the ClarIDHy study, and explained that they both could not easily identify which patients were on active treatment versus placebo, whereas in other placebo-controlled studies it would normally be possible to make an informed guess as to which treatment the patient was receiving due to the impact on their QoL. (27)

B.2.7 Subgroup analysis

The prespecified subgroups included (60):

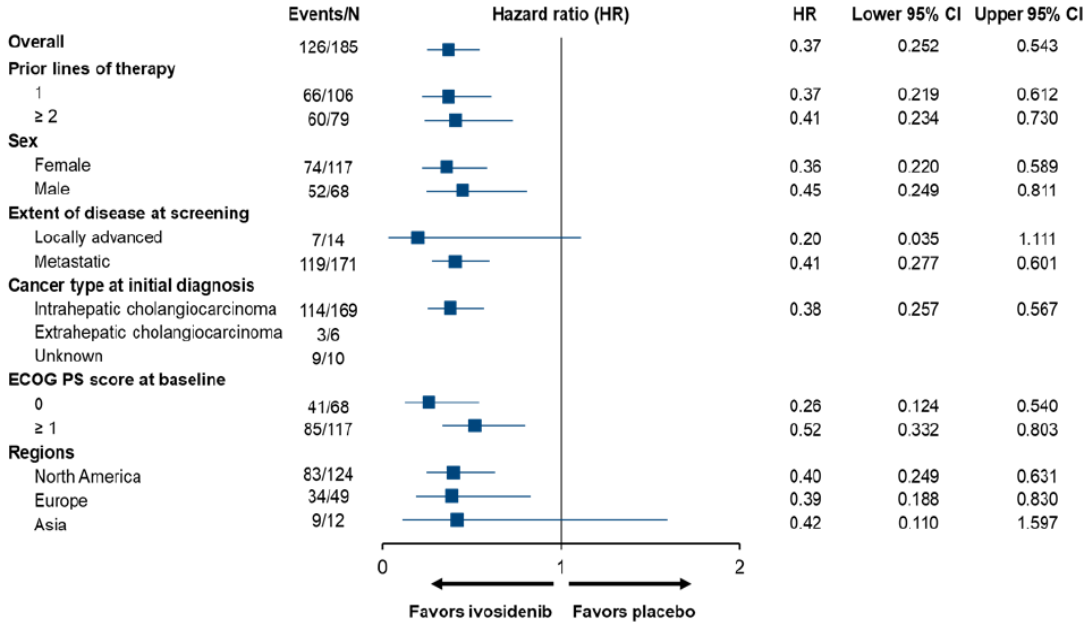
- The actual number of prior line of therapies in advanced setting (1 vs. ≥2)
- Gender (female vs. male)
- Extent of disease at screening (locally advanced vs. metastatic)
- CCA type (intrahepatic vs. extrahepatic)
- ECOG at baseline (0 vs. ≥1[1])

[1] 'ECOG PS 0 or 1' is a listed inclusion criterion in the study. However, the baseline characteristics show patients with ECOG PS of ≥1. When screened all patients had ECOG PS values of either zero or one. However, baseline characteristics refer to ECOG PS at baseline rather than at screening.

- Regions (North America vs. Europe vs. Asia)

The observed PFS benefit in the ivosidenib arm compared to placebo was generally consistent across key patient subgroups (Figure 10). In general, most of the subgroups favoured ivosidenib over placebo (statistically significant), except for two subgroups (locally advanced disease and Asian region) where the upper confidence level crossed unity due to very low sample sizes (59).

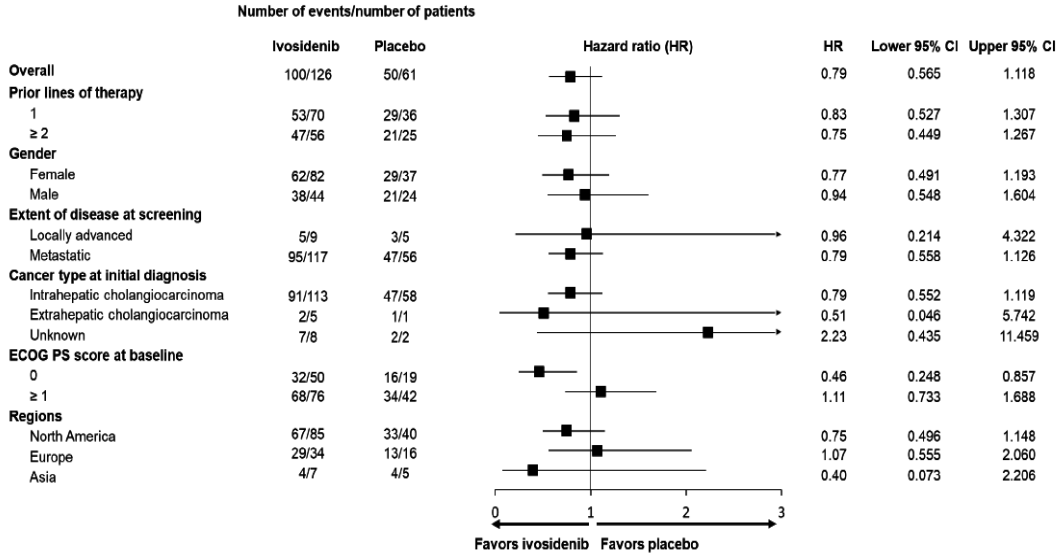
Figure 10. ClarIDHy: ivosidenib vs. placebo by subgroup – PFS (31 January 2019 data cut-off)



Source: Abou-Alfa 2020 (59).
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PS, performance status.

The subgroup analyses for OS are presented in Figure 11 and were consistent with the overall OS analysis. The results based on the subgroup analyses should be interpreted with caution due to the small sample size and not accounting for crossover adjustment (78)

Figure 11. ClarIDHy: ivosidenib vs. placebo by subgroup – OS (31 May 2020 data cut-off)



Source: Zhu 2021 (78)
Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PS, performance status.

Provide a summary of the results for the subgroups in appendix E.

B.2.8 Meta-analysis

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

B.2.9 Indirect and mixed treatment comparisons

In appendix D include full details of the methodology for the indirect comparison or mixed treatment comparison.

Following the SLR two studies were considered eligible for evidence synthesis, which reported outcomes of interest for the treatments ivosidenib (ClarIDHy study (59)), and folinic acid + fluorouracil + oxaliplatin + active symptom control (FOLFOX + ASC; ABC-06 study (17)). ABC-06 was a randomised phase 3, multicentre, open-label study of ASC alone or mFOLFOX+ASC for patients with locally advanced/metastatic BTCs previously treated with cisplatin/gemcitabine chemotherapy.

There is notable heterogeneity across each of these studies, with regard to trial design and patient population. Key differences include:

- ClarIDHy was a double-blind study, whereas ABC-06 was open label
- ClarIDHy was a multinational study, whereas ABC-06 was based in the UK
- ABC-06 investigated all BTCs, whereas the population of ClarIDHy investigated patients with advanced/metastatic or surgically unresectable CCA who had progressed on at least one line of prior systemic therapy and included a majority of patients with iCCA
- ClarIDHy included only patients with *IDH1* mutations; the proportion of patients with these mutations was not reported in ABC-06

Nevertheless, despite these differences, the ABC-06 study was the only study identified that could be used to form an indirect comparison to the ivosidenib arm of the ClarIDHy study. In the tables that follow, further information is provided comparing the ClarIDHy and ABC-06 studies.

Table 11. Summary of the key inclusion and exclusion criteria

Study	Inclusion criteria	Exclusion criteria
ClarIDHy (59)	• Aged 18 years or older • Histologically confirmed, advanced, *IDH1*-mutant CCA • Up to two previous treatment regimens for advanced disease (unresectable or metastatic), with one gemcitabine-based or fluorouracil-based chemotherapy and no previous mutant *IDH* inhibitor therapy, were required • Life expectancy of at least 3 months • ECOG performance status score of 0 or 1 • A measurable lesion as defined by RECIST 1.1 • Adequate haematological, hepatic, and renal function	• Patients were excluded if they had received systemic anticancer therapy or an investigational agent less than 2 weeks before day 1 (washout from previous immune-based anticancer therapy being 4 weeks) • Had received radiotherapy to metastatic sites of disease less than 2 weeks before day 1; or had undergone hepatic irradiation, chemoembolisation, and radiofrequency ablation less than 4 weeks before day 1
ABC-06 (17)	• Histologically / cytologically verified, non-resectable or recurrent / metastatic CCA, gallbladder or ampullary carcinoma • Patients must have failed no more than one prior course of chemotherapy (gemcitabine and cisplatin) with clear evidence of disease progression. • ECOG performance status 0-1 • Age ≥18 years and life expectancy >3 months	• Incomplete recovery from previous therapy or unresolved biliary tree obstruction (includes ongoing neuropathy of grade >1 from cisplatin) • Any evidence of severe or uncontrolled systemic diseases which, in the view of the investigator, makes it

Study	Inclusion criteria	Exclusion criteria

	• Adequate renal function:
	  ○ Serum urea and serum creatinine < 1.5 times ULN
	  ○ Creatinine clearance ≥ 30ml/min. Creatinine clearance to be estimated using the Cockroft-Gault formula
	• Adequate haematological function: Hb ≥ 100g/l, WBC ≥ 3.0 x 10^9/L, ANC ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/l
	• Adequate liver function: total bilirubin < 60 µmol/L and ALP, along with AST and/or ALT ≤ 5 x ULN
	• Adequate biliary drainage, with no evidence of ongoing infection (patients on maintenance antibiotics are eligible when acute sepsis has resolved)
	• Women of child bearing age must have a negative pregnancy test prior to study entry and be using an adequate contraception method. This must be continued for 4 months after completion of chemotherapy, unless child bearing potential has been terminated by surgery/radical radiotherapy
	• Men must be willing to use an adequate method of contraception during chemotherapy and until 6 months after chemotherapy
	• Patients must have given written informed consent
	• All patients must be randomised and sites must ensure that patients allocated chemotherapy (ARM B only) start treatment within 6 weeks of radiological progression
		undesirable for the patient to participate in the trial
		• Evidence of significant clinical disorder or laboratory finding which, in the opinion of the investigator makes it undesirable for the patient to participate in the trial
		• Any patient with a medical or psychiatric condition that impairs their ability to give informed consent
		• Any other serious uncontrolled medical conditions
		• Clinical evidence of metastatic disease to brain
		• Any pregnant or lactating woman
		• Clinically significant cardiovascular disease. (i.e. active; or <12 months since e.g. cerebrovascular accident, myocardial infarction, unstable angina, NYHA grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, uncontrolled hypertension)
		• Patients must not have a history of other invasive malignant diseases within the last 5 years (other than adequately treated non-melanotic skin cancer or in-situ carcinoma of the uterine cervix)

Table 12. Summary of disease characteristics at baseline

Study	Sample size (N)	Previous LoT (%)	Extent of disease at screening (%)	Type of mutation (%)

ClarIDHy (59)	• Ivosidenib: 124
	• Placebo: 61
		• Ivosidenib:
		  ○ 1: 53
		  ○ 2: 47
		  ○ ≥3: 0
		• Placebo:
		  ○ 1: 54
		  ○ 2: 46
		  ○ ≥3: 0
			• Ivosidenib:
			  ○ Local–regional: 7
			  ○ Metastatic: 93
			• Placebo:
			  ○ Local–regional: 8
			  ○ Metastatic: 92
				• Ivosidenib: *IDH1* 100%
				• Placebo: *IDH1* 100%

	• ASC: 81	• ASC:	• ASC:	NR

Study	Sample size (N)	Previous LoT (%)	Extent of disease at screening (%)	Type of mutation (%)
ABC-06 (17)	• FOLFOX + ASC: 81	○ 1: 100 ○ ≥2: 0 • FOLFOX + ASC: ○ 1: 100 ○ ≥2: 0	○ Local–regional: 19 ○ Metastatic: 81 • FOLFOX + ASC: ○ Local–regional: 17 ○ Metastatic: 83	

Table 13. Proportion of CCA subtypes

Study	CCA	iCCA	eCCA	pCCA
ClarIDHy (59)	100%	91%	5%*	2%
ABC-06 (17)	72%	44%	27%	0%

Table 14. Summary of patient characteristics at baseline

Study	Sample size (N)	Median age, years (range)	Male, (%)	ECOG PS (%)
ClarIDHy (59)	• Ivosidenib: 124 • Placebo: 61	• Ivosidenib: 61 (33–80) • Placebo: 63 (40–83)	• Ivosidenib: 35 • Placebo: 39	• Ivosidenib: ○ 0: 40 ○ 1: 60 ○ 2: 0 ○ 3: 1 • Placebo: ○ 0: 31 ○ 1: 67 ○ 2: 2 ○ 3: 0
ABC-06 (17)	ASC: 81 FOLFOX + ASC: 81	ASC: 65 (59–72) FOLFOX + ASC: 65 (59–72)	ASC: 46 FOLFOX + ASC: 53	• ASC: ○ 0: 35 ○ 1: 64 ○ Missing: 1 • FOLFOX + ASC: ○ 0: 31 ○ 1: 68 • Missing: 1

Table 15. Definition of outcomes of interest

Study	PFS	OS	ORR	CR	SAEs	Discontinuation due to AEs
ClarID Hy (59)	Defined as the time from the date of randomisation to the date of first documentation of disease progression or death owing to any cause, whichever occurred first	Defined as the time from date of randomisation to the date of death due to any cause.	Sum of CR and PR per RECIST 1.1	RECIST 1.1	NCI CTCAE, version 4.03	NCI CTCAE, version 4.03
ABC-06 (17)	Defined as the time between randomisation and radiological disease progression or death of any cause, whichever occurred first	Defined as the time from randomisation to death from any cause	RECIST 1.1	RECIST 1.1	CTCAE, version 4.03	NR

B.2.9.1 Results

For the comparison of OS between ClarIDHy and ABC-06, a frequentist approach using the Bucher method was preferred over a Bayesian approach due to the limited evidence base (n = 2 studies). Bucher analysis is used to compare outcomes between two indirect treatments across different studies, where different interventions are compared to a common comparator (i.e., placebo/ASC). This method assumes that the trials included in the ITC are sufficiently similar with regards to the study population, study design, outcome measurements, and the distribution of treatment effect modifiers.

However, a Bucher ITC versus mFOLFOX was only possible for the OS endpoint, because PFS data were not reported for the ASC (control) arm of ABC-06. Therefore, a connection between common comparators could not be formed for the outcome of PFS. In the absence of the ability to perform an formal indirect comparison via a common comparator, a naïve comparison was undertaken using unadjusted PFS estimates for mFOLFOX (based parametric curves fitted to pseudo patient-level data, which was re-created using the approach of Guyot *et al.* (81)

The primary analysis of OS followed the ITT principle, which does not account for the effect of crossover adjustment (36). Consequently, the prespecified rank-preserving structural failure time (RPSFT) model was used to correct for crossover. The RPSFT

method is based on a common treatment assumption: the treatment effect of ivosidenib is the same for all individuals, regardless of when treatment is received. Table 16 shows the results for OS before and after crossover adjustment.

Table 16. Bucher analysis results for OS

Analysis	HR	95% CI
Unadjusted		
ClarIDHy (ivosidenib vs placebo)	[redacted]	
ABC-06 (FOLFOX + ASC vs ASC)		
Ivosidenib vs FOLFOX +ASC		
Crossover adjustment		
ClarIDHy (ivosidenib vs Placebo)	[redacted]	
ABC-06 (FOLFOX + ASC vs ASC)		
Ivosidenib vs FOLFOX +ASC		

Abbreviations: ASC, Active symptom control; CI, Confidence interval; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HR, Hazard ratio; OS, Overall survival.

While no statistically significant differences are observed in either analysis using the Bucher method, the crossover-adjusted results have higher validity given the correction for high levels of treatment switching in ClarIDHy (around 70% of the placebo arm), with a HR of [redacted] which is within the commonly associated threshold for a clinically meaningful improvement over SoC (82).

As a Bucher analysis could not be conducted for PFS and a naïve comparison was necessary in the base case, an exploratory scenario analysis was conducted based on restricted mean survival times (RMSTs) observed in ABC-06. This analysis is discussed further in Section B.3.3.4.3.

The main strength of the ITC conducted relates to the rigidity and comprehensiveness of the SLR conducted to identify relevant studies, the evaluation of between-study heterogeneity and potential sources of bias. However, even though the ClarIDHy trial provides CCA-specific results for the endpoints of interest (PFS, OS and ORR) the KM estimates available from ABC-06 were not specific to CCA patients and included BTC patients. Additionally, the Bucher analysis assumes that the trials included in the ITC are similar with regards to the study population, study design, outcome measurements, and the distribution of treatment EMs (i.e., study and patient characteristics that have an independent influence on treatment outcome).

The conclusions are hence only tentative and should be interpreted with caution in light of the aforementioned limitations associated with this analysis.

B.2.10 Adverse reactions

At the time of final database lock (21 June 2021), the median treatment duration was 2.8 months (range, 0.1 to 45.1) in the ivosidenib arm, both including and excluding patients who crossed over. A total of 26 patients (15.7%) remained on ivosidenib for ≥ 12 months. The median treatment duration for patients in the placebo arm was 1.6 months (range, 0 to 6.9) (79).

Ivosidenib had a favourable safety profile over placebo. The most common (>15%) TEAEs among all patients who received ivosidenib (including those who crossed over) were nausea (38.6%), diarrhoea (33.1%), fatigue (28.9%), abdominal pain (22.3%), cough (21.7%), decreased appetite (21.7%), vomiting (20.5%), ascites (19.9%), anaemia (18.7%), peripheral oedema (15.7%), and constipation (15.1%) (79).

Ivosidenib patients reported few severe TEAEs. Grade ≥3 TEAEs were reported in 89 patients (53.6%) in the ivosidenib arm versus 22 patients (37.3%) in the placebo arm (49). The most common TEAEs of grade ≥ 3 (all patients who received ivosidenib vs. placebo) were ascites (9.0% vs. 6.8%), anaemia (7.8% vs. 0%), blood bilirubin increase (6.0% vs. 1.7%), hyponatremia (4.8% vs. 10.2%), hypophosphatemia (3.6% vs. 5.1%), hypertension (3.0% vs. 1.7%), and blood alkaline phosphatase increase (1.8% vs. 5.1%). Reported toxicities are manageable in patients with advanced CCA. TEAEs requiring a dose reduction occurred in 3.0% of patients receiving ivosidenib vs. none receiving placebo (49). TEAEs leading to discontinuation were less common in the ivosidenib arm when compared to the placebo arm (6.6% vs. 8.5%). No event of IDH differentiation syndrome was identified in patients with CCA (79).

Eight patients (4.8%) in the ivosidenib arm experienced a TEAE leading to death, none of which were assessed by the investigator as being associated with ivosidenib and were considered to be complications associated with the underlying disease or comorbid conditions (79). Serious TEAEs were reported for 43 patients (35.0%) receiving ivosidenib and were considered associated with treatment for three

patients (2%) (grade 4 hyperbilirubinemia, grade 3 cholestatic jaundice, grade 2 prolonged QTc on ECG, and grade 3 pleural effusion; hyperbilirubinemia and cholestatic jaundice were observed in the same patient). Serious TEAEs were reported for 14 patients (23.7%) receiving placebo; none were associated with treatment. Prolonged QTc ECG, a TEAE of special interest, was reported for 13 patients (8%) receiving ivosidenib and two patients (3.4%) receiving placebo. TEAE requiring a dose reduction and interruption were uncommon, dose reductions were reported in five patients (3.0%) in the ivosidenib group vs. none in the placebo group (79).

The observed safety profile of ivosidenib at the time of final database lock (21 June 2021) was consistent with the secondary analysis (31 May 2020 data cut-off date) (49). Also, the overall safety profile of ivosidenib in ClarIDHy trial was similar to that observed in the multicentre single-arm open-label phase I AG120-C-002 study that enrolled patients with advanced solid tumours and an *IDH1* mutation (including 73 patients with CCA) (59, 83).

Table 17. ClarIDHy: most common (≥ 15%) TEAEs (21 June 2021 database lock)

Adverse Event, n (%)	ivosidenib (n=123)	Placebo (n=59)	After Crossover to ivosidenib (n=43)	Total ivosidenib (n=166)
Any TEAE	120 (97.6)	57 (96.6)	41 (95.3)	161 (97.0)
Most common TEAE, n (%)				
Nausea	52 (42.3)	17 (28.8)	12 (27.9)	64 (38.6)
Diarrhea	43 (35.0)	10 (16.9)	12 (27.9)	55 (33.1)
Fatigue	38 (30.9)	10 (16.9)	10 (23.3)	48 (28.9)
Abdominal pain	30 (24.4)	9 (15.3)	7 (16.3)	37 (22.3)
Cough	31 (25.2)	5 (8.5)	5 (11.6)	36 (21.7)
Decreased appetite	30 (24.4)	11 (18.6)	6 (14.0)	36 (21.7)
Vomiting	28 (22.8)	11 (18.6)	6 (14.0)	34 (20.5)
Ascites	28 (22.8)	9 (15.3)	5 (11.6)	33 (19.9)
Anemia	23 (18.7)	3 (5.1)	8 (18.6)	31 (18.7)
Edema peripheral	17 (13.8)	6 (10.2)	9 (20.9)	26 (15.7)
Constipation	20 (16.3)	11 (18.6)	5 (11.6)	25 (15.1)

[1]Total ivosidenib group includes 43 patients initially assigned to placebo who had crossed over to ivosidenib upon radiographic disease progression.
Source: AG120-C-005 – CSR Addendum. Database lock: June 21, 2021 [Data on file] (79), Zhu et al. 2021 (78).
Abbreviation: n, number; TEAE, treatment-emergent adverse event.

In appendix F, provide details of any studies that report additional adverse reactions to those reported in the studies in section 2.2.

B.2.11 Ongoing studies

No additional ongoing studies planned

B.2.12 Interpretation of clinical effectiveness and safety evidence

Given the poor prognosis in patients with advanced/metastatic CCA and the lack of effective options in the treatment of 2nd or 3rd line CCA, there is a substantial unmet need for effective and well tolerated treatments which extend survival. Ivosidenib is an innovative treatment with a first-in-class mode of action, which specifically targets and inhibits mutated *IDH1* activity, limiting cell proliferation. Ivosidenib has EMA orphan drug designation for BTC and will specifically target a small, underserved 2nd line patient population with *IDH1* mutation (84)

Treatment options for patients with previously treated, unresectable, locally advanced, or metastatic CCA with *IDH1* mutations are limited to older chemotherapy regimens that yield suboptimal benefit, with low response rates and rapid progression. Furthermore, AEs related to systemic chemotherapy are burdensome to patients and have a detrimental effect on HRQoL. Many patients who progress after 1st line systematic chemotherapy move directly to ASC, including biliary drainage, antibiotics, and analgesia, to relieve symptoms. A significant unmet need exists for a targeted therapy that is effective in this patient group where there have previously been limited efficacious treatment options.

In ClarIDHy, ivosidenib demonstrated a clinically meaningful benefit in patients with previously treated, unresectable, locally advanced, or metastatic CCA with *IDH1* mutations. The indirect treatment comparison results showed that in comparison to mFOLFOX+ASC or ASC alone (and accounting for adjustment for crossover in ClarIDHy), patients receiving ivosidenib demonstrated greater improvements in OS. This improvement was also mirrored in an exploratory analysis of PFS (discussed further in Section B.3.3.4.3). In summary, ivosidenib is a highly effective and well-tolerated targeted treatment for patients with previously treated, unresectable, locally advanced, or metastatic CCA with *IDH1* mutations.

B.3 Cost effectiveness

Ivosidenib is a novel and clinically effective treatment option for IDH1m CCA, which significantly improves life years and QALYs compared with BSC and mFOLFOX. The safety and efficacy of ivosidenib for patients with locally advanced metastatic IDH1m CCA was demonstrated in ClarIDHy (a multicentre, randomized, double-blind, placebo-controlled phase III study).

The primary analysis is well-aligned to the decision problem and reflective of UK clinical practice. Results are generated based on ClarIDHy data, and a Bucher analysis of ClarIDHy and ABC-06 for OS and a naïve comparison for PFS (as no PFS data are reported in the BSC [ASC alone] arm of ABC-06).

The most clinically plausible extrapolations of PFS and OS data were selected for the base case analysis, and extensive scenario analyses were presented to test methodological uncertainty (with only a small impact to cost-effectiveness results). Parametric uncertainty was tested in OWSA and PSA.

The base case modelling approach, including the selected model structure, cost inputs, and source of utility values is consistent with the NICE reference case, and broadly consistent with methods accepted in TA722 for pemigatinib in CCA (where applicable).

Due to the severity of CCA, ivosidenib meets the criteria for the highest severity weighting; as such, a QALY weighting of 1.7 is applied in the cost-effectiveness analysis.

In the base case analysis, the probabilistic ICER for ivosidenib vs BSC was [redacted] per QALY gained, and mFOLFOX was extendedly dominated by ivosidenib. Ivosidenib therefore represents a cost-effective use of NHS resources for patients with IDH1m locally advanced or metastatic CCA.

B.3.1 Published cost-effectiveness studies

A systematic review of the literature was conducted to identify published economic evaluations and cost-effectiveness studies of potential relevance to the decision problem addressed in this appraisal. Electronic database searches were initially conducted on 21 June 2021, and subsequently updated on 24 January 2023.

Initially, the scope of the economic SLR was limited to treatments of interest for unresectable, advanced or metastatic CCA. However, as very limited data were identified, the scope was expanded to include all interventions (including stenting, but not surgery) for advanced CCA and advanced or metastatic BTC. Appendix G provides details of the search strategies, inclusion and exclusion criteria and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Searches were conducted using the following electronic databases: Embase®, MEDLINE®, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment database, National Health Service Economic Evaluation Database (NHS EED) and EconLit®.

The paucity of economic evidence identified is indicative of the lack of available targeted therapies for patients with previously treated locally advanced or metastatic CCA with an IDH1 mutation, highlighting the clear unmet need for safe and efficacious treatment options for this group of patients. Nonetheless, the results of the economic modelling SLR are reported in Appendix G.

As the evidence identified in the SLR was considered of limited relevance, the only prior NICE single technology appraisal in previously treated locally advanced or metastatic CCA (NICE TA722) is arguably one of the most relevant sources of information.(85) As such, insights are drawn from NICE TA722 (which is summarized in Table 18) throughout this appraisal. However, it should be noted that the population of interest in NICE TA722 was specifically CCA patients with FGFR2 fusions/rearrangements, and not those with an IDH1 mutation.

Table 18: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	LYs / QALYs	Costs (£)	ICER (per QALY gained)
NICE TA722 (85)	2021	Cohort-level PartSA model, informed using independently modelled OS, PFS, and ToT curves	Adult patients with previously treated, unresectable, locally advanced, or metastatic CCA with FGFR2 fusions/rearrangements (55.3 years; SD = 12.02)	• ASC: 0.51 / NR • mFOLFOX: 0.60 / NR • Pemigatinib: 2.34 / NR	• ASC: NR • mFOLFOX: NR • Pemigatinib: NR	• mFOLFOX extendedly dominated by pemigatinib • Pemigatinib versus ASC: £61,084 • Pemigatinib versus mFOLFOX: £57,315

Abbreviations: CCA, cholangiocarcinoma; ICER, incremental cost-effectiveness ratio; LY, life years; NICE, National Institute for Health and Care Excellence; NR, not reported; OS, overall survival; PartSA, partitioned survival analysis; PFS, progression-free survival; QALYs, quality-adjusted life years; SD, standard deviation; TA, technology appraisal; ToT, time on treatment.

B.3.2 Economic analysis

The systematic review of the literature did not identify any published economic evaluations considering ivosidenib for the treatment of patients with locally advanced or metastatic CCA with an IDH1 R132 mutation. It was therefore necessary to develop a *de novo* model to assess the cost effectiveness of ivosidenib against relevant treatment options, in an NHS England setting, for the patient population relevant to this appraisal. The key features of the *de novo* model are described in the sub-sections that follow.

B.3.2.1 Patient population

The population considered in the analysis is patients with locally advanced or metastatic CCA with an IDH1 mutation, who were previously treated with at least one prior line of systemic therapy. It is understood that IDH1 testing for patients with CCA is routinely available in NHS England practice, per the National genomic test directory. (86)

The population considered in the economic evaluation is in line with the anticipated marketing authorization for ivosidenib and the final scope issued by NICE. Furthermore, the population corresponds with patients from the active arm of the ClarIDHy study. As described in Section B.2.2, ClarIDHy was an international, multicentre, randomized, double-blind, placebo-controlled phase 3 study which included adult patients aged 18 or over with histologically confirmed, advanced, IDH1-mutant CCA who had progressed on previous therapy. Patients in ClarIDHy could have received up to two previous treatment regimens for advanced disease (including one gemcitabine- or fluorouracil-based regimen, but no targeted IDH-inhibitor therapy); however, most patients in ClarIDHy (54.51%) received one prior treatment, which is more aligned with the anticipated positioning of ivosidenib in NHS England practice.

B.3.2.2 Model structure

B.3.2.2.1 Model health states

A *de novo* cost-effectiveness model was developed in Microsoft Excel®. The model structure (Figure 12) comprises three overarching health states: progression free (or pre-progression), progressed disease (or post-progression), and death. The health

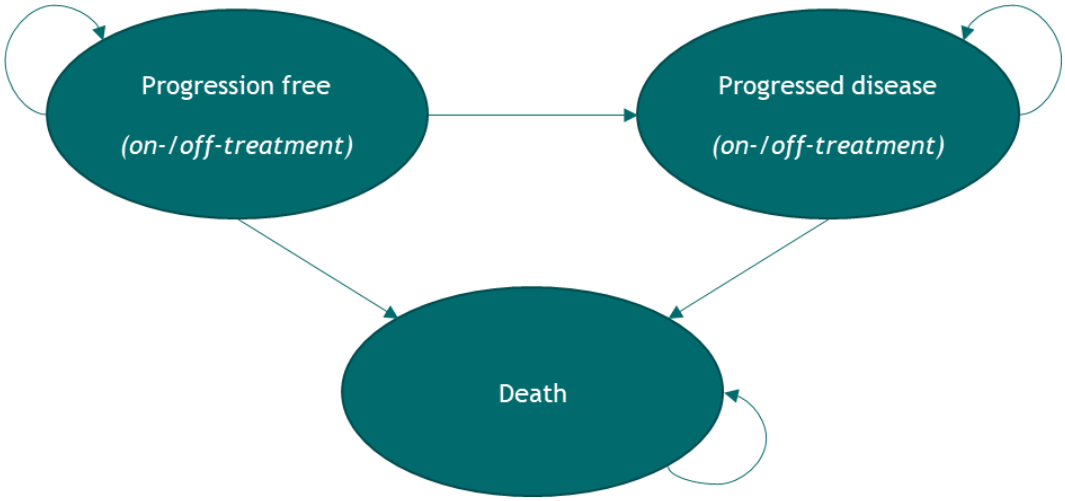
states are defined using a partitioned survival analysis (PartSA) framework, in which survival curves are used to determine health state occupancy (described further in the sub-section that follows).

A progression-based model structure was chosen as it is reflective of the natural history of CCA, which is a progressive disease, which in turn allows lifetime cost and health outcomes to be accurately estimated. Furthermore, the model health states are consistent with the only prior NICE appraisal in CCA (85).

Patients enter the model in the progression free state where they receive treatment with ivosidenib or comparator therapy (described in Section B.3.2.3). In each model cycle, patients may remain free of progression, their disease may progress, or they may die. Once in the progressed health state, patients may remain in their current health state in each model cycle, or they can die. Death is an absorbing health state.

To accurately reflect cost and health outcomes, the progression free and progressed disease health states are further divided into on- and off-treatment periods, as in practice patients may discontinue therapy prior to progression. In the model base case, it is assumed that patients discontinue active treatment with ivosidenib upon progression, based on the licensed indication and clinical expert opinion. In the ivosidenib SmPC, it is noted that treatment should be continued until disease progression or until treatment is no longer tolerated by the patient. Furthermore, three clinical experts were individually interviewed (appendix N) to ensure the economic modelling approach and assumptions in this submission are consistent with clinical expectations in NHS England practice. All consultants independently confirmed that treatment beyond progression with ivosidenib would be unlikely to occur in real-world NHS England practice.

Figure 12: Model structure diagram



Abbreviations: PartSA, partitioned survival analysis.

Note: Health state occupancy determined using a PartSA approach (see Section B.3.2.2.2).

B.3.2.2.2 Health state occupancy

Health state occupancy, or the distribution of patients across health states each model cycle, was determined using a PartSA approach. This modelling approach is consistent with the previous NICE appraisal in CCA (85).

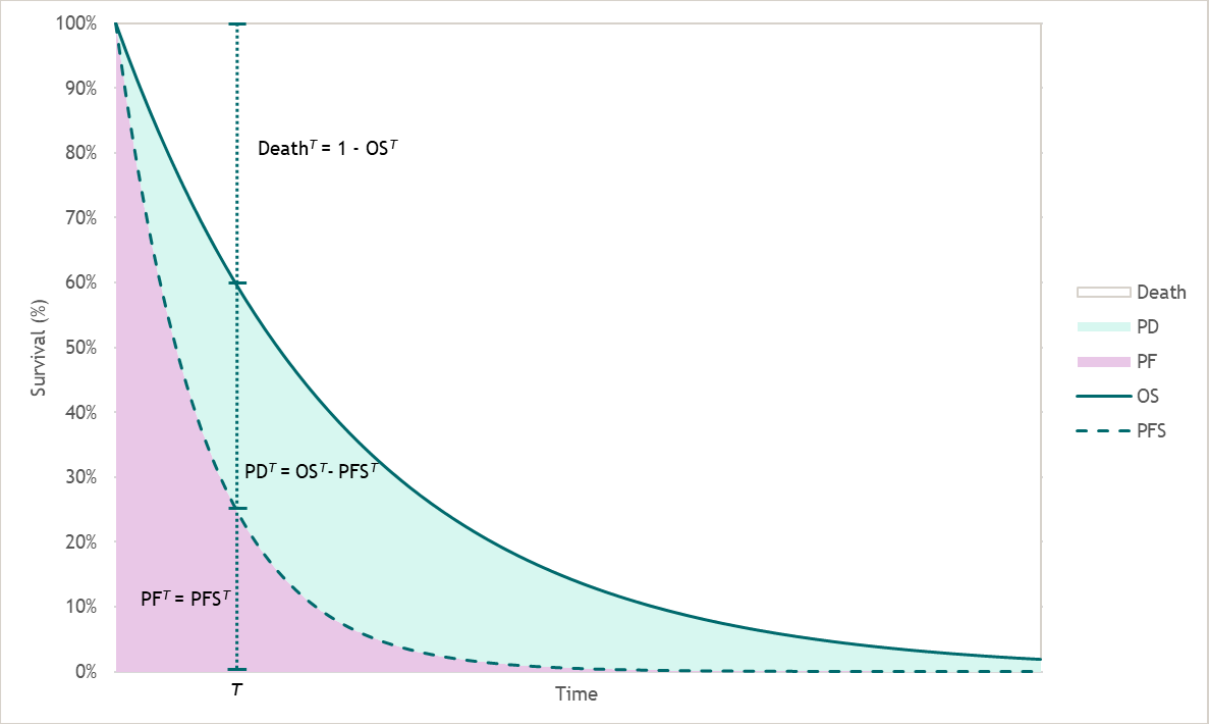
PartSA models are commonly utilised for economic evaluations in oncology, as they provide a framework which is capable of transparently reflecting patient experience for those living with a disease which is progressive in nature. Furthermore, PartSA models are suitable for incorporating relevant treatment effectiveness data from clinical trials, particularly in the context of time-to-event data (discussed further in Section B.3.3).

PartSA models are characterised by independently modelled but non-mutually exclusive survival curves; namely, overall survival (OS) and progression-free survival (PFS) curves. Time on treatment (ToT) curves are used to further partition alive health states into on- and off-treatment periods.

Within a PartSA framework, the proportion of patients alive and free of progression at time T is equal to the PFS curve (PFS^T), the proportion of patients with progressed disease at time T is the difference between OS^T and PFS^T, and the proportion of patients in the death state is 1 minus OS^T. Figure 13 visually demonstrates how

extrapolated parametric survival curves are used to derive health state occupancy within a PartSA model.

Figure 13: Health state occupancy, illustrative partitioned survival model



Abbreviations: OS, overall survival, PD, progressed disease; PF, progression free; PFS, progression-free survival.

B.3.2.2.3 Model settings

The perspective of the economic evaluation is that of the NHS and Personal Social Services (PSS) in England for costs, and direct health effects for patients, in line with the NICE reference case (87). As such, the model considers direct costs relating to drug acquisition and administration, healthcare resource use, adverse event management and end-of-life care (described further in Section B.3.5). Direct health effects for patients are reported as life years (LYs) and quality-adjusted life years (QALYs), with health state utility values estimated using the EQ-5D-5L descriptive system (collected during the ClarIDHy study) and the EQ-5D-3L mapping function recommended in the NICE manual (87) (described further in Section B.3.3.6).

The NICE reference case stipulates that the time horizon of economic evaluations should be long enough to reflect all important differences in costs or outcomes between health technologies (87). Therefore, the cost-effectiveness analysis adopts

a lifetime horizon. It is assumed that 20 years is sufficient to constitute a lifetime horizon, based on the proportion of patients alive across all modelled treatment arms being <1% at 20 years.

The cohort model uses a 1-week cycle length, which is assumed to be short enough to adequately capture meaningful changes in health status for patients with previously treated locally advanced or metastatic CCA with an IDH1-mutation, being treated with ivosidenib or a comparator. Due to the short cycle length, a half-cycle correction is not applied. In line with the NICE reference case, costs and QALYs are time-preference discounted at an annual rate of 3.50% (87).

Table 19 summarises the key features of the economic analysis within this evaluation (with justification for choices made); and compares these features with the prior NICE appraisal in advanced or metastatic CCA (85). It should be noted that, while TA722 considered patients with previously treated locally advanced or metastatic CCA, the population in that evaluation was specifically those with FGFR2 fusions/rearrangements, not patients with an IDH1 mutation. As such, pemigatinib is not a relevant comparator within the context of this appraisal, as FGFR2 fusions/rearrangements and IDH1-mutations are mutually exclusive in patients with locally advanced/metastatic CCA.

Table 19: Features of the economic analysis

	Previous evaluations	Current evaluation	
Factor	**TA722**	**Chosen values**	**Justification**
Perspective	NHS and PSS	NHS and PSS	Consistent with the NICE reference case
Model type	Cohort-level PartSA model	Cohort-level PartSA model (developed in Microsoft Excel®)	Reflects the natural history of CCA (progressive disease). Partitions survival into pre- and post-progressed health states, allowing costs and health outcomes to be estimated accurately and transparently. Consistent with the prior NICE appraisal in CCA, as well as several previous appraisals of treatments for a range of other cancer types (88)
Time horizon	Lifetime, 40 years	Lifetime, 20 years	Lifetime horizon chosen to capture relevant differences in costs and outcomes between treatments, in line with the NICE reference case. 20 years is considered sufficient for representing a lifetime horizon in the modelled patient population, as >99% of patients experience death across treatment arms at 20 years
Cycle length	1 week	1 week	A 1-week cycle length was considered short enough to adequately capture meaningful changes in health status
Half-cycle correction	No	No	Half-cycle correction was not considered necessary due to the short cycle length
Annual time-preference discount rate	3.50% for costs and benefits	3.50% for costs and QALYs	Consistent with NICE reference case
Source of utility values	EORTC QLC C30 (FIGHT-202) mapped to EQ-5D utility values	EQ-5D-5L (ClarIDHy) mapped to EQ-5D-3L (Hernández Alava et al. mapping function)	Consistent with NICE reference case
Outcomes	QALYs, life years, costs, incremental results	QALYs, life years, costs, incremental results	Consistent with NICE reference case

Abbreviations: CCA, cholangiocarcinoma; EORTC QLC C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PartSA, partitioned survival analysis; PSS, Personal Social Services; QALY, quality-adjusted life year; TA, technology appraisal.

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention

The intervention considered within the scope of this evaluation is ivosidenib. Ivosidenib is incorporated into the analysis according to its anticipated marketing authorisation and in line with the decision problem described in Section B.1.1.

As described in Section B.1.2, ivosidenib is an is an oral, potent, targeted inhibitor of mutated IDH1, administered at a dose of 500 mg once daily in continuous 28-day cycles. In the ivosidenib SmPC, it is noted that treatment should be continued until disease progression or until treatment is no longer tolerated by the patient.

The efficacy and safety of ivosidenib for treating IDH1-mutant, chemotherapy-refractory CCA was investigated in the randomised, phase 3 study, ClarIDHy. In ClarIDHy, treatment with ivosidenib was continued until investigator-assessed disease progression or unacceptable toxicity. Treatment with ivosidenib beyond progression was permitted where the investigator deemed that there was clinical benefit; however, clinical opinion has indicated that treatment beyond progression is unlikely to occur in real-world practice (appendix N)

The anticipated date of marketing authorization for ivosidenib in the UK is [redacted] Notably, in the US, ivosidenib is the first and only targeted therapy approved by the Food and Drug Administration for patients with previously treatment IDH1-mutated CCA. Furthermore, in a European setting, ivosidenib is included in the latest ESMO guidelines (updated November 2022) for BTCs (as shown in the treatment algorithm in Figure 4).

B.3.2.3.2 Comparators

As described in Section B.1.3, treatment options are very limited and there are currently no approved targeted therapies for previously treated patients with locally advanced or metastatic CCA with an IDH1 mutation. Consequently, there is not a clearly established standard of care for patients with IDH1-mutated CCA.

In NICE TA722, pemigatinib was recommended as an option for treating patients with locally advanced or metastatic CCA with an FGFR2 fusion or rearrangement

(85). As FGFR2 fusions/rearrangements and IDH1 mutations are mutually exclusive in patients with CCA, pemigatinib is not a relevant treatment option for the patient population considered within this evaluation (patients with an IDH1 mutation) and was therefore not included in the scope issued by NICE (and is not considered a comparator relevant to this assessment).

In NHS England practice, patients with advanced or metastatic CCA who have progressed on systemic chemotherapy may be offered modified folinic acid, fluorouracil and oxaliplatin (mFOLFOX). In NICE TA722, it was reported that clinical expert opinion to the company suggested that that mFOLFOX is considered standard of care for previously treated patients with CCA, based on the results of the ABC-06 study (17, 85). As described in Section B.2.9, ABC-06 was a randomised, multicentre, open-label study of the efficacy and safety of FOLFOX chemotherapy with ASC vs ASC alone for patients in the UK with locally advanced/metastatic BTCs previously treated with cisplatin/gemcitabine chemotherapy. Therefore, in line with the scope issued by NICE, mFOLFOX is included as a comparator in the economic evaluation. mFOLFOX is administered every 2 weeks in line with the following dosing schedule: oxaliplatin (85 mg/m^2), calcium folinate (350 mg), fluorouracil (400 mg/m^2 bolus) and fluorouracil (2,400 mg/m^2 as a 46-hour continuous infusion).

As per the final scope issued by NICE, BSC is also included as a comparator in the cost-effectiveness analysis, due to the lack of an established standard of care for patients with IDH1-mutated CCA. Clinical outcomes in the BSC arm of the cost-effectiveness model are informed by the placebo arm of the ClarIDHy study (discussed in further detail in Section B.3.3). In the final scope issued by NICE, it was indicated that BSC comprises active symptom control (including stent insertion). However, in line with NICE TA722, stent insertion was not explicitly considered within the BSC arm of the cost-effectiveness model. As reported in NICE TA722, biliary stents are most likely to be used in patients with hilar or extrahepatic CCAs; however, >90% of patients in ClarIDHy presented with intrahepatic CCA. Furthermore, biliary stent insertion is primarily a treatment option in the earlier stages of disease and, although maintenance or replacement of stents may be required, insertion of a new stent is less likely to be considered after failure of previous lines of chemotherapy. Conservatively, the BSC arm of the model is assumed to be

associated with zero acquisition or administration costs (described further in Section B.3.5.1).

In summary, the following comparators are considered in the economic evaluation:

- BSC (also referred to as ASC)
- mFOLFOX

B.3.3 Clinical parameters and variables

Clinical data informing the ivosidenib, BSC, and mFOLFOX arms of the model are summarised in Table 20 and described in further detail throughout this Section.

Table 20: Summary of clinical data sources used in the model

Component	Application within the model	Source(s) for ivosidenib	Source(s) for BSC	Source(s) for mFOLFOX
Baseline characteristics	Used to estimate age- and sex-matched general population mortality and utility values, and used in weight-based dosing calculations	ClarIDHy (baseline patient characteristics of the modelled cohort are not treatment specific)		
OS	Parametric survival curves to estimate lifetime OS outcomes and determine health state occupancy	ClarIDHy PLD	ClarIDHy PLD (placebo)	ABC-06 (Bucher comparison)
PFS	Parametric survival curves to estimate lifetime PFS outcomes and determine health state occupancy	ClarIDHy PLD	ClarIDHy PLD (placebo)	ABC-06 (naïve comparison [base case] and exploratory RMST analysis [scenario analysis])
ToT	Parametric survival curves to estimate lifetime ToT outcomes and capture cost and HRQoL consequences	ClarIDHy PLD	N/A	ABC-06 (and necessary assumptions in the absence of reported KM data)
AEs	Inform the proportion of patients who incur AE management costs and utility decrements	ClarIDHy PLD	N/A	ABC-06

Abbreviations: AE, adverse event; BSC, best supportive care; HRQoL, health-related quality of life; KM, Kaplan-Meire; N/A, not applicable; OS, overall survival; PFS, progression-free survival. PLD, patient-level data; RMST, restricted mean survival time; ToT, time on treatment.

B.3.3.1 Baseline patient characteristics

Baseline patient characteristics of the cohort entering the model were aligned with the population in the ClarIDHy study (Table 21). Mean age and the proportion of female patients were used in the model to calculate age- and sex-matched general population mortality rates and utility values. Height and weight were used to estimate BSA (using the Mosteller formula) (89), which was required to calculate drug acquisition costs for treatments with a weight-based dosing regimen.

Table 21: Baseline patient characteristics

Characteristic	Mean	Standard error
Age	[redacted]	[redacted]
Female (%)	63.24	N/A
Height (cm)	[redacted]	[redacted]
Weight (kg)	[redacted]	[redacted]
BSA (m^2)	[redacted]	N/A

Abbreviations: BSA, body surface area; N/A, not applicable.

B.3.3.2 Clinical effectiveness overview

B.3.3.2.1 Ivosidenib and BSC

Ivosidenib and BSC (placebo) clinical effectiveness data used to inform the cost-effectiveness analysis are based on data from the ClarIDHy study. Survival analysis was conducted for the ITT population.

For OS, the analysis for ivosidenib (n = 126) and BSC (placebo, n = 61) was conducted using individual patient level data from ClarIDHy using the May 2020 cut-off data. As described in Section B.2.3.1, in ClarIDHy, once the primary end point of PFS was met, any patients still receiving placebo were permitted to cross over to the ivosidenib group if they continued to meet eligibility criteria (59). Within ClarIDHy, the prespecified rank-preserving structural failure time (RPSFT) model was used to adjust for crossover (59). The RPSFT method is based on a common treatment assumption; that is, the treatment effect of ivosidenib is the same for all individuals, regardless of when treatment is received (90). OS data in the BSC arm of the model are informed by RPSFT-adjusted placebo data from ClarIDHy.

KM data for OS from ClarIDHy are presented in Section B.2.6.3 (Figure 8); due to the poor prognosis in patients with advanced/metastatic CCA, KM data are mature but incomplete. Median OS was 10.3 months in the ivosidenib arm, and 7.5 months in the placebo arm (before adjusting for crossover). After adjusting for crossover using the RPSFT method, the median OS in the placebo arm was 5.1 months (HR, 0.49; 95% CI, 0.34 to 0.70; p < 0.0001).

Survival analysis for PFS (assessed by independent central review [cost-effectiveness model base case] and assessed by investigators [scenario analysis]) for ivosidenib (n = 124) and BSC (placebo, n = 61) was conducted using the January 2019 data cut from ClarIDHy. This data cut represents the latest data cut available containing PFS data.

PFS KM data from ClarIDHy are presented in Section B.2.6.2 (Figure 7). Consistent with OS, due to the poor prognosis in patients with advanced/metastatic CCA, PFS KM data are relatively mature. Median PFS was 2.7 months for patients who received ivosidenib, compared with 1.4 months for patients who received placebo (HR, 0.37; 95% CI, 0.25 to 0.54; p < 0.0001).

B.3.3.2.2 mFOLFOX

As no head-to-head trial data are available comparing ivosidenib with mFOLFOX, an indirect treatment comparison was necessary. Indirect comparison methods are introduced in Section B.2.9, and discussed further in Section B.3.3.3.3 (OS) and B.3.3.4.4 (PFS).

As noted in Sections B.2.1 and B.2.9, following completion of the SLR and feasibility assessment, ABC-06 was the only study identified for which an ITC was considered feasible, which assessed outcomes relevant to the decision problem and cost-effectiveness analysis in patients treated with mFOLFOX.

Notably in the clinical SLR, a wider scope was used (i.e., not limiting to IDH1 patients) due to the absence of data in the population of interest, given the well-established lack of therapies targeting IDH1 mutations (other than ivosidenib). As such, the population in ABC-06 was patients with histologically/cytologically verified, non-resectable or recurrent/metastatic CCA, gallbladder or ampullary carcinoma. Furthermore, the proportion of patients within ABC-06 who had an IDH1-mutation is

not reported. Section B.3.3.2.3 discusses evidence on the prognostic effect of IDH1-mutations, and potential implications for the ITC.

In the ABC-06 study, OS was longer in the mFOLFOX plus ASC group than in the ASC alone group, with a median overall survival of 6.2 months versus 5.3 months (adjusted HR 0.69 [95% CI 0·50–0·97]; p = 0·031). Notably, in ABC-06, PFS data were reported for the mFOLFOX plus ASC group, but not reported in the ASC alone arm.

B.3.3.2.3 Extrapolation

Although the OS and PFS data observed in the ClarIDHy study are relatively mature, the data are not complete, and as such it is necessary to extrapolate beyond the trial period to estimate outcomes over a lifetime horizon. Furthermore, use of KM estimates directly in a cost-effectiveness model may introduce issues related to overfitting trial data, due to the stepped nature of the curves. Therefore, a range of parametric survival models were fitted to time-to-event data (OS, PFS, and ToT) to inform the model.

A range of standard parametric models were fitted to the data in line with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14, including:

- Exponential
- Generalized gamma
- Gompertz
- Log-logistic
- Log-normal
- Weibull

NICE DSU TSD 14 reports that it is generally considered unnecessary to rely on the proportional hazards assumption where patient-level data are available; as such, curves were fit separately to the ivosidenib and placebo (BSC) data from ClarIDHy.

As recommended in NICE DSU TSD 14, goodness-of-fit and the plausibility of the extrapolation were assessed as part of the curve selection process; more specifically, the following factors were considered:

- The visual fit of the parametric curve to the KM estimate
- The statistical goodness-of-fit to the data based on comparisons of Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics
- The plausibility of the long-term extrapolation based on clinical expert opinion, and where possible, external data sources

B.3.3.2.4 IDH1 prognostic effect

As described in Section B.1.3.1, CCAs vary across individuals at histological, genomic, epigenetic, and molecular levels. Genetic alterations can allow for personalised/precision medicine in CCA, where patients harbouring a particular mutation can be treated specifically with a targeted therapy.

Although ClarIDHy provides clinical effectiveness data for patients with IDH1-mutated CCA treated with ivosidenib or placebo, no studies were identified in the systematic review of the literature which assessed mFOLFOX specifically in IDH1-mutated CCA patients. Furthermore, the ABC-06 study did not report the proportion of included patients with IDH1-mutated CCA.

To gain insight on potential implications for the ITC between ClarIDHy and ABC-06, clinical expert opinion was sought on the prognostic effect of IDH1-mutations in CCA. However, clinical opinion suggested that the prognostic effect is currently unknown, in the absence of available data (appendix N)

In a recent study, Rimini et al. 2023 aimed to assess the prognostic impact of IDH1 mutations in a cohort of advanced iCCA patients after progression on first-line therapies (91). One hundred and nineteen patients were studied from 5 institutions (4 Italian and 1 Spanish), of which 56 (47%) were IDH1 mutated and 63 (53%) IDH1 wild type. Overall, 23% of patients received mFOLFOX as second-line therapy, while 24% of patients were treated with only BSC at second line. Univariate analysis for OS found that the presence of an IDH1 mutation was associated with a worse

median survival (8.2 vs. 14.1 months; HR 1.9, p = 0.0047). Furthermore, after adjustment for clinical covariates that had a prognostic impact at univariate analysis, multivariate analysis confirmed IDH1 mutation to be an independent negative prognostic factor for OS (HR 1.7, p = 0.0256).

Furthermore, in patients receiving mFOLFOX (n = 26) as second-line therapy, a worse trend in OS and PFS was observed in IDH1 mutation versus IDH1 wild type patients, although this was not statistically significant (HR 1.60, 95% CI 0.51–5.10, p = 0.4229; HR 2.11, 95% CI 0.89–5.04, p = 0.0735, respectively). A worse ORR and DCR was also shown for patients with an IDH1-mutation treated with mFOLFOX (p < 0.0001 for both).

While acknowledging the limitations of a retrospective study compared with an RCT, Remini et al. 2023 demonstrates a negative prognostic role of IDH1 mutations in CCA patients who have progressed on first-line chemotherapy. As such, it is possible that the ITC versus ABC-06 may provide a conservative estimate of the relative treatment effect of ivosidenib versus mFOLFOX, in patients with IDH1-mutated CCA.

B.3.3.3 Overall survival

B.3.3.3.1 Ivosidenib

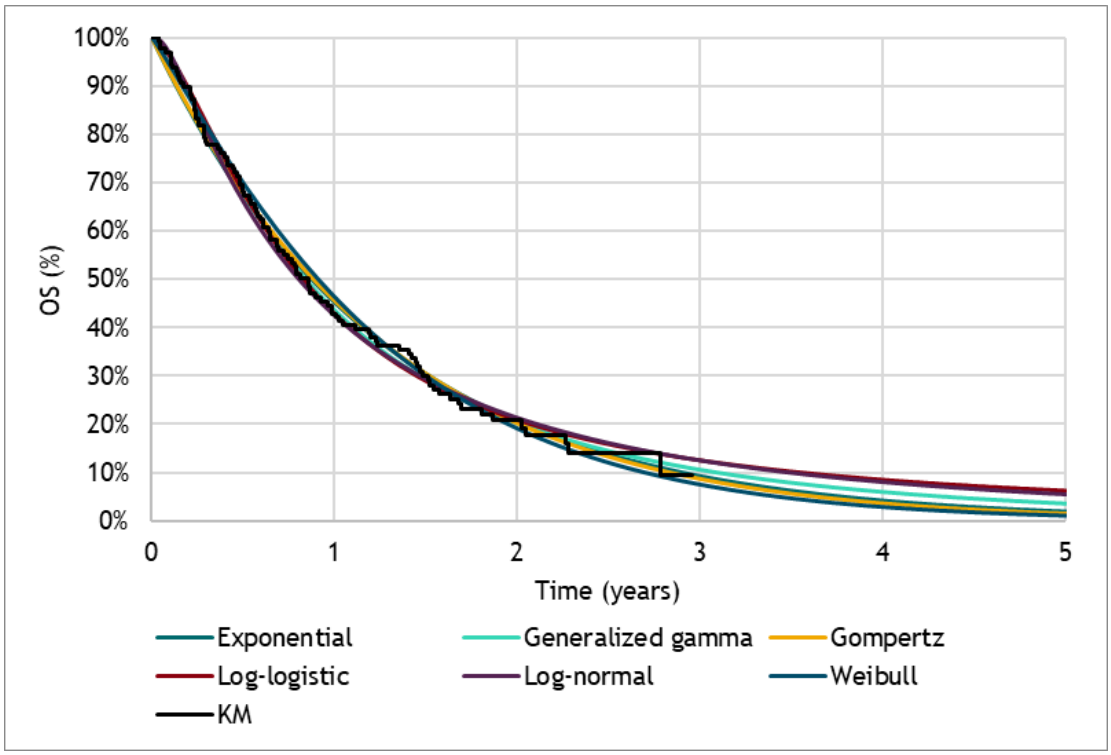
Figure 14 (5-year scale) and Figure 15 (20-year scale) compare standard parametric models with the ivosidenib KM estimate from ClarIDHy, for OS. All curves appear to provide a good visual fit to the data, while the log-normal curve has the lowest AIC and the exponential curve the lowest BIC. Lower AIC and BIC values are typically indicative of a better statistical goodness of fit to the data, suggesting these models may provide an improved fit to the data, compared with the other candidate model explored. In the base case, the log-normal curve was selected based on the statistical goodness-of-fit to the observed data, and the plausibility of the long-term extrapolation according to clinical expert opinion (discussed below and found in appendix N).

In separate interviews with three NHS consultants (appendix N), one expert noted it was challenging to comment on the long-term plausibility of different curves in the absence of longer-term follow up data, while one expert indicated that the log-logistic

or log-normal curves were likely to be the best fitting models. The second expert expressed a preference for the log-logistic curve over the log-normal curve (as the log-logistic curve produces a survival estimate that is marginally closer to the observed KM data at 2 years) but highlighted this was difficult to ascertain. The third expert concluded that, while it is difficult to state if one curve is more accurate than another, none of the curves appear to be implausible.

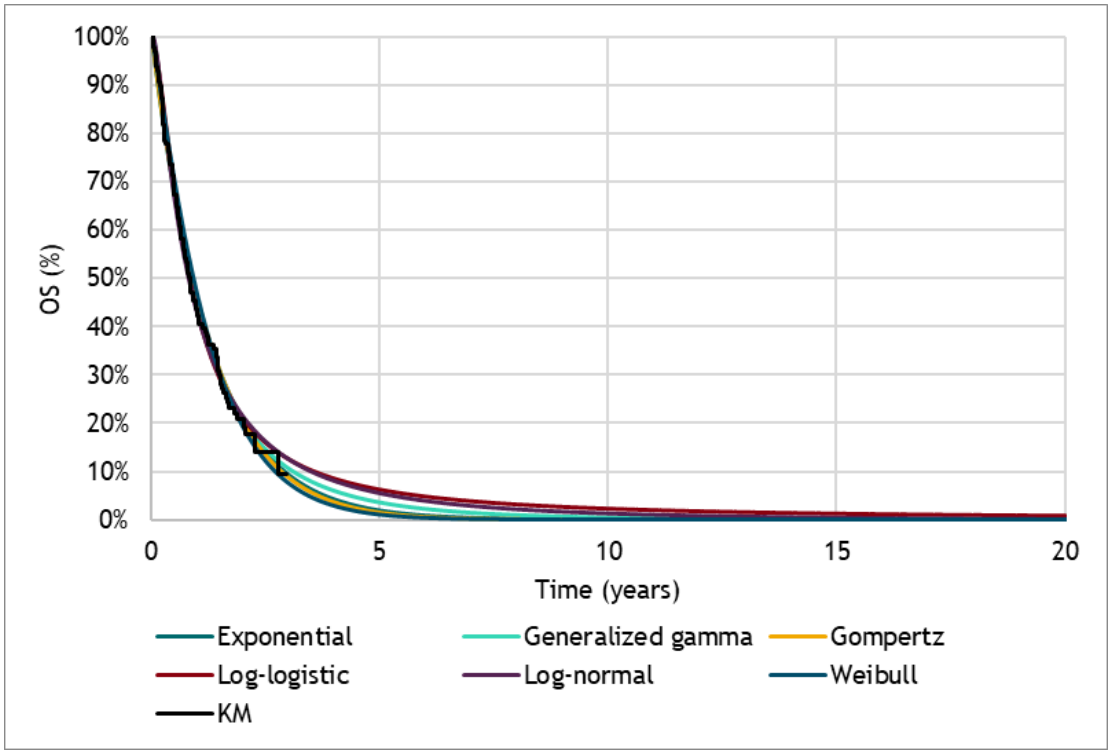
The log-normal was selected in the base case, as it provides a more conservative estimate of long-term survival (at 5 years and beyond) when compared with the log-logistic curve. The log-logistic and exponential curves are explored in scenario analysis. The log-normal predicts 5.6% and 1.4% of patients to be alive at 5 and 10 years, respectively (Table 22).

Figure 14: Ivosidenib, OS (5-year scale)



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

Figure 15: Ivosidenib, OS (20-year scale)



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

Table 22: Ivosidenib OS, survival estimates and statistical fit

Model	Median OS	AIC	BIC	OS landmarks (years)				
	Months			1	2	5	10	20
KM	10.28	-	-	42.8%	20.7%	-	-	-
Exponential	10.35	248.10	**250.93**	45.3%	20.5%	1.9%	0.0%	0.0%
Generalized gamma	9.89	247.13	255.64	43.7%	20.3%	3.6%	0.5%	0.0%
Gompertz	10.58	250.05	255.72	45.7%	20.3%	1.5%	0.0%	0.0%
Log-logistic	9.89	246.59	252.27	43.0%	20.9%	6.2%	2.3%	0.8%
Log-normal	9.66	**246.19**	251.86	42.6%	21.5%	5.6%	1.4%	0.3%
Weibull	10.81	248.69	254.37	46.5%	19.2%	1.1%	0.0%	0.0%

Abbreviations: AIC; Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan-Meier; OS, overall survival.

Note: Bold text indicates lowest AIC/BIC.

B.3.3.3.2 BSC

Figure 16 (5-year scale) and Figure 17 (20-year scale) present BSC OS KM estimate from ClarIDHy and fitted standard parametric curves. This KM estimate reflects the

adjustment made to account for crossover using an RPSFT model (see Section B.3.3.1 for more details).

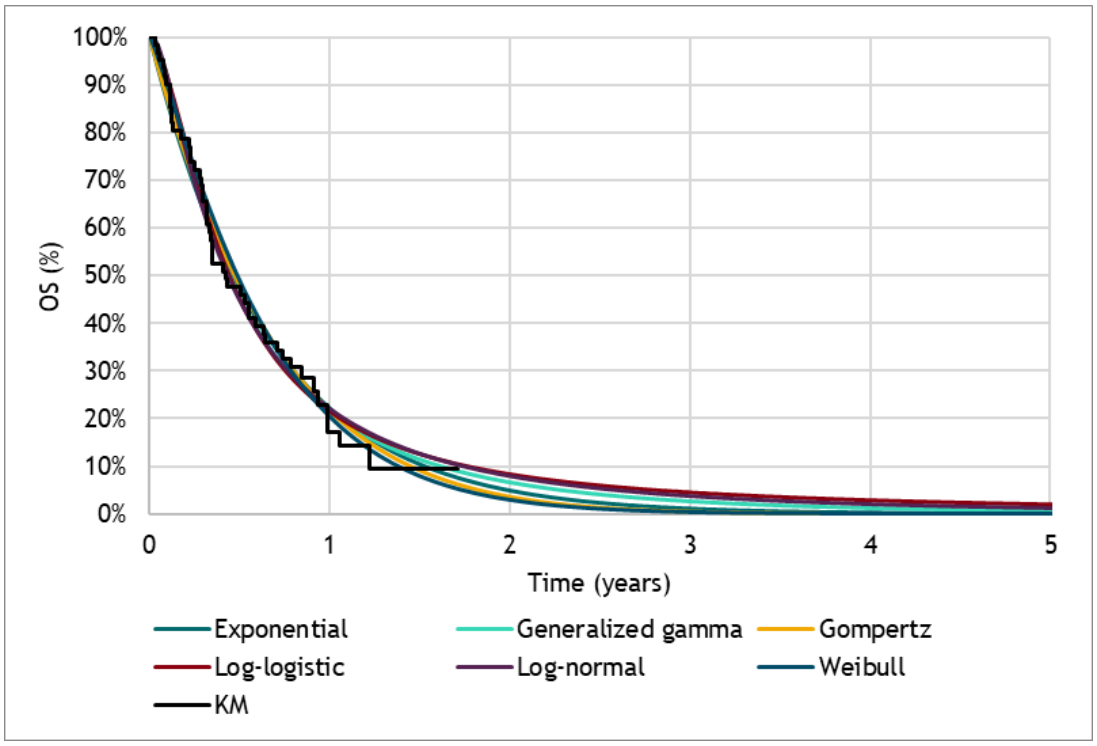
All the curves present a good visual fit to the data and all AIC/BIC statistics demonstrate similar goodness-of-fit scores. Given the similar goodness of fit (visual and statistical) to the observed portion of the data across curves, clinical plausibility of the long-term extrapolation was prioritized during the curve selection process.

The Weibull curve was selected in the base case, based on the plausibility of the long-term extrapolation. The Weibull curve predicts that 2.9% and 0.0% of patients would be alive at 2 and 5 years on BSC, respectively.

In clinical expert interviews conducted separately with three NHS consultants, one expert indicated that all the parametric curves appeared to be similar upon visual inspection, but at 5 years, close to 0% of patients receiving BSC are expected to be alive. The second expert indicated that the 2-year estimates produced by the log-logistic and generalized gamma models appear implausible high, survival estimates in the BSC arm are expected to be similar to those projected by either the Gompertz or Weibull models. The third expert indicated that, due to the poor prognosis of patients with local advanced/metastatic CCA, the curve which produces the lowest estimate of long-term survival is most plausible, as very few patients are expected to be alive at 2-years on BSC.

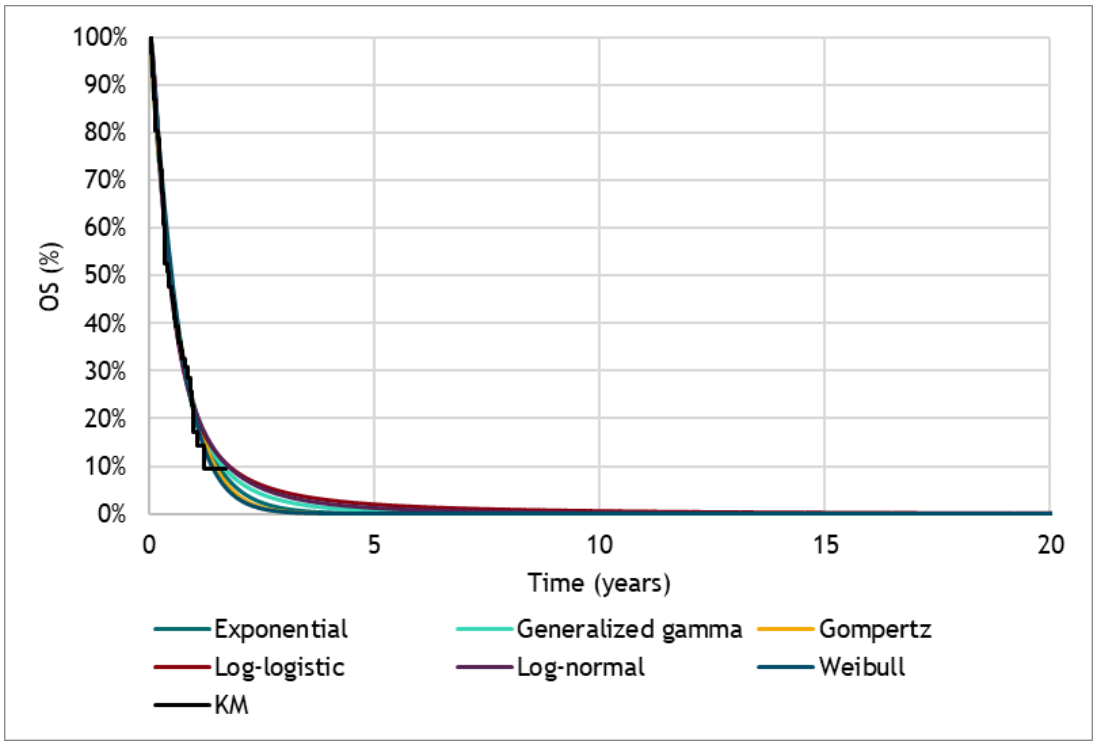
Therefore, when considering clinical expert opinion, the Weibull model was selected in the base case, with the Gompertz model tested in scenario analysis.

Figure 16: BSC, OS (RPSFT crossover adjusted; 5-year scale)



Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival; RPSFT, rank preserving structural failure time.

Figure 17: BSC, OS (RPSFT crossover adjusted; 20-year scale)



Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival; RPSFT, rank preserving structural failure time.

Table 23: BSC OS (RPSFT crossover adjusted), survival estimates and statistical fit

Model	Median OS	AIC	BIC	OS landmarks (years)				
	Months			1	2	5	10	20
KM	5.05	-	-	17.1%	-	-	-	
Exponential	5.29	59.45	**61.56**	22.2%	4.9%	0.1%	0.0%	0.0%
Generalized gamma	5.29	59.81	66.14	21.4%	6.6%	0.6%	0.0%	0.0%
Gompertz	5.52	61.31	65.54	21.6%	3.6%	0.0%	0.0%	0.0%
Log-logistic	5.29	58.78	63.00	21.6%	8.5%	2.1%	0.7%	0.2%
Log-normal	5.06	**58.00**	62.22	22.1%	8.0%	1.2%	0.2%	0.0%
Weibull	5.75	60.13	64.35	20.4%	2.9%	0.0%	0.0%	0.0%

Abbreviations: AIC; Akaike information criterion; BIC, Bayesian information criterion; BSC, best supportive care; OS, overall survival; RPSFT, rank preserving structural failure time.

Note: Bold text indicates lowest AIC/BIC.

B.3.3.3.3 mFOLFOX

As described in Section B.2.9.1, for the comparison of OS between ClarIDHy and ABC-06, a frequentist approach using the Bucher method was preferred over a Bayesian approach due to the limited evidence base (n = 2 studies). A Bucher approach is used to compare outcomes between two indirect treatments across different studies, where different interventions are compared to a common comparator. It assumes that the trials included in the ITC are similar with regards to the study population, study design, outcome measurements, and the distribution of treatment effect modifiers; and that there is no 'closed loop' of evidence that may introduce inconsistencies in effect measures (i.e., no direct evidence for ivosidenib and mFOLFOX).

In the prior NICE appraisal in locally advanced/metastatic CCA (TA722), the company noted that standard techniques such as Bucher ITCs and network meta-analyses could not be explored as clinical data in the analysis were informed by a single arm study. The company subsequently noted it was necessary to consider an unanchored indirect comparison in the absence of a common comparator. Within the context of this appraisal, a connection can be formed between the placebo arm of ClarIDHy and the ASC arm of ABC-06, meaning that a Bucher ITC can be conducted for the OS endpoint, and it is not necessary to rely on an unanchored approach to

indirectly compare with mFOLFOX. Additionally, as previously described, IDH1-mutation specific data from the placebo arm of ClarIDHy can be used to inform outcomes in the BSC arm of the model directly (rather than having to rely on the ASC arm of ABC-06 to inform BSC outcomes, as was necessary in TA722).

Furthermore, if an adjusted comparison was conducted, patient-level data from the ClarIDHy trial would need to be matched to aggregate data from the ABC-06 study. However, most other inputs (such as baseline patient characteristics) used to inform the cost-effectiveness analysis are aligned with the unadjusted ClarIDHy population. Therefore, the Bucher approach was preferred, as this approach allows for ivosidenib, BSC, and mFOLFOX to be compared simultaneously in fully incremental analysis (without adjusting the ClarIDHy population to inform clinical effectiveness estimates in the model).

Finally, although it is acknowledged that there is some heterogeneity between the ClarIDHy and ABC-06 trials (ABC-06 investigated all BTCs, whereas ClarIDHy investigated patients with IDH1-mutated CCA), it would not be possible to fully adjust for these differences in any statistical analysis, as the proportion of patients with IDH1-mutations was not reported in ABC-06. Although this is the case, as noted in Section B.3.3.2.4, a recent study demonstrated a negative prognostic role of IDH1 mutations in CCA patients; and as such, it is possible that the Bucher ITC provides a conservative estimate of the relative treatment effect of ivosidenib versus mFOLFOX, in patients with IDH1-mutated CCA. In conclusion, the Bucher approach was deemed the most suitable approach to inform OS estimates in the mFOLFOX arm of the cost-effectiveness analysis.

The results of the Bucher analysis for OS are presented in Table 24. In the base case, the log-normal parametric curve for ivosidenib was the reference curve (Section B.3.3.3.1), with mFOLFOX OS being estimated via the constant HR of [redacted] (adjusting for crossover in the placebo arm of ClarIDHy).

Table 24: Results of the Bucher analysis for OS, crossover adjusted

Analysis	HR (95% CI)
ClarIDHy: ivosidenib vs BSC	[redacted]
ABC-06: mFOLFOX + ASC vs ASC	[redacted]
ITC: ivosidenib vs mFOLFOX + ASC	[redacted]

Abbreviations: ASC, active symptom control; BSC, best supportive care; CI, confidence interval; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; HR, hazard ratio.

B.3.3.3.4 OS summary

Figure 18 presents a summary of the selected OS curves for ivosidenib (log-normal), BSC (Weibull), and mFOLFOX (HR of [redacted] from Bucher ITC applied to ivosidenib reference curve). In the cost-effectiveness analysis, all survival outcomes were adjusted for background mortality post-hoc within the cost-effectiveness model (by ensuring the hazard of death for the OS curve is equal to or greater than the hazard of death for the age- and sex-matched general population).

A range of alternative parametric survival models for OS are tested in scenario analysis (discussed in Section B.3.10.3).

Figure 18: Summary of selected OS curves

Abbreviations: BSC, best supportive care; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; OS, overall survival.

B.3.3.4 Progression-free survival

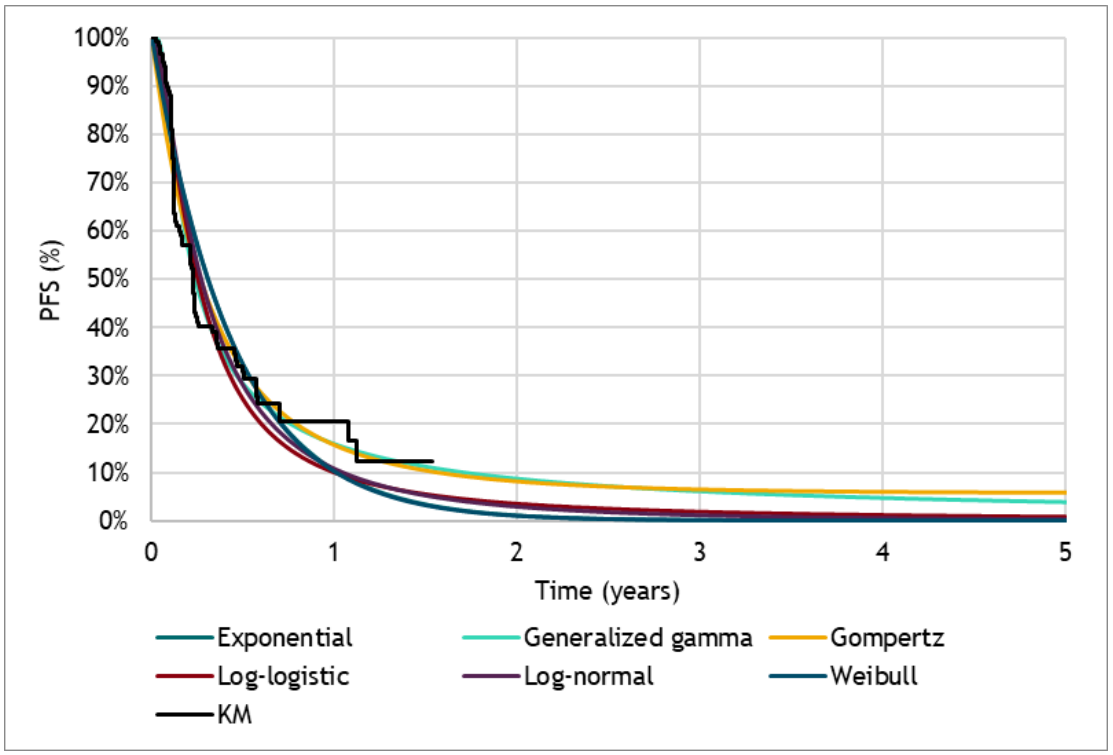
B.3.3.4.1 Ivosidenib

Ivosidenib PFS extrapolations are presented alongside the KM estimate from ClarIDHy in Figure 19 (5-year scale) and Figure 20 (20-year scale). Although the generalized gamma model provides the best statistical goodness of fit to the data according to AIC and BIC presented in Table 25, this curve was not selected in the base case due to the plateau in the tail of this curve, which implausibly produces a higher proportion of patients alive and free of progression at 20 years than the modelled OS curve. Nonetheless, based on the statistical goodness-of-fit, the generalized gamma curve was tested in scenario analysis (with the implementation of a cap within the PartSA framework to ensure PFS remains less than or equal to OS). The Gompertz curve was similarly ruled out of the base case due to the plateau in the tail. Of the remaining curves, the log-normal curve had the best statistical fit to the observed data and produced clinically plausible long-term extrapolations.

In separate clinical expert interviews (appendix N), two experts highlighted that the long-term PFS estimates produced by the generalized gamma and Gompertz curves were implausible. One of these experts suggested that 1-3% was likely to be a more plausible estimate of 2-year PFS, and the other indicated that all other curves appear to be plausible. Another clinical expert noted that the log-logistic model could potentially provide a more realistic estimate in the longer-term but may not accurately estimate PFS in the shorter term.

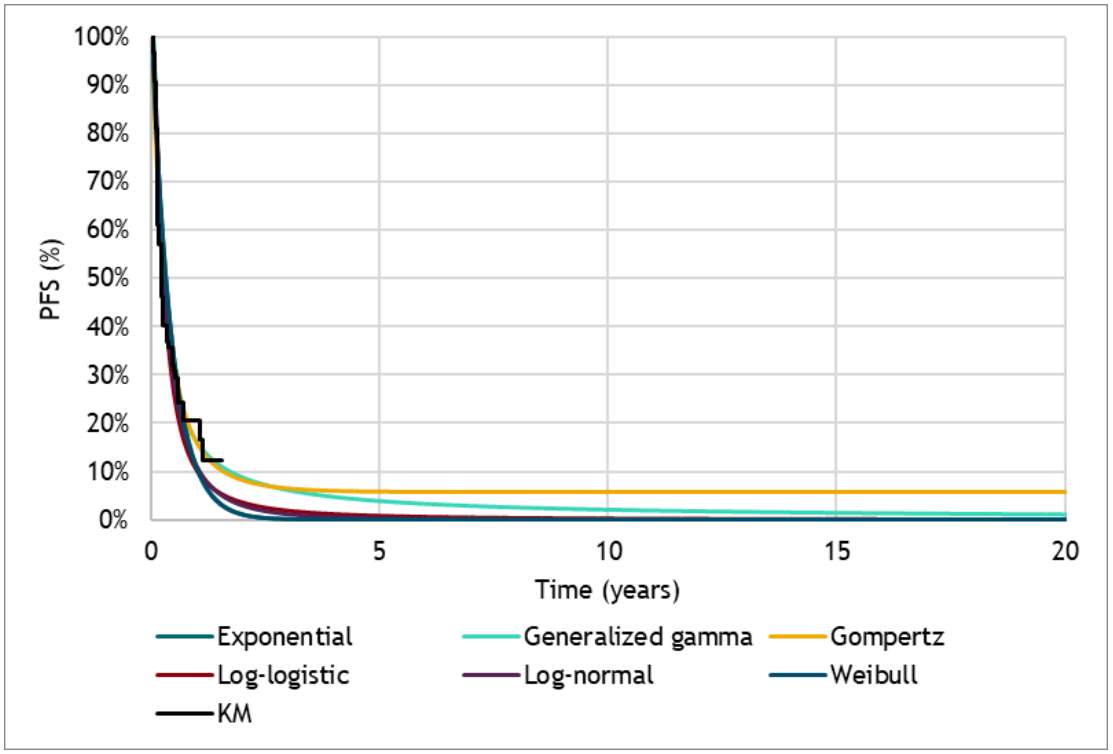
As such, the log-normal was selected in the base case, with the log-logistic and generalized gamma curves tested in scenario analysis. The choice of base case curve was therefore consistent across OS and PFS, which are correlated outcomes.

Figure 19: Ivosidenib, PFS (5-year scale)



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

Figure 20: Ivosidenib, PFS (20-year scale)



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

Table 25: Ivosidenib PFS, survival estimates and statistical fit

Model	Median PFS	AIC	BIC	OS landmarks (years)				
	Months			1	2	5	10	20
Exponential	3.45	31.89	34.71	10.5%	1.1%	0.0%	0.0%	0.0%
Generalized gamma	2.76	**-1.87**	**6.59**	16.0%	8.8%	4.0%	2.2%	1.2%
Gompertz	2.99	28.07	33.71	15.8%	8.3%	6.0%	5.9%	5.9%
Log-logistic	2.99	12.76	18.40	10.1%	3.6%	0.9%	0.3%	0.1%
Log-normal	3.22	9.45	15.09	10.8%	2.9%	0.3%	0.0%	0.0%
Weibull	3.68	33.87	39.51	10.2%	1.0%	0.0%	0.0%	0.0%

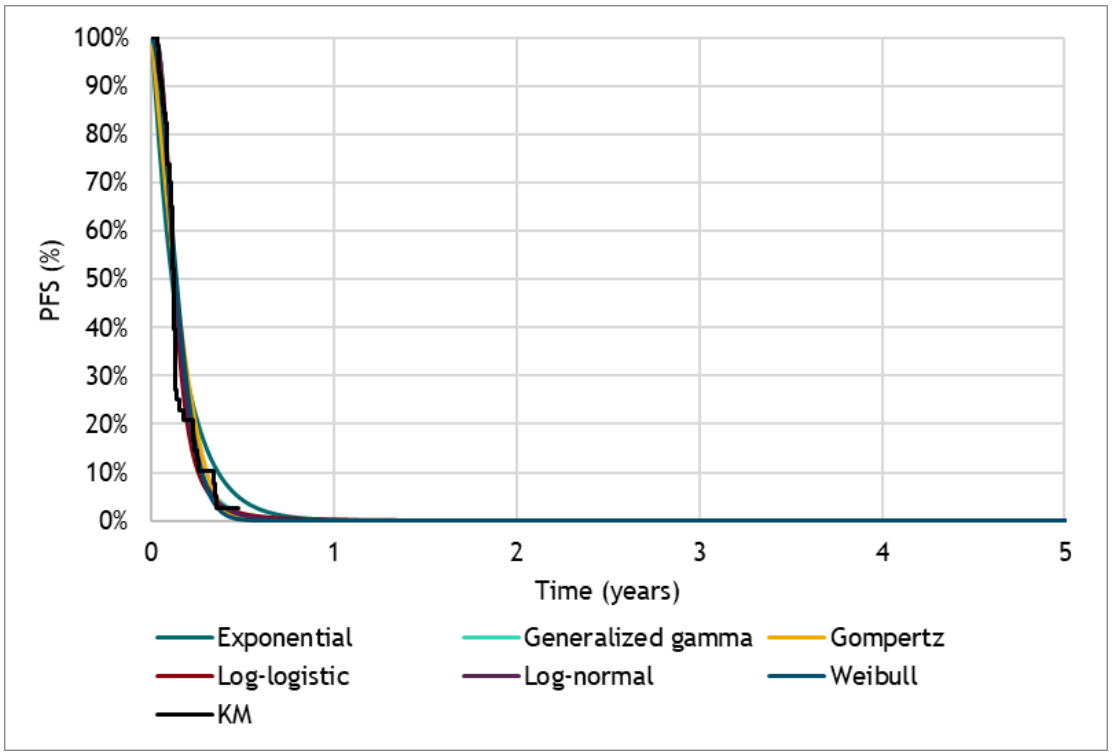
Abbreviations: AIC; Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Note: Bold text indicates lowest AIC/BIC.

B.3.3.4.2 BSC

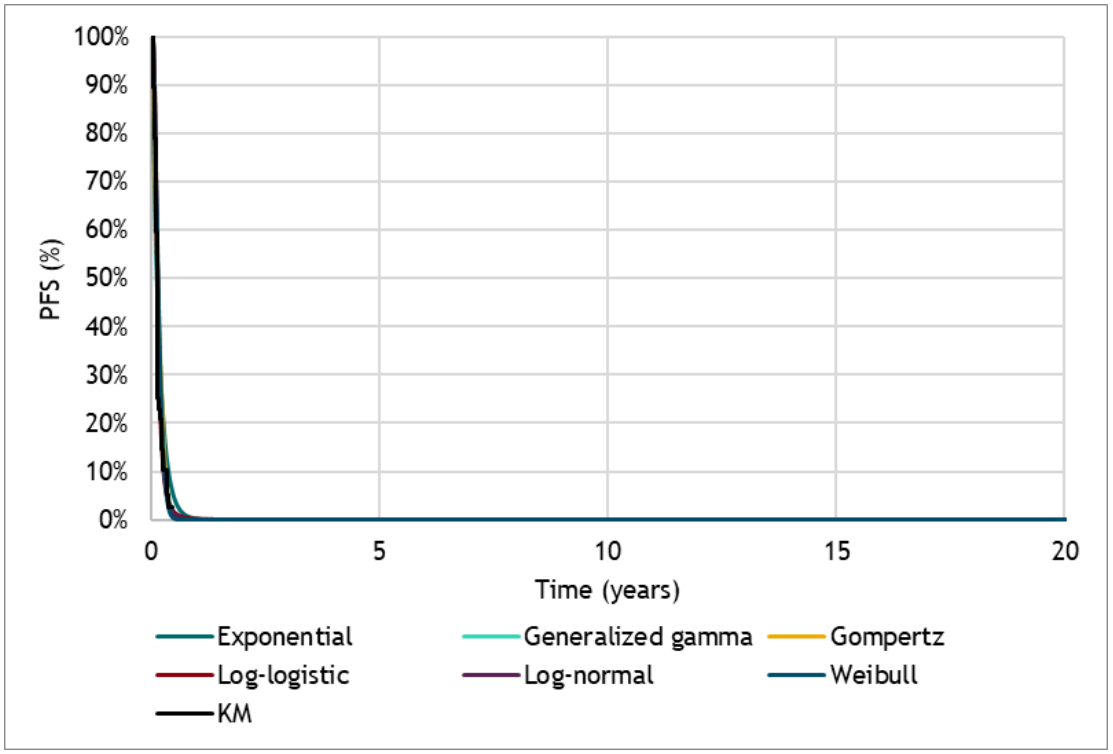
BSC PFS extrapolations are presented alongside the KM estimate from the placebo arm of ClarIDHy in Figure 21 (5-year scale) and Figure 22 (20-year scale). Due to the rapid nature of progression in the absence of active treatment, and in turn maturity of the PFS data, all curves produce similar outcomes. In separate clinical expert interviews, all NHS consultants independently noted the parametric curves for PFS in the BSC arm are similar, and that there did not appear to be any meaningful differences. One expert went on to note that, consistent with OS, the curve which produces the lowest estimate of long-term survival is anticipated to be the most plausible. The Weibull curve was selected in the base case due to the plausibility of the long-term extrapolations and for consistency with OS; however, the best statistically fitting log-logistic curve was tested in scenario analysis.

Figure 21: BSC, PFS (5-year scale)



Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; PFS, progression-free survival.

Figure 22: BSC, PFS (20-year scale)



Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; PFS, progression-free survival.

Table 26: BSC PFS, survival estimates and statistical fit

Model	Median PFS	AIC	BIC	OS landmarks (years)				
	Months			1	2	5	10	20
Exponential	1.15	-82.95	-80.84	0.2%	0.0%	0.0%	0.0%	0.0%
Generalized gamma	1.38	-109.24	-102.91	0.1%	0.0%	0.0%	0.0%	0.0%
Gompertz	1.38	-87.81	-83.59	0.0%	0.0%	0.0%	0.0%	0.0%
Log-logistic	1.38	**-112.66**	**-108.44**	0.2%	0.0%	0.0%	0.0%	0.0%
Log-normal	1.38	-111.02	-106.80	0.0%	0.0%	0.0%	0.0%	0.0%
Weibull	1.38	-100.35	-96.13	0.0%	0.0%	0.0%	0.0%	0.0%

Abbreviations: AIC; Akaike information criterion; BIC, Bayesian information criterion; BSC, best supportive care; PFS, progression-free survival.

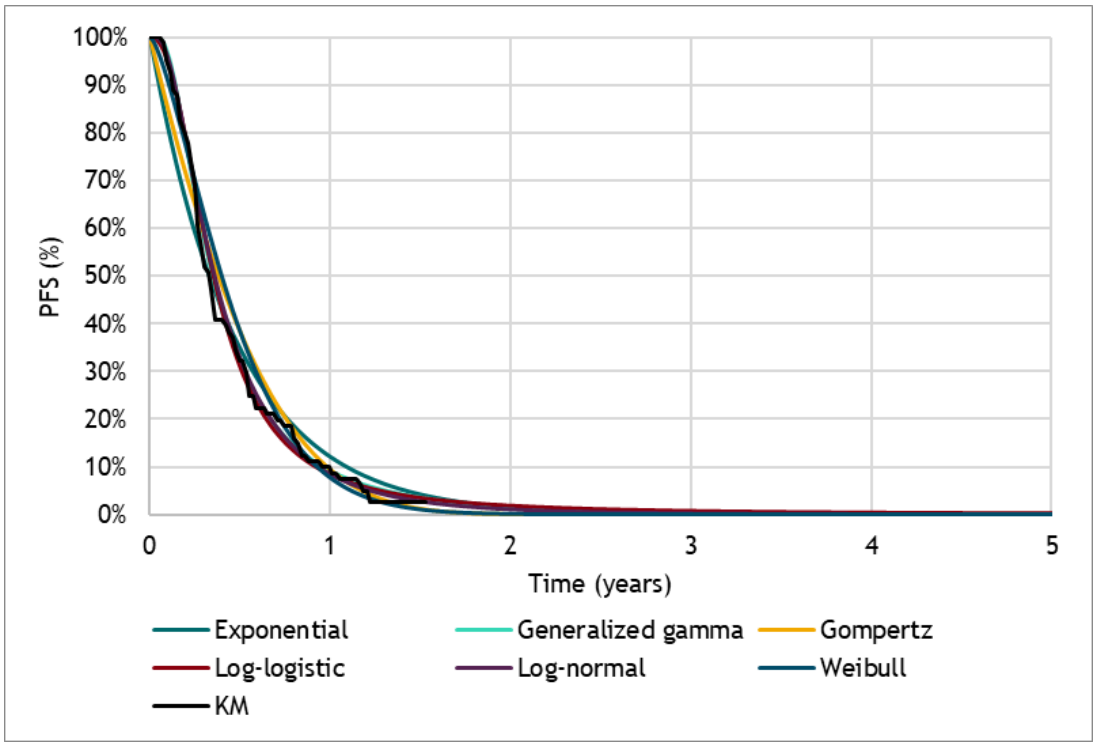
Note: Bold text indicates lowest AIC/BIC.

B.3.3.4.3 mFOLFOX

Unadjusted PFS (base case)

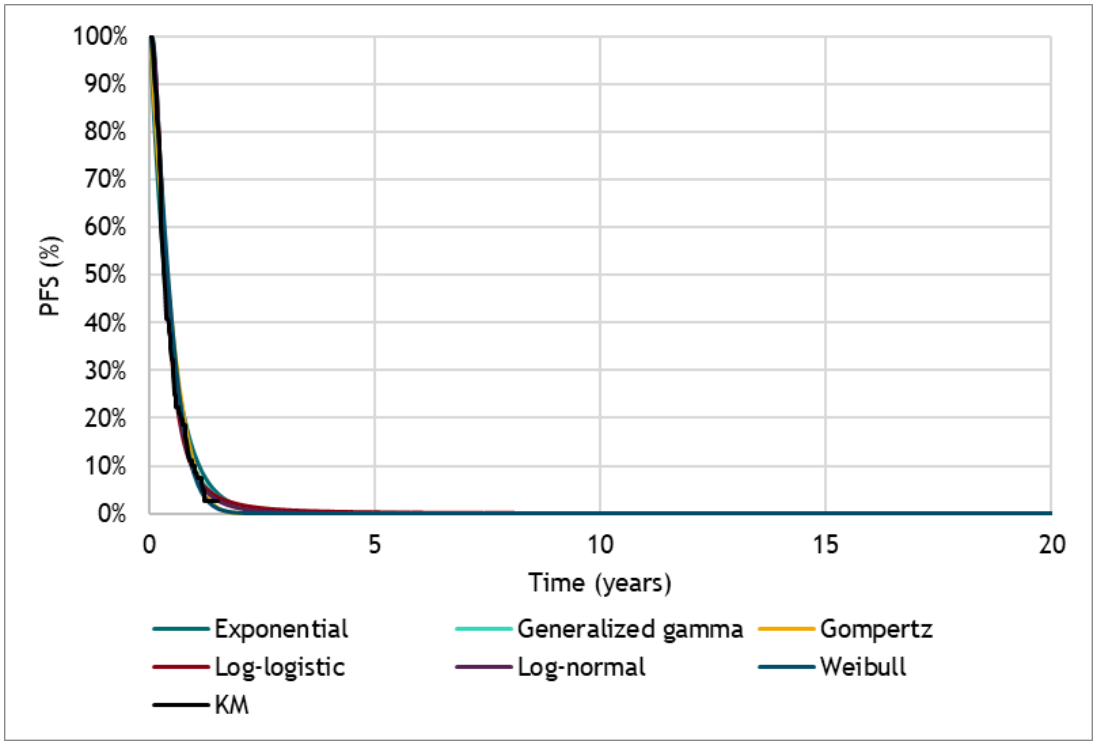
As described in Section B.2.9.1, a Bucher ITC versus mFOLFOX was only possible for the OS endpoint, because PFS data were not reported in the ASC (control) arm of ABC-06. Therefore, a connection between common comparators could not be formed for the outcome of PFS. In the absence of the ability to perform an formal indirect comparison via a common comparator, a naïve comparison was undertaken using unadjusted PFS estimates for mFOLFOX (based parametric curves fitted to pseudo patient-level data, which was re-created using the approach of Guyot *et al.*) (81). All curves provided a good visual fit to the data, and due to the maturity of the data, the curve with the best statistical fit based on AIC and BIC was selected in the base case (log-normal).

Figure 23: mFOLFOX, PFS (ABC-06 unadjusted; 5-year scale)



Abbreviations: KM, Kaplan-Meier; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; PFS, progression-free survival.

Figure 24: mFOLFOX, PFS (ABC-06 unadjusted; 20-year scale)



Abbreviations: KM, Kaplan-Meier; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; PFS, progression-free survival.

Table 27: mFOLFOX, survival estimates and statistical fit

Model	Median PFS	AIC	BIC	OS landmarks (years)				
	Months			1	2	5	10	20
Exponential	3.91	428.66	431.06	12.1%	1.5%	0.0%	0.0%	0.0%
Generalized gamma	4.14	406.76	413.95	9.2%	1.7%	0.1%	0.0%	0.0%
Gompertz	4.37	425.98	430.77	9.5%	0.1%	0.0%	0.0%	0.0%
Log-logistic	4.14	407.95	412.74	8.4%	1.9%	0.2%	0.0%	0.0%
Log-normal	4.14	**405.31**	**410.10**	8.5%	1.1%	0.0%	0.0%	0.0%
Weibull	4.60	416.97	421.76	7.7%	0.1%	0.0%	0.0%	0.0%

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

Note: Bold text indicates lowest AIC/BIC.

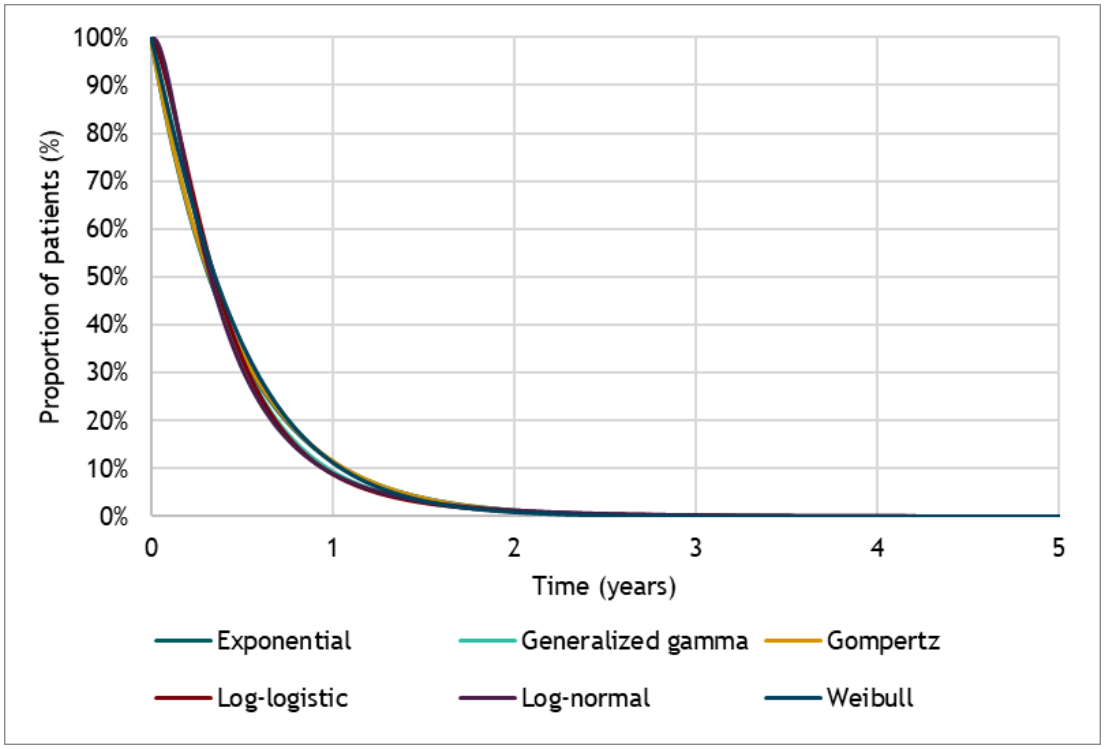
Exploratory RMST analysis (scenario analysis)

As a Bucher analysis could not be conducted for PFS and a naïve comparison was necessary in the base case, an exploratory scenario analysis was conducted based on restricted mean survival times (RMSTs) observed in ABC-06.

In this exploratory analysis:

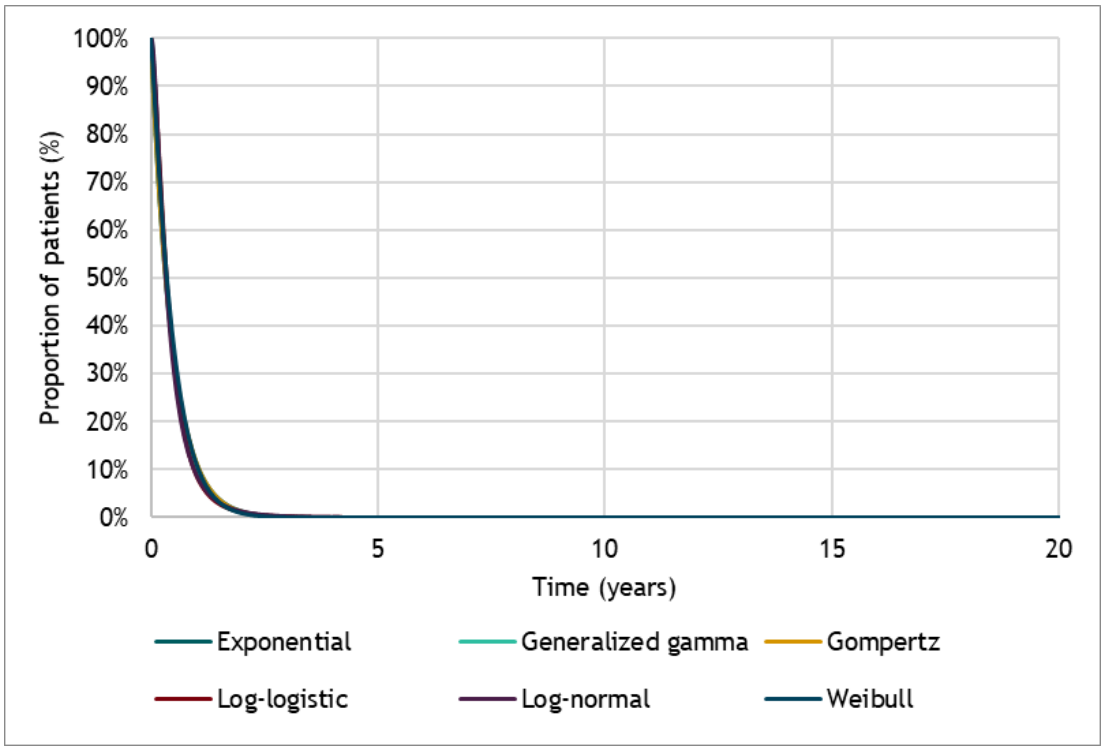
- The ratio of time spent in PFS versus time spent in OS for patients receiving mFOLFOX in ABC-06 was calculated, based on the 1-year RMST (75%, based on the ratio between the area under the KM estimates up to 1 year)
- Next, HRs to estimate mFOLFOX PFS (versus the mFOLFOX OS curve in the cost-effectiveness model) are estimated, ensuring that the observed 1-year RMST PFS to OS ratio (75%) is maintained when mFOLFOX OS is derived from the Bucher ITC
- The exploratory analysis, which is presented as a scenario, generates similar outcomes to when using the base-case unadjusted ABC-06 PFS curves for mFOLFOX (Figure 25 [5-year scale] and Figure 26 [20-year scale])
- Unadjusted curves are preferred in the base case, since this approach better keeps with guidance set out in NICE DSU TSD 14, and allows for exploration of structural uncertainty (via model selection) within scenario analysis

Figure 25: mFOLFOX, PFS (RMST exploratory scenario analysis; 5-year scale)



Abbreviations: KM, Kaplan-Meier; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; PFS, progression-free survival; RMST, restricted mean survival time.

Figure 26: mFOLFOX, PFS (RMST exploratory scenario analysis; 20-year scale)



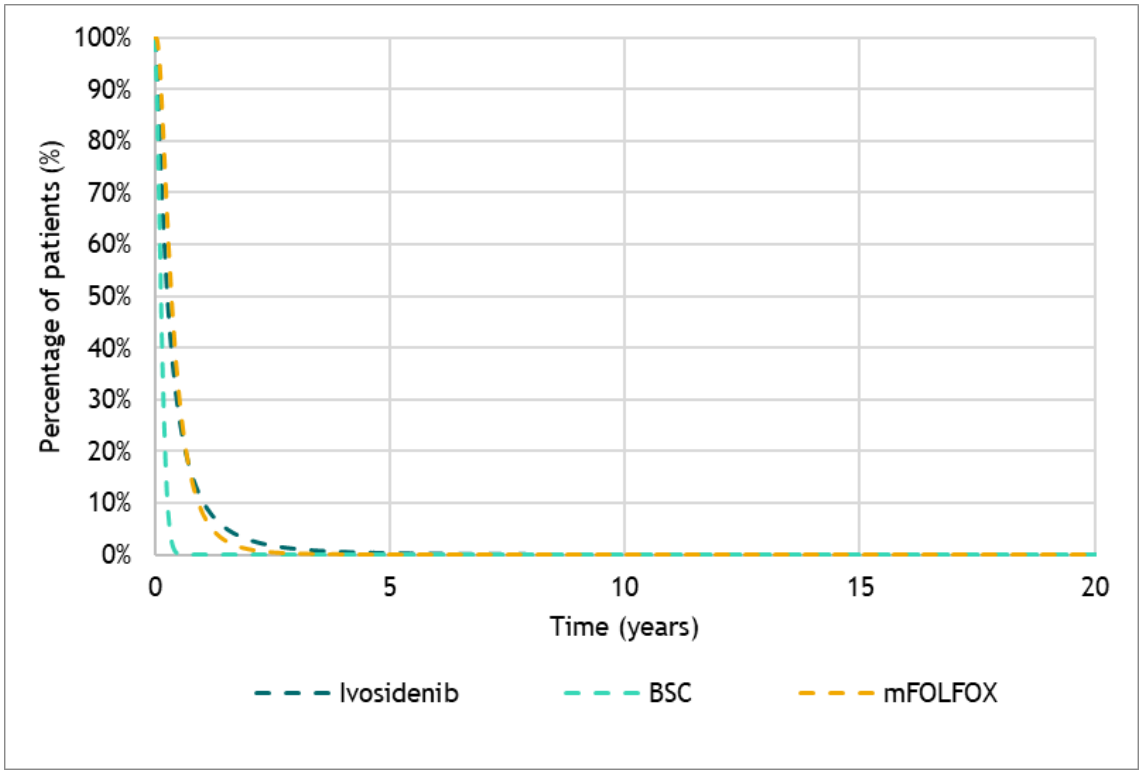
Abbreviations: KM, Kaplan-Meier; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; PFS, progression-free survival; RMST, restricted mean survival time.

B.3.3.4.4 PFS summary

Figure 27 presents a summary of the selected PFS curves for ivosidenib (log-normal), BSC (Weibull), and mFOLFOX (log-normal fit to unadjusted ABC-06 data). In the cost-effectiveness analysis, all survival outcomes were adjusted for background mortality (by ensuring the hazard of progression or death in the PFS curve is equal to or greater than the hazard of death for the age- and sex-matched general population).

A range of alternative parametric survival models for PFS are tested in scenario analysis (discussed in Section B.3.10.3). Furthermore, the exploratory analysis using RMST from the ABC-06 to estimate mFOLFOX PFS (in relation to mFOLFOX OS from the Bucher ITC) is tested in scenario analysis.

Figure 27: Summary of selected PFS curves



Abbreviations: BSC, best supportive care; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; PFS, progression-free survival.

B.3.3.5 Time on treatment

B.3.3.5.1 Ivosidenib

Figure 28 (5-year scale) and Figure 29 (20-year scale) present ToT curves for ivosidenib against KM estimate from ClarIDHy. As ToT data were available from a later data cut of ClarIDHy (June 2021), the KM data were notably mature. As such, the parametric survival curves produce similar long-term ToT estimates. In the base case, the log-normal curve is selected based on the statistical goodness of fit (Table 28) and for consistency with the curve choice for OS and PFS, which are correlated endpoints.

Clinical expert advice (appendix N) indicated that treatment beyond progression is unlikely to occur in real-world practice; as such, in the model base case the ivosidenib ToT curve is capped by the PFS curve. Furthermore, based on the selected base case PFS extrapolation (in which 2.9% of patients are alive and free of progression at 2-years), [redacted]

Figure 28: Ivosidenib, ToT (5-year scale)

Abbreviations: KM, Kaplan-Meier; ToT, time on treatment.

Figure 29: Ivosidenib, ToT (20-year scale)

Abbreviations: KM, Kaplan-Meier; ToT, time on treatment.

Table 28: Ivosidenib ToT, survival estimates and statistical fit

Model	Median ToT	AIC	BIC	ToT landmarks (years)				
	Months			1	2	5	10	20
Exponential								
Generalized gamma								
Gompertz								
Log-logistic								
Log-normal								
Weibull								

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

Note: Bold text indicates lowest AIC/BIC.

B.3.3.5.2 BSC

BSC ToT curves are not considered within the analysis, as no treatment acquisition or administration costs are applied in the BSC arm of the model.

B.3.3.5.3 mFOLFOX

In the absence of reported ToT KM data for mFOLFOX, parametric survival models could not be explored. As such, in the base case analysis, ToT in the mFOLFOX arm of the model is assumed to be equal to PFS (until the point of a maximum treatment duration). Treatment with mFOLFOX is administered every 2-weeks for a maximum of 12-cycles (24 weeks).

A scenario analysis is explored in which an exponential curve is estimated based on the median reported treatment duration of 10 weeks in ABC-06 (17)(the medium number of mFOLFOX cycles was 5 x 2-week cycles), until the maximum treatment duration.

B.3.3.5.4 ToT summary

Figure 30 presents a summary of the selected ToT curves for ivosidenib (log-normal, prior to application of a PFS cap) and mFOLFOX (assumed equal to PFS until the maximum number of cycles).

Figure 30: Summary of selected ToT curves

Abbreviations: mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; ToT, time on treatment.

Note: Figure accounts for the maximum number of mFOLFOX cycles (12 x 2-week cycles).

B.3.3.6 Adverse events

The cost and HRQoL implications of experiencing AEs were captured in the cost-effectiveness analysis. Table 29 shows the AEs frequencies incorporated within the model (treatment-related grade 3+ AEs occurring in 5% or more of patients), from ClarIDHy (May 2020 data cut) and ABC-06 (59, 17). For mFOLFOX, if data for a specific AE was not reported in the ABC-06 study publication, the frequency was assumed to be 0. In the cost-effectiveness model, AE management costs and HRQoL decrements were applied as a one off in the first model cycle (described further in Sections B.3.5.3 and B.3.4.4, respectively). The simplifying assumption of applying AE costs and consequences as a one off in the first model cycle is commonly observed in economic evaluations and is not expected to have a large impact on cost-effectiveness outcomes.

Table 29: Grade 3+ AEs occurring in 5% or more of patients

Adverse event	Ivosidenib (n =123) (ClarIDHy)	BSC (n = 59) (ClarIDHy)	mFOLFOX (n = 81) (ABC-06)
Ascites	8.94%	6.78%	0.00% (available)
Anaemia	6.50%	0.00%	2.47% (available)
Blood bilirubin increased	5.69%	1.69%	0.00% (unavailable)
Fatigue	3.25%	1.69%	11.11% (available)
Hyponatremia	5.69%	10.17%	0.00% (available)
Hypophosphatemia	3.25%	5.09%	0.00% (available)
Infection	0.00%	0.00%	9.88% (available)
Neutropenia	0.00%	0.00%	12.34% (available)

Abbreviations: BSC, best supportive care; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin.

B.3.4 Measurement and valuation of health effects

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

In the ClarIDHy trial, HRQoL outcomes were assessed using multiple disease specific and generic instruments, including the EuroQol Five-dimension (EQ-5D) five-level (5L). EQ-5D-5L questionnaires were completed by patients on day 1 of cycles 1 and 3, at the end of treatment and on day 1 of crossover cycle 1.

In the ClarIDHy trial, patients in the placebo (BSC) arm were permitted to ‘crossover’ to the experimental (ivosidenib) arm upon radiographic progression. Thus, to avoid generating biased results, only assessments (EQ-5D questionnaires) in the first

analysis period (i.e., excluding the post-crossover assessments) were included. According to the protocol, in the first analysis period, patients in both arms received an EQ-5D assessment at “cycle 1 day 1”, “cycle 3 day 1”, “end of treatment, period 1”. In addition, some patients in the placebo arm received an assessment on “crossover cycle 1 day 1”. i.e., for patients in the placebo arm ‘crossing’ over, a pre-dose assessment on the first day of crossover was taken (60). Furthermore, some additional assessments in the ivosidenib arm were performed outside of the pre-specified time points but within the first analysis period. All assessments within the first analysis period were considered in this analysis.

B.3.4.2 Mapping of EQ-5D-5L to EQ-5D-3L

In line with NICE guidance, the EQ-5D-5L responses from the ClarIDHy trial were ‘cross-walked’ to EQ-5D-3L responses using the mapping approach developed by Hernandez-Alava et al (87). The following health states were considered for the health-state utility values in addition to considering treatment-related adverse events:

- Baseline (before treatment initiation)
- Pre-progression (on treatment)
- Pre-progression (off treatment)
- Post-progression (on treatment)
- Post-progression (off treatment)

Baseline was the EQ-5D assessment collected at cycle 1, day 1. The progression variable was defined by comparing a patient’s ‘date of progression’ and their EQ-5D assessment date – thus where an EQ-5D assessment date occurred after the progression date, the patient’s assessment was a ‘post-progression’ assessment. Otherwise, the progression status variable took the value “pre-progression”. Furthermore, the pre-progression value was stratified according to whether the assessment occurred at baseline or not. For records where the date of progression was missing, the treatment discontinuation date, death/censoring (whichever came first) was considered a proxy for date of progression.

The treatment status variable was defined by comparing a patient’s ‘treatment end-date’ and their EQ-5D assessment date – thus where an EQ-5D assessment date occurred after the treatment end-date the patient was “off treatment” (otherwise they

were considered to be “on treatment”). For records where the treatment end-date was missing, it was assumed that patients remained on treatment until they experienced disease progression or death/censoring.

A treatment-related adverse event (TRAE) was defined as any event with an onset date on or after the date of the first dose of study treatment or any ongoing event on the date of the first dose of study treatment that worsened in severity after the date of the first dose of study treatment. Grade 3+ TRAEs were considered.

The analysis included [redacted] observations from [redacted] patients (Table 30).

Table 30: Progression, treatment and adverse event status assessment records

Health state	Ivosidenib	Placebo (BSC)	Total
Progression-status			
Baseline	[redacted]		
Pre-progression			
Post-progression			
[redacted]			
On-treatment			
Off-treatment			
[redacted]			
Yes			
No			
Total			

Abbreviations: BSC, best supportive care; TRAE, treatment-related adverse event.

Descriptive analysis of utility scores corresponding to EQ-5D-3L for both arms by progression and treatment status are presented in Table 31.

Table 31: Descriptive analysis of utility values by progression and treatment status

Health state	Patients	Observations	Ivosidenib Mean (SD) 95% CI	Placebo (BSC) Mean (SD) 95% CI	Total Mean (SD) 95% CI
Baseline	[redacted]				
Pre-progression (on treatment)					
Pre-progression (off treatment)					
Pre-progression (overall)					
Post-progression (on treatment)					
Post-progression (off treatment)					
Post-progression (overall)					

Abbreviations: BSC, best supportive care; CI, confidence interval; SD, standard deviation

The EQ-5D-3L utility values were analysed using both univariate and multivariate model structures and clustering by time-periods. As patients may provide multiple assessments within the same time-period, a Mixed Model for Repeated Measures (MMRM) was tested. This model allows for the consideration of repeated EQ-5D-3L measurements at the patient level. The variables that were considered were:

- Treatment status at time of EQ-5D assessment (still on treatment/discontinued)
- Progression status (pre-progression/post-progression) at time of EQ-5D assessment
- Arm of treatment (ivosidenib/BSC)
- TRAEs at time of EQ-5D assessment

A stepwise procedure was followed to determine the independent variables to be included in the final model. The selection of the preferred model was based on the AIC estimates. The results of the final, best-fitting, MMRM is provided below (Table 32).

The final model includes only the treatment status and TRAEs variables. Before discontinuing treatment, with no TRAEs, and irrespective of progression status, the utility score is [redacted] If a patient discontinues treatment the utility score decreases by [redacted] If a TRAE is reported, the utility score decreases by [redacted]

Table 32: Final MMRM model coefficients (base case)

Coefficient	Value	SE	95% CI	p-value
Intercept	[redacted]			
Off treatment				
TRAE grade ≥3				

Abbreviations: CI, confidence interval; MMRM, mixed model for repeated measures; SE, standard error.

In addition to the best-fitting model presented above, alternative models that consider progression status only (Table 33) and progression status and treatment status (Table 34) were included in the cost-effectiveness model for consideration in scenario analysis.

Table 33: MMRM model coefficients (scenario 1, progression status only)

Coefficient	Value	SE	95% CI	p-value
Intercept	[redacted]			
Progression				

Abbreviations: CI, confidence interval; MMRM, mixed model for repeated measures; SE, standard error.

Table 34: MMRM model coefficients (scenario 2, progression status and treatment status)

Coefficient	Value	SE	95% CI	p-value
Intercept	[redacted]			
Progression				
Off treatment				

Abbreviations: CI, confidence interval; MMRM, mixed model for repeated measures; SE, standard error.

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

A systematic review of the literature was conducted to identify relevant published HRQoL data for previously treated patients with advanced or metastatic CCA. Searches were performed alongside the economic evaluation SLR reported in Section B.3.1 and Appendix G (initially conducted in June 2021 and updated in January 2023). Details of the HRQoL systematic review are provided in Appendix D.

In the original searches, 1,245 publications were screened for inclusion. After the removal of duplicates and screening titles and abstracts, five were included for data extraction. Another six publications considered for data extraction were obtained from other sources. Out of the 11 publications, seven were unique studies. In the SLR update, 403 records were identified from electronic searches. After combining the results from the original and the updated SLR, 13 studies reported in 17 publications were included for data extraction. Most included studies reported on clinical trials, three observational studies were identified, and one cost-effectiveness study identified.

Only one study reported health-state utility values in CCA (the cost-effectiveness analysis); however, the values were not considered of direct relevance to the decision problem in this appraisal due to the country setting (not UK based).

B.3.4.3.1 Utilities used in previous appraisals

As well as consideration of the utility values reported within the literature, health utility values reported within prior NICE appraisals in similar disease areas were also assessed for appropriateness of inclusion within the economic model.

In the prior NICE appraisal in previously treated advanced or metastatic CCA (TA722), utility values (derived from EORTC QLQ-C30 data from the FIGHT 202 pemigatinib study mapped to EQ-5D-3L) were redacted and could therefore not be explored as scenario within this analysis (85). Therefore, a range of other STAs of treatments for other cancer types were explored for the purpose of allowing for sensitivity analysis within the cost-effectiveness model. These were: sorafenib for treating advanced hepatocellular carcinoma (HCC) (92), trastuzumab for treating HER2-positive metastatic gastric cancer (mGC) (93), and trifluridine-tipiracil for treating mGC or gastro-oesophageal junction adenocarcinoma (94). Inputs based on proxy indications were included in the cost-effectiveness model to allow alternative utility values to be tested in a scenario analysis.

A summary of utility values identified in previous submissions are presented in Table 35. In clinical expert interviews (appendix N), one expert identified HCC as a potentially suitable proxy indication for HRQoL estimates; therefore, utility values from TA474 are tested in scenario analysis (Section B.3.10.3).

Table 35: Summary of final utility values in previous submissions

NICE appraisal (indication)	Treatment	Progression-free	Post-progression
TA722 (CCA)	Pemigatinib	Not reported	Not reported
TA474 (HCC)	Sorafenib	0.6900	0.7100
TA208 (mGC)	Trastuzumab	0.7292	0.5770
TA669 (mGC)	Trifluridine-tipiracil	0.7644	0.6522

Abbreviations: HCC, hepatocellular carcinoma; mGC, metastatic gastric cancer; NICE, National Institute for Health and Care Excellence.

B.3.4.4 Adverse reactions

Adverse event-specific disutility values sourced from the literature (primarily the prior NICE appraisal in CCA [TA722]) are used in the cost-effectiveness model base case (Table 36). In scenario analysis, a utility decrement of [redacted] is applied across all AEs (given that grade ≥3 TRAEs were considered in the final MMRM utility model derived

from the ClarIDHy trial, Table 32). AE durations reported in the literature are applied in the base case analysis (where durations were not reported, AEs were assumed to last one model cycle [Table 37]).

Table 36: Adverse event disutility values

Adverse event	Duration	Source
Ascites	-0.125	HRQoL study in hepatic encephalopathy
Anaemia	-0.085	TA722/TA439
Blood bilirubin increased	0.000	Assumption
Fatigue	-0.085	TA722 (assumed same as anaemia)
Hyponatremia	0.000	Assumption
Hypophosphatemia	0.000	TA722
Infection	-0.085	TA722 (assumed same as anaemia)
Neutropenia	-0.061	TA722/TA439

Table 37: Adverse event durations

Adverse event	Duration	Source
Ascites	7.0	Assumption (one model cycle)
Anaemia	9.9	TA722
Blood bilirubin increased	2.6	TA722 (biliary event)
Fatigue	2.6	TA722
Hyponatremia	7.0	Assumption (one model cycle)
Hypophosphatemia	29.3	TA722
Infection	8.3	TA722
Neutropenia	7.0	TA722

Using the TRAE frequencies from the relevant clinical trials (reported in Table 29), the AE disutility values (Table 36), and the AE durations (Table 37), a one-off QALY decrement per treatment arm was calculated and applied in the first cycle of the cost-effectiveness model (Table 38).

Table 38: Adverse event one-off QALY decrement

Treatment arm	Disutility
Ivosidenib	-0.0004
BSC	-0.0002
mFOLFOX	-0.0005

Abbreviations: BSC, best supportive care; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin.

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

In the base case analysis, utility values derived from ClarIDHy are used to inform the health states based on treatment status (on or off treatment). The values derived from ClarIDHy are based directly on the relevant population and measure the health states using EQ-5D-5L cross-walked to EQ-5D-3L, which is the preferred measure as stated within the NICE methods guide (87).

Scenario analyses exploring alternative utility models from ClarIDHy (Section B.3.4.1), and alternative utility values from the literature are also explored (see Section B.3.4.3).

Age-related utility decrements have also been included in the model base case to account for the natural decline in quality of life associated with age. Utility values from the general population at each age were calculated using the algorithm by Ara and Brazier, 2010 (95). The utility multiplier was the calculated per increase in age and applied in each cycle throughout the model time horizon.

$$General\ population\ utility\ value = 0.9508566 + 0.0212126 \times male - 0.0002587 \times age - 0.0000332 \times age^2$$

Table 39 summarises the utility values included within the cost-effectiveness analysis base case, and Table 40 summarises utility values tested in scenario analysis.

Table 39: Summary of utility values for cost-effectiveness analysis (base case)

State	Base case	Reference in submission (section)	Justification
Progression-free (on treatment)	[redacted]	Section B.3.4.2	Derived directly from the ClarIDHy trial, and using the best-fitting model (treatment status and TRAE grade ≥3).
Progression-free (off treatment)			
Post-progression (on treatment)			
Post-progression (off treatment)			

Table 40: Summary of utility values for cost-effectiveness analysis (scenario analysis)

State	Scenario 1 (ClarIDHy, progression status only)	Scenario 2 (ClarIDHy, progression status and treatment status)	Scenario 3 (TA474)	Reference in submission (section)
Progression-free (on treatment)	[redacted]		0.6885	Section B.3.4.2 and Section B.3.4.3.1
Progression-free (off treatment)			0.6885	
Post-progression (on treatment)			0.7111	
Post-progression (off treatment)			0.7111	

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

A systematic review of the literature was conducted to identify relevant published cost and resource use data for previously treated patients with advanced or metastatic CCA. Searches were performed alongside the economic evaluation SLR reported in Section B.3.1 and Appendix G (initially conducted in June 2021 and updated in January 2023).

Details of the cost and healthcare resource use SLR are provided in Appendix I; however, in line with the systematic review of cost-effectiveness studies, limited cost and resource use data were identified for the patient population relevant to this appraisal. Notably, none of the identified healthcare resource use studies were conducted in a UK setting.

Due to the lack of relevant evidence identified as part of the SLR, the only prior NICE appraisal in advanced or metastatic CCA (TA722) was considered the most relevant source for informing healthcare resource use estimates (85). Cost inputs, which are described in further detail throughout this section, were obtained from sources deemed typical for informing UK-based economic evaluations, and in line with the NICE reference case. The following sources were used to identify costs:

- The electronic drugs and pharmaceutical electronic market information tool (eMIT) for generic treatment acquisition costs
- The British National Formulary (BNF) for branded treatment acquisition costs
- The NHS National Cost Collection (also known as NHS reference costs) for administration, resource use costs, and adverse event management costs
- Published literature and prior NICE appraisals for end-of-life care costs

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Treatment acquisition costs

Table 41 presents drug costs used to inform the analysis (namely, pack prices for treatments administered orally and vial prices for treatments administered

intravenously). The list price of ivosidenib is £12,500 (60 x 250 mg tablets); however, there is a proposed simple patient access scheme (PAS) discount for ivosidenib of [redacted] which is reflected within the cost-effectiveness model results presented. Ivosidenib is administered at a dose of 500 mg once daily, resulting in a PAS price of [redacted] per 30-day treatment cycle (equivalent to [redacted] per 7-day model cycle). Ivosidenib drug costs were adjusted for dose interruptions using two alternative approaches in the cost-effectiveness analysis. In the model base case, relative dose intensity from ClarIDHy [redacted] calculated as actual dose intensity over planned dose intensity, where the planned total daily dose was the dose assigned at the study entry) was applied to treatment cycle costs. In a scenario analysis, instead of applying RDI, dose interruptions were modelled as a one-off cost saving in the first model cycle, based on the proportion of ClarIDHy patients who experienced a held dose [redacted] and the average dose interruption duration [redacted]

As previously described, mFOLFOX is administered every 2-weeks for up to 12 cycles and comprises oxaliplatin (85 mg/m^2), calcium folinate (350 mg), fluorouracil (400 mg/m^2 bolus) and fluorouracil (2,400 mg/m^2 as a 46-hour continuous infusion). The dose per administration for oxaliplatin and fluorouracil is calculated using an average patient BSA of [redacted] which was estimated the average baseline height [redacted] (and weight [redacted] observed at baseline in ClarIDHy (59) (Mosteller formula) (89). For treatments with a BSA-based dosing regimen, wastage was incorporated by fitting a parametric distribution to the cumulative density of patient BSA, which allows the average number of vials required per dose to be more accurately reflected (96). The resulting cost of mFOLFOX is [redacted] per 2-week treatment cycle. It is conservatively assumed that patients in the BSC arm of the economic model do not incur drug acquisition costs.

Table 41: Drug unit costs

Treatment	Units	Pack size	Pack cost	Source
Ivosidenib	250 mg	60	£12,500 (PAS price, [redacted]	Servier
Oxaliplatin	50 mg	1	£20.45	eMIT (2022)(97)
	100 mg	1	£46.78	
	200 mg	1	£60.29	
Calcium folinate	350 mg	10	£125.15	eMIT (2022)(97)
Fluorouracil	500 mg	1	£3.04	eMIT (2022)(97)
	1000 mg	1	£3.46	
	2500 mg	1	£4.52	
	5000 mg	1	£9.73	

Abbreviations: eMIT, electronic drugs and pharmaceutical electronic market information tool; PAS, patient access scheme.

B.3.5.1.2 Treatment administration costs

Table 42 presents the unit administration costs for treatments given by intravenous infusion (i.e., components of the mFOLFOX regimen). The cost of infusion was represented by the delivery of complex chemotherapy, including prolonged infusion treatment, at first attendance (NHS National Cost Collection 2020/21, Code SB14Z). As fluorouracil is administered continuously over a 46-hour period, an additional cost of £190.59 per visit is applied for patients returning to the hospital to have their peripherally inserted central catheter (PICC) line removed by a nurse. The sources and approach for capturing mFOLFOX administration costs are consistent with prior NICE appraisals which included a prolonged fluorouracil infusion (85, 98). The resulting administration cost of mFOLFOX is £717.11 per 2-week treatment cycle. As ivosidenib is administered orally, it is assumed that no administration costs are incurred. In line with acquisition costs, patients in the BSC arm do not incur administration costs.

Table 42: Administration unit costs (NHS National Cost Collection, 2020/21) (99)

Administration	Cost	Description
Complex IV	£526.52	Deliver complex chemotherapy, including prolonged infusional treatment, at First Attendance (SB14Z); Total HRGs
Oncology nurse	£190.59	Non-admitted face-to-face attendance, follow-up, medical oncology (WF01A); non-consultant led

Abbreviations: HRGs, Healthcare Resource Groups; IV, intravenous; NHS, National Health Service.

B.3.5.2 Health-state unit costs and resource use

As previously described, healthcare resource use estimates were sourced from the published NICE appraisal of pemigatinib for previously treated advanced or metastatic CCA with FGFR2 alterations, which were based on ESMO guidelines for biliary cancer follow-up and clinical expert opinion reported by the company (85). Table 43 presents the monitoring strategy, which comprises clinical examinations, computerized tomography (CT) scans, and blood tests. In TA722, it was assumed based on clinical expert opinion that CT scans were performed once every 12 months following progression (85). For patients in the progressed state, the cost of daily pain medication (morphine sulphate) was also captured, in line with clinical feedback reported in TA722 (85).

In clinical validation interviews (appendix N) conducted separately with three NHS consultants, one clinical expert suggested that, in practice, monitoring could be more frequent in the mFOLFOX arm than the ivosidenib arm (in line with the 2-week treatment cycle of mFOLFOX compared with the 28-day treatment cycle of ivosidenib). However, the model conservatively assumes that clinical examinations/blood tests are only dependant on health state and not treatment arm.

In ClarIDHy, electrocardiogram (ECG) monitoring occurred monthly due to a risk of QT prolongation. In clinical validation interviews (appendix N), one clinical expert opinion indicated that, in practice, the frequency of ECG scans would be every two-to-three months (as clinicians gain experience with ivosidenib). Another clinical expert indicated that ivosidenib patients may receive an ECG at baseline (and up to 1 or 2 follow up ECGs in total as treatment continues). In the cost-effectiveness model, it is assumed that patients treated with BSC or mFOLFOX do not incur ECG

costs, while patients on treatment with ivosidenib are assumed to receive quarterly ECG monitoring.

Table 43: Healthcare resource use estimates (85)

Resource item	Resource usage, annual frequency (every X months)	
	Progression free	Progressed disease
Clinical examination	4 (every 3 months)	4 (every 3 months)
CT scan	4 (every 3 months)	1 (every 12 months)
Blood test	4 (every 3 months)	4 (every 3 months)
Daily morphine sulphate	0	365.25 (daily)

Abbreviations: CT, computerized tomography; ECG, electrocardiogram; NICE, National Institute for Health and Care Excellence.

Table 44 presents unit costs for healthcare resource use items, which were sourced from the NHS National Cost Collection (2020/21) and the BNF (for morphine sulphate). The resulting healthcare resource use costs per 7-day model cycle are £28.58 and £48.61 in the progression free and progressed disease health states, respectively.

Table 44: Healthcare resource use unit costs (86)

Resource item	Unit cost	Reference
Clinical examination	£224.55	NHS National Cost Collection (2020/21), non-admitted face-to-face attendance, follow-up, medical oncology (WF01A); consultant led
CT scan	£144.59	NHS National Cost Collection (2020/21), computerised Tomography Scan of One Area, with Pre- and Post-Contrast (IMAGOP RD22Z); diagnostic imaging
Blood test	£3.63	NHS National Cost Collection (2020/21), haematology (DAPS05); directly accessed pathology services
Daily morphine sulphate	£4.05	BNF, morphine sulfate, 1 mg per 1 ml vial (£40.50 per 10 pack)
ECG monitoring	£162.46	NHS National Cost Collection (2020/21), electrocardiogram monitoring or stress testing, medical oncology (EY51Z); outpatient procedures

Abbreviations: CT, computerized tomography; NHS, National Health Service.

B.3.5.3 Adverse reaction unit costs and resource use

Unit costs for the management of treatment-related grade 3+ AEs occurring in 5% or more of patients (Section B.3.4.4) are presented in Table 45. Unit costs were sourced from the NHS National Cost Collection (2020/21) and BNF, using consistent

assumptions with NICE TA722 (85) and prior NICE appraisal across multiple proxy indications (TA405, TA490, and TA692).

Consistent with the approach for modelling AE utility decrements (Section B.3.4.4), an one-off AE management cost was calculated and applied in the first model cycle. One-off AE costs were £172.77 for ivosidenib, £103.95 for BSC, and £242.69 for mFOLFOX.

Table 45: Adverse event management unit costs (86)

Adverse event	Unit cost	Reference
Ascites	£991.77	NHS National Cost Collection (2020/21), malignant gastrointestinal tract disorders without interventions/with single intervention (FD11D-FD11K); non-elective short stay
Anaemia	£735.80	NHS National Cost Collection (2020/21), iron deficiency anaemia (SA04G-SA04L); non-elective short stay
Blood bilirubin increased	£0.00	Watchful waiting (and thus no cost assumed)
Fatigue	£677.24	NHS National Cost Collection (2020/21), nutritional disorders without interventions (FD04C-FD04E); non-elective short stay
Hyponatremia	£238.41	BNF, one pack of oral demeclocycline 150mg capsules
Hypophosphatemia	£19.39	BNF, one pack of oral phosphate supplements (Phosphate Sandoz effervescent tablet)(100)
Infection	£677.24	Assumed equal to fatigue
Neutropenia	£667.35	NHS National Cost Collection (2020/21), other haematological or splenic disorders (SA08G-SA08J); non-elective short stay

Abbreviations: BNF, British National Formulary; NHS, National Health Service.

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 End-of-life care costs

End-of-life care costs were applied to patients upon entering the death health state in the cost-effectiveness model. In line with NICE TA722, end-of-life care costs were sourced (101) and uplifted to the latest cost year (2020/21), using inflation indices reported in the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2021 (Table 46).

Table 46: End-of-life care costs (101)

Category	Cost	
	2013/14	**2020/21**
Health care	£4,254.00	£4,827.08
Social care	£1,829.00	£2,075.39
Total end of life costs		**£6,902.47**

B.3.5.4.2 IDH1-mutation testing costs

As previously described, genetic testing for CCA is part of routine NHS England practice, under the National genomic test directory for cancer (which specifies the genomic tests commissioned by the NHS in England for cancer, the technology by which they are available, and the patients who will be eligible to access to a test) (86). Therefore, IDH1-mutation testing costs in the base case analysis are assumed to be zero, as any testing costs would be applied equally across treatments arms and thus have no impact on incremental cost-effectiveness results. In clinical validation interviews (appendix N) conducted separately with three NHS consultants, one clinical expert confirmed that, since testing for IDH1 mutations was made available in genomic hubs and the test directory, it is undertaken in NHS clinical practice.

However, two of the experts suggested that, although IDH1-mutation testing in CCA is included in the National genomic test directory, clinicians may currently be unlikely to routinely test in clinical practice as no targeted IDH1 treatments are reimbursed in NHS England practice. Therefore, a scenario analysis is explored in which the one-off cost of identifying an IDH1-mutation positive patient is applied to treatment acquisition costs in the ivosidenib arm only. In this scenario, the cost per test (£34.00, sourced from the NICE TA722 (85) Final Appraisal Determination) is divided by the IDH1 incidence rate (16.5%) (14). The resulting cost per positive test is £206.06.

B.3.6 Severity

CCA is a rare and severe form of cancer, which is associated with a poor patient prognosis. Approximately 70% of patients are diagnosed late with unresectable, locally advanced, or metastatic disease, and these patients have an estimated 5-year survival rate of ≤10% (39–41). Within the context of the patient population

considered in this appraisal – patients with advanced or metastatic CCA with an IDH1 mutation – median OS in the BSC of the economic model falls between 5.06 and 5.75 months (even when considering all six standard parametric models). There is a clear unmet need for safe and efficacious targeted treatments for patients with advance or metastatic IDH1-mutated CCA.

QALY shortfall was calculated using the R-Shiny tool by Schneider et al., (2021) (102). Summary features used to estimate lifetime QALYs without the disease were sourced from ClarIDHy (Table 47).

Table 47: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Sex distribution (% female)	63.24%*	Table 21 (Section B.3.3.1)
Starting age (years)	[redacted]	Table 21 (Section B.3.3.1)

Abbreviations: QALYs, quality-adjusted life-years.

Note: *Sex distribution and starting age rounded to 0 decimal places per the requirements of the published QALY shortfall tool.

A summary of the health state utility values and base case undiscounted life years on BSC and mFOLFOX are presented in Table 48.

Table 48: Summary of health state benefits and utility values for QALY shortfall analysis

Health state	Utility value: mean	Undiscounted life years	
		BSC	mFOLFOX
Progression free (on treatment)	[redacted]	[redacted]	[redacted]
Progression free (off treatment)			
Progressed disease (on treatment)			
Progressed disease (off treatment)			

Abbreviations: QALYs, quality-adjusted life-years

Total remaining discounted QALYs for patients treated with BSC or mFOLFOX were taken from the cost-effectiveness model ‘results’ worksheet (and inputted into the QALY shortfall tool to 2 decimal places). For completeness, all 6 available standard parametric curves for estimating BSC OS were tested in QALY shortfall calculations. OS in the mFOLFOX arm (used to estimate LYs and subsequently QALYs) was calculated using the Bucher ITC (as described in Section B.2.9 and B.3.3.3.3).

Results of the QALY shortfall calculator are presented in Table 49. The published QALY shortfall tool provides 5 methods for estimating population quality-adjusted life expectancy, which are described in turn below:

- Reference case:
  - Scoring algorithm: EQ-5D-3L value set from the 1993 MVH study
  - Health state profiles: EQ-5D-3L from the Health Survey for England 2014
  - Model: ALDVMM by Hernandez Alava, et al. 2022
- Alternative A:
  - Scoring algorithm: EQ-5D-5L to 3L mapping by by Hernandez Alava, et al. 2020
  - Health state profiles: Health Survey for England 2017 and 2018 (pooled)
  - Model: empirical means/no interpolation
- Alternative B:
  - Scoring algorithm: EQ-5D-5L to 3L mapping by van Hout et al. 2012
  - Health state profiles: Health Survey for England 2017 and 2018 (pooled)
  - Model: empirical means/no interpolation
- Alternative C:
  - Scoring algorithm: EQ-5D-3L value set from the 1993 MVH study
  - Health state profiles: EQ-5D-3L from the 1993 MVH study by Kind et al., 1999
  - Model: empirical means/no interpolation
- Alternative D:
  - Scoring algorithm: EQ-5D-3L value set from the 1993 MVH study
  - Health state profiles: Health Survey for England 2012 + 2014 (pooled)
  - Model: empirical means/no interpolation

For each of the 5 methods, all 6 available standard parametric curves for BSC OS were testing to estimate discounted BSC LYs and in turn QALYs.

In 30 out of 30 scenarios tested (see Table 49), the criteria for a x1.7 QALY weight was met versus BSC, based on a proportion shortfall above 95%. In 5 out of 5

scenarios tested (see Table 50), the criteria for a x1.7 QALY weight was met versus mFOLFOX, based on a proportion shortfall above 95%.

Within the context of this appraisal, the criteria for applying x1.7 severity modifier/QALY weight are met.

Table 49: QALY shortfall scenarios (BSC)

Parametric model	BSC QALYs (discounted)	Proportional QALY shortfall (scenario)*				
		Reference case	A	B	C	D
Exponential	[redacted]	96.53%	96.45%	96.47%	96.45%	96.54%
Generalized gamma		96.29%	96.20%	96.23%	96.20%	96.30%
Gompertz		96.61%	96.53%	96.56%	96.53%	96.62%
Log-logistic		95.64%	95.54%	95.57%	95.54%	95.65%
Log-normal		96.05%	95.95%	95.98%	95.95%	96.06%
Weibull		**96.69%**	96.61%	96.64%	96.61%	96.70%

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year.

Note: A proportional QALY shortfall >95% indicates a x 1.7 QALY weight. Value in bold indicates the base case analysis. * Alternative QALY shortfall methods described in text above.

Table 50: QALY shortfall scenarios (mFOLFOX)

Approach	mFOLFOX QALYs (discounted)	Proportional QALY shortfall (scenario)				
		Reference case	A	B	C	D
Bucher ITC	[redacted]	**95.64%**	95.55%	95.58%	95.54%	95.66%

Abbreviations: mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY, quality-adjusted life year.

Note: A proportional QALY shortfall >95% indicates a x 1.7 QALY weight. Value in bold indicates the base case analysis. * Alternative QALY shortfall methods described in text above.

B.3.7 Uncertainty

Among the GI cancers, BTCs are very infrequent (3). Additionally, IDH1 mutations are rare, occurring in 16.5% of iCCA patients and 1% of eCCA patients (13). Therefore, identified evidence is unlikely to be reported specifically in a locally advanced/metastatic previously treated IDH1-mutated CCA population (as demonstrated in ABC-06 study, which included patients with BTCs and did not report mutation-specific data). Nevertheless, data are available from the randomized,

phase 3, placebo controlled ClarIDHy study, for the population of interest within this appraisal.

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1 Summary of base-case analysis inputs

A summary of key inputs from the base case analysis are presented in Table 51. A full list of model parameters is presented in Appendix M.

Table 51: Summary of variables applied in the economic model

Variable	Value	Distribution	Confidence interval
Model settings (Section B.3.2.2.3)			
Time horizon (years)	20	Scenario analysis	-
Annual discount rate: Costs	3.50%	Scenario analysis	-
Annual discount rate: LYs	0.00%	Scenario analysis	-
Annual discount rate: QALYs	3.50%	Scenario analysis	-
Patient characteristics (Section B.3.3.1)			
Age (mean, years)	[redacted]	Not varied	-
Proportion female (%)	63.24%	Not varied	-
Height (mean, cm)	[redacted]	Not varied	-
Weight (mean, kg)	[redacted]	Not varied	-
Parametric survival models (Section B.3.3.3-B.3.3.5)			
Ivosidenib OS (log normal), meanlog	[redacted]	Multivariate normal	-
Ivosidenib OS (log normal), sdlog	[redacted]	Multivariate normal	-
Ivosidenib PFS (log normal), meanlog	[redacted]	Multivariate normal	-
Ivosidenib PFS (log normal), sdlog	[redacted]	Multivariate normal	-
Ivosidenib ToT (log normal), meanlog	[redacted]	Multivariate normal	-
Ivosidenib ToT (log normal), sdlog	[redacted]	Multivariate normal	-
BSC OS (Weibull), shape	[redacted]	Multivariate normal	-
BSC OS (Weibull), scale	[redacted]	Multivariate normal	-
BSC OS (Weibull), shape	[redacted]	Multivariate normal	-
BSC OS (Weibull), scale	[redacted]	Multivariate normal	-
Indirect treatment comparison (Section B.3.3.3-B.3.3.5)			
OS HR: Ivosidenib versus mFOLFOX	[redacted]	Lognormal	[redacted]
PFS, ABC-06 (log normal), meanlog	[redacted]	Multivariate normal	-
PFS, ABC-06 (log normal), sdlog	[redacted]	Multivariate normal	-

mFOLFOX, maximum treatment duration (weeks)	24	Not varied	-
Treatment costs (Section B.3.5.1.1)			
Drug cost: Ivosidenib (250 mg)	[redacted]	Not varied	-
Drug cost: Oxaliplatin (50 mg)	£20.45	Normal	£20.18-£20.71
Drug cost: Oxaliplatin (100 mg)	£46.78	Normal	£46.27-£47.28
Drug cost: Oxaliplatin (200 mg)	£60.29	Normal	£58.75-£61.83
Drug cost: Calcium folinate (350 mg)	£125.15	Normal	£120.71-£129.59
Drug cost: Fluorouracil (500 mg)	£3.04	Normal	£3.02-£3.05
Drug cost: Fluorouracil (1000 mg)	£3.46	Normal	£3.42-£3.51
Drug cost: Fluorouracil (2500 mg)	£4.52	Normal	£4.49-£4.54
Drug cost: Fluorouracil (5000 mg)	£9.73	Normal	£9.66-£9.81
Ivosidenib, RDI (%)	[redacted]	Normal	[redacted]
Administration costs (Section B.3.5.1.2)			
Administration cost: complex IV	£526.52	Normal	£423.32-£629.71
Administration cost: oncology nurse	£190.59	Normal	£153.24-£227.95
Healthcare resource use costs (Section B.3.5.2)			
HCRU cost: Clinical examination	£224.55	Normal	£180.54-£268.56
HCRU cost: CT scan	£144.59	Normal	£116.25-£172.93
HCRU cost: Blood test	£3.63	Normal	£2.92-£4.34
HCRU cost: Daily morphine sulphate	£4.05	Normal	£3.26-£4.84
HCRU cost: ECG	£162.46	Normal	£130.62-£194.3
HCRU frequency (progression-free): Clinical examination	4.00	Normal	3.22-4.78
HCRU annual frequency (progression-free): CT scan	4.00	Normal	3.22-4.78
HCRU annual frequency (progression-free): Blood test	4.00	Normal	3.22-4.78
HCRU annual frequency (progression-free): Daily morphine sulphate	0.00	Normal	0-0
HCRU annual frequency (progressed disease): Clinical examination	4.00	Normal	3.22-4.78
HCRU annual frequency (progressed disease): CT scan	1.00	Normal	0.8-1.2
HCRU annual frequency (progressed disease): Blood test	4.00	Normal	3.22-4.78
HCRU annual frequency (progressed disease): Daily morphine sulphate	365.25	Normal	293.66-436.84
HCRU frequency (ivosidenib on treatment): ECG	4.00	Normal	3.22-4.78
Adverse event frequency (Section B.3.3.6)			
AE frequencies, ivosidenib	ClarIDHy (full list presented in appendix)		

AE frequencies, mFOLFOX	ABC-06 (full presented in appendix)		
Adverse event costs (Section B.3.5.3)			
AE cost: Ascites	£991.77	Normal	£797.39-£1186.15
AE cost: Anaemia	£735.80	Normal	£591.59-£880.01
AE cost: Blood bilirubin increased	£0.00	Normal	£0.00-£0.00
AE cost: Fatigue	£677.24	Normal	£544.5-£809.98
AE cost: Hyponatremia	£238.41	Normal	£191.68-£285.14
AE cost: Hypophosphatemia	£19.39	Normal	£15.59-£23.19
AE cost: Infection	£677.24	Normal	£544.50-£809.98
AE cost: Neutropenia	£667.35	Normal	£536.55-£798.15
End-of-life costs (Section B.3.5.4.1)			
EOL cost: Round et al. (2015), health	£4,254.00	Normal	£3420-£5088
EOL cost: Round et al. (2015), social	£1,829.00	Normal	£1470.52-£2187.48
Health state utility values (Section B.3.4.2)			
ClarIDHy, utility model, intercept	[redacted]	Multivariate normal	-
ClarIDHy, utility model, off treatment		Multivariate normal	-
ClarIDHy, utility model, TRAE grade ≥3		Multivariate normal	-
Adverse event utility decrements (Section B.3.4.4)			
AE disutility values	Full list presented in appendix		
AE durations	Full list presented in appendix		
IV administration disutility	0.025	Beta	0.02-0.03
General population utility, coefficients (Section B.3.4.5)			
Male	0.02121	Not varied	-
Age	-0.00026	Not varied	-
Age²	-0.00003	Not varied	-
Constant	0.95086	Not varied	-

Abbreviations:

B.3.8.2 Assumptions

Table 52 presents a summary of key modelling assumptions.

Table 52: Summary of key modelling assumptions

Assumption	Description	Justification
Model settings		
Time horizon	20 years constitutes a lifetime horizon	>99% of the modelled cohort have entered the death state by 20 years, across treatment arms
Cycle length	A weekly cycle length with no half-cycle correction	This relatively short cycle length is considered appropriate due to the

Assumption	Description	Justification
		poor prognosis of patients with advanced/metastatic CCA, frequently resulting in rapid disease progression. Due to the short cycle length, half-cycle correction is not required.
No treatment beyond disease progression	In the base case, patients are assumed to discontinue treatment upon progression. In a scenario analysis, treatment beyond progression was permitted in the model	The SmPC notes that treatment with ivosidenib should be continued until disease progression or until treatment is no longer tolerated by the patient. Expert advice indicated that treatment beyond progression would not occur in real-world practice. However, treatment beyond progression was permitted in the ClarIDHy trial and therefore tested as a scenario in the model.
Parametric survival analysis		
Ivosidenib (OS, PFS, ToT)	Log-normal curves selected in the base case. Alternative parametric models tested in scenario analysis.	Based on clinical plausibility of the long-term extrapolations (based on clinical expert opinion), statistical goodness-of-it and consistency across correlated endpoints
BSC (OS, PFS)	Weibull curves selected in the base case. Alternative parametric models tested in scenario analysis.	Based on clinical plausibility of the long-term extrapolations (based on clinical expert opinion), statistical goodness-of-it and consistency across correlated endpoints
Indirect comparison		
ITC	Comparisons between ivosidenib and mFOLFOX were drawn from an ITC	No direct (head-to-head) evidence are available comparing ivosidenib with mFOLFOX
mFOLFOX OS approach	Bucher ITC	A frequentist approach using the Bucher method was preferred over a Bayesian analysis due to the limited evidence base (n=2 studies)
mFOLFOX PFS approach	Unadjusted PFS data were used in the base case. An exploratory scenario was presented in which mFOLFOX PFS was estimated in the model by assuming the ratio of time spent in PFS versus OS from the ABC-06 study based on a 1-year RMST analysis (75%) would hold when using	As PFS data were not reported in the control (ASC) arm of ABC-06, an analysis via a common comparator such as the Bucher ITC was not possible Therefore, unadjusted PFS data were used to naively compare against ivosidenib and BSC in the model. As a Bucher comparison could not be performed for PFS, an

Assumption	Description	Justification
	the mFOLFOX OS curve produced via the Bucher comparison for OS	exploratory analysis (based on RMST in the ABC-06 trial) was presented as a scenario
mFOLFOX ToT	ToT was assumed equal to PFS (until the maximum treatment duration), as treatment is administered until progression for a maximum of 12-cycles	In the absence of reported ToT KM data for mFOLFOX, a range of parametric survival models could not be fitted. A scenario analysis is explored in which an exponential curve is estimated based on the median reported treatment duration (until the maximum treatment duration).
Adverse events		
Adverse event frequency	The incidence of treatment-related, grade ≥3 AEs, affecting ≥5% of patients for any relevant comparator, were modelled (irrespective of the incidence being <5% for other comparators)	Grade ≥3 AEs are expected to have the greatest impact on patients

B.3.9 Base-case results

B.3.9.1 Base-case incremental cost-effectiveness analysis results

Base case cost-effectiveness results are presented in Table 53. As there are two comparators relevant to the decision problem, results are presented using fully incremental analysis. In the NICE manual, it is stated that the cost-effectiveness estimates should be derived from a probabilistic analysis, when possible. Therefore, incremental analysis is performed using probabilistic results in the base case. However, deterministic incremental analysis results are also presented (Table 54).

When considering a x1.7 QALY weight (Section B.3.6), the base case results demonstrate that mFOLFOX is extendedly dominated by ivosidenib (meaning ivosidenib generates more QALYs at a lower cost per QALY than mFOLFOX). Ivosidenib is associated with a probabilistic ICER of [redacted] versus BSC, which falls below the upper limit of the NICE decision-making threshold. Deterministic results are close to the results of the probabilistic analysis.

Table 55 and Table 56 presents the net-heath benefit (NHB) at the £20,000/QALY and £30,000/QALY willingness-to-pay (WTP) thresholds.

Table 53: Base-case results (probabilistic)

Technologies	Total			Incremental (versus BSC)			ICER versus BSC (£/QALY) (x1.7 modifier)	ICER incremental (£/QALY) (x1.7 modifier)
	Costs	LYG	QALYs	Costs	LYG	QALYs (x1.7 modifier)		
BSC	[redacted]							
mFOLFOX								
Ivosidenib								

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

Table 54: Base-case results (deterministic)

Technologies	Total			Incremental (versus BSC)			ICER versus BSC (£/QALY) (x1.7 modifier)	ICER incremental (£/QALY) (x1.7 modifier)
	Costs	LYG	QALYs	Costs	LYG	QALYs (x1.7 modifier)		
BSC	[redacted]							
mFOLFOX								
Ivosidenib								

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

Table 55: Net health benefit (probabilistic, versus BSC)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs (x1.7 modifier)	NHB at £20,000 (x1.7 modifier)	NHB at £30,000 (x1.7 modifier)
BSC	[redacted]					
Ivosidenib						

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY(s), quality-adjusted life year(s); NHB, net health benefit.

Table 56: Net health benefit (probabilistic, versus mFOLFOX)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs (x1.7 modifier)	NHB at £20,000 (x1.7 modifier)	NHB at £30,000 (x1.7 modifier)
mFOLFOX	[redacted]					
Ivosidenib						

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s); NHB, net health benefit.

B.3.10 Exploring uncertainty

B.3.10.1 Probabilistic sensitivity analysis

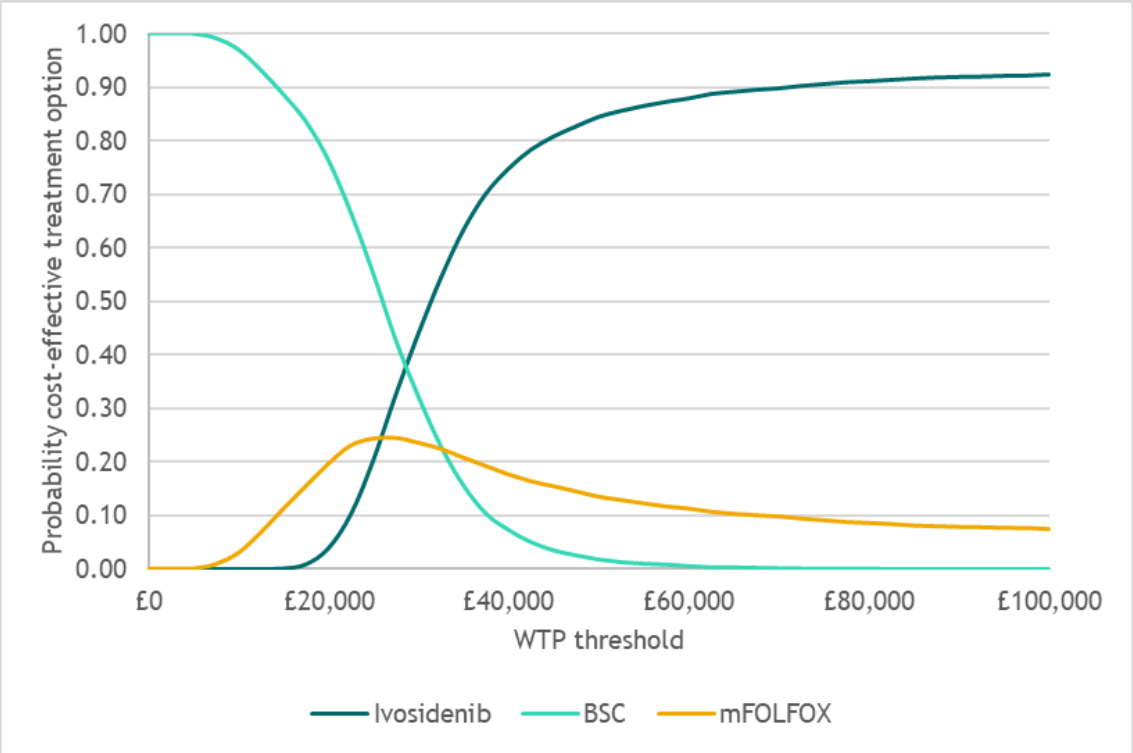
Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA). In PSA, all parameters are simultaneously varied from an assigned probability distribution (see Table 51). PSA inputs were randomly drawn, and results recorded across 5,000 iterations, by which point costs and outcomes had stabilised and were considered reliable for capturing uncertainty (assessed by visual inspection of convergence plots in the submitted cost-effectiveness model).

As described in Section B.3.9.1, mean probabilistic results are presented and used in fully incremental analysis in Table 53.

Figure 31 presents the cost-effectiveness acceptability curve for ivosidenib versus BSC and mFOLFOX. At a WTP threshold of £30,000 per QALY gained, ivosidenib is the treatment with the highest probability of being the cost-effective option (when considering the x1.7 severity modifier).

Figure 32 and Figure 33 present an incremental cost-effectiveness plane for ivosidenib versus BSC and mFOLFOX, respectively. Of 5,000 PSA iterations, 100% and 96% indicate that ivosidenib provides more QALYs at an increased cost per patient, versus BSC and mFOLFOX, respectively.

Figure 31: Cost-effectiveness acceptability curve



Abbreviations: BSC, best supportive care; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; WTP, willingness-to-pay

Figure 32: Incremental cost-effectiveness plane (ivosidenib versus BSC)

[redacted]

Abbreviations: BSC, best supportive care; PSA, probabilistic sensitivity analysis; WTP, willingness-to-pay; QALYs, quality-adjusted life years.

Figure 33: Incremental cost-effectiveness plane (ivosidenib versus mFOLFOX)

Abbreviations: mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; PSA, probabilistic sensitivity analysis; WTP, willingness-to-pay; QALYs, quality-adjusted life year.

B.3.10.2 Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted to test the impact of individual parameter uncertainty on cost-effectiveness results, holding all else constant. In turn, inputs were set to their respective lower and upper limits (presented in Table 51), while all other parameters were maintained at their base case setting. If the variance of a parameter was not available, a simplifying assumption was made assuming that the standard error was 10% of the mean value. Correlated inputs with joint uncertainty, such as parametric survival model coefficients and utility regression model coefficients, which are varied in PSA using a multivariate normal distribution, were not included in the OWSA.

Figure 34 and Figure 35 present the tornado plots showing the 10 parameters which had the largest impact on the incremental net-monetary benefit (INMB) for ivosidenib versus BSC and mFOLFOX, respectively.

In the pairwise comparison of ivosidenib versus BSC, the OWSA demonstrates that model findings are robust to reasonable variation in parameters, with ivosidenib RDI, and healthcare resource use estimates and associated unit costs having the largest impact on results.

Figure 34: Tornado plot of OWSA results (INMB, ivosidenib versus BSC)

Abbreviations: AE, adverse event; BSC, best supportive care; ECG, electrocardiogram; HCRU, health-care resource use; INMB, incremental net-monetary benefit; OWSA, one-way sensitivity analysis; QALY, quality-adjusted life year; RDI, relative dose intensity; WTP, willingness to pay.

Note: INMB calculated using a WTP threshold of £30,000 per QALY gained. Incremental QALYs account for a x1.7 severity modifier. Correlated inputs with joint uncertainty (such as parametric survival model coefficients and utility regression model coefficients) are not included in the OWSA.

In the pairwise comparison of ivosidenib versus mFOLFOX, the parameter with the largest impact on cost-effectiveness results was the HR for OS from the Bucher comparison. Other than when varying the OS HR, cost-effectiveness results were relatively insensitive to individual parameter uncertainty.

Figure 35: Tornado plot of OWSA results (INMB, versus mFOLFOX)

Abbreviations: HCRU, health-care resource use; HR, hazard ratio; INMB, incremental net-monetary benefit; IV, intravenous; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; RDI, relative dose intensity; ToT, time on treatment.

Note: INMB calculated using a WTP threshold of £30,000 per QALY gained. Incremental QALYs account for a x1.7 severity modifier. Correlated inputs with joint uncertainty (such as parametric survival model coefficients and utility regression model coefficients) are not included in the OWSA.

B.3.10.3 Scenario analysis

Scenario analyses were performed to test key structural and methodological assumptions within the model. As the base case probabilistic results and deterministic results were close, scenario analyses were conducted deterministically. A list of scenarios explored is presented in Table 57. Results of the scenario analysis are presented in Table 58 with an indication of whether each scenario meets the criteria for the x1.7 QALY weighting.

The scenarios with the largest impact on cost-effectiveness results occurred when simultaneously exploring alternative parametric survival models for ivosidenib OS, PFS, and ToT, and when varying the ivosidenib OS model alone.

Table 57: List of scenario analyses

Scenario #	Parameter/setting	Base case	Scenario
1	Time horizon	20 years	10 years
2			25 years
3	Discount rates for costs and QALYs	3.5%	1.5%
4			6.0%
5	Ivosidenib OS	Log-normal	Log-logistic
6			Generalized gamma
7			Exponential
8	BSC OS	Weibull	Gompertz
9			Exponential
10	Ivosidenib PFS	Log-normal	Generalized gamma
11			Log-logistic
12	BSC PFS	Weibull	Log-logistic
13	Ivosidenib ToT	Log-normal	Exponential
14	Ivosidenib efficacy (OS, PFS and ToT simultaneously)	Log-normal	Log-logistic
15			Generalized gamma
16			Exponential
17	BSC efficacy (OS and PFS simultaneously)	Weibull	Gompertz
18	PFS assessment	Independent	Investigator
19	mFOLFOX PFS	Log-normal	Generalized gamma
20	mFOLFOX PFS approach	PSMs (naïve ABC-06)	Naïve HR versus ivosidenib
21			Exploratory RMST analysis
22	mFOLFOX ToT approach	HR versus PFS	Exponential through median
23	Ivosidenib dose interruptions approach	RDI (%)	One-off cost reduction based on average duration of interruption
24	Treatment beyond progression	No	Yes
25	Include IDH1 testing costs?	No	Yes
26	Utility source	ClarIDHy model 1 (treatment status and Grade ≥3 TRAEs)	NICE TA474
27			ClarIDHy model 2 (progression status)
28			ClarIDHy model 3 (progression and treatment status)
29	Include IV administration disutility?	Yes	No
30	Include AE disutility values?	Yes	No

Abbreviations: AE, adverse event; BSC, best supportive care; HR, hazard ratio; NICE, National Institute of Health and Care Excellence; OS, overall survival; PFS, progression-free survival; PSMs, parametric survival models; RDI, relative dose intensity; TA, technology appraisal; ToT, time on treatment.

Table 58: Deterministic scenario analysis results

Scenario #	Incremental versus BSC			Incremental versus mFOLFOX			x1.7 modifier versus BSC met?
	Costs (£)	QALYs (x1.7 modifier)	ICER (£/QALY) (x1.7 modifier)	Costs (£)	QALYs (x1.7 modifier)	ICER (£/QALY) (x1.7 modifier)	
Base case	[redacted]						
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
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16							
17							
18							
19							

20	[redacted]
21	
22	
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Abbreviations: BSC, best supportive care; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; ToT, time on treatment

B.3.11 Subgroup analysis

There are no subgroups considered within the cost-effectiveness analysis.

B.3.12 Benefits not captured in the QALY calculation

Under existing treatments, patients potentially face the harmful side effects of systemic chemotherapy, which can be avoided with an oral targeted treatment. This oral targeted treatment will mean patients and their carers will not have as many hospital treatments reducing the anxiety, time and cost pressures associated with this . For carers it may also mean less time off work, reducing financial burden

B.3.13 Validation

B.3.13.1 Validation of cost-effectiveness analysis

As described in Section B.1.3, due to the lack of available targeted therapies for patients with advanced or metastatic CCA in NHS England practice, the prognosis for locally advanced or metastatic CCA patients is poor. Approximately 70% of patients are diagnosed late with unresectable, locally advanced, or metastatic disease – these patients have an estimated 5-year survival rate of ≤10% (12, 43, 44). In patients with BTC who have progressed on 1L treatment, median OS is 6.2 months when treated with systemic chemotherapy (i.e., mFOLFOX + active symptom control [ASC]) (21). Base case deterministic cost-effectiveness results suggest a mean undiscounted life expectancy of [redacted] or [redacted] years for patients with locally advanced or metastatic IDH1-mutated CCA receiving BSC or mFOLFOX, respectively.

Internal validation of the cost-effectiveness analysis demonstrated that modelled median OS and PFS estimates closely reflected outcomes reported in the published literature (Table 59 and Table 60).

Table 59: Internal validation, comparison of median OS

Treatment	Median OS (months)		
	Literature	Source	Model
Ivosidenib	10.3	ClarIDHy(78)	[redacted]
BSC	• 5.1 • 5.3	• ClarIDHy (crossover adjusted)(78) • ABC-06(17)	
mFOLFOX	6.2	ABC-06(17)	

Abbreviations: BSC, best supportive care; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; PFS, progression-free survival.

Table 60: Internal validation, comparison of median PFS

Treatment	Median PFS (months)		
	Literature	Source	Model
Ivosidenib	2.7	ClarIDHy(59)	[redacted]
BSC	• 1.4 • NR	• ClarIDHy(59) • ABC-06(17)	
mFOLFOX	4.0	ABC-06(17)	

Abbreviations: BSC, best supportive care; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; OS, overall survival.

Prior to submission, the cost-effectiveness model (Microsoft Excel® workbook) was quality assured as part of the internal processes of the external analysts who built the model. As part of this quality-control process, the model was reviewed for potential coding errors, inconsistencies, and the plausibility of inputs by an economist who was not involved in the model development process. The review comprised of a sheet-by-sheet check and a checklist (based on publicly available and peer review checklists). Examples of the basic validity checks followed included:

- Extreme value testing (e.g., how do results change if the time horizon is set to be as short or as long as possible?)
- Logical relationship testing (e.g., if intervention drug costs are increased, do total costs in the intervention arm increase, and is the impact on the ICER in line with expectations?)
- Consistency checks (e.g., is an input parameter value in one cell reflected elsewhere/used consistently throughout the model?)

Key model assumptions were also validated by UK clinical experts (appendix N), including:

- Treatment discontinuation upon progression in NHS practice
- The plausibility of parametric survival models
- Health care resource use estimates

B.3.14 Interpretation and conclusions of economic evidence

The current prognosis for patients with previously treated locally advanced/metastatic IDH1-mutated CCA is poor; there is a clear unmet need for safe and effective treatment options in the second- and third-line settings. Ivosidenib is an innovative treatment with a first-in-class mode of action, which specifically targets and inhibits mutated *IDH1* activity. Ivosidenib has EMA orphan drug designation for BTC and will specifically target a small, underserved patient population with *IDH1* mutations. (84)

ClarIDHy provides evidence which demonstrates the clinically meaningful benefit of ivosidenib in patients with previously treated, unresectable, locally advanced, or metastatic IDH1-mutated CCA; including improvements in OS and PFS compared with placebo. The ITC results showed that, when accounting for crossover on the placebo arm of ClarIDHy, ivosidenib demonstrates improvements in OS compared with mFOLFOX.

It is acknowledged that the absence of mFOLFOX data specifically in patients with IDH1-mutated CCA is a limitation of the ITC; and as such, there is a degree of uncertainty around the magnitude of the benefit of ivosidenib compared with mFOLFOX in clinical practice. However, as described throughout Section B.3 of this appraisal, the methods and data used to analyse the cost effectiveness of ivosidenib for IDH1-mutated CCA have been carefully considered and justified and are believed to be the most appropriate available to support decision making. The model includes comprehensive sensitivity and scenario analysis to explore the impact of parametric and methodological uncertainties on cost-effectiveness results.

Due to the poor prognosis for patients with IDH1-mutated CCA in the absence of a targeted treatment option, the criteria for a x1.7 QALY weighting are met in all

scenarios explored, when applying current expected discounted QALYs in the BSC and mFOLFOX arms of the economic model.

When using probabilistic analysis in line with the NICE manual, the cost-effectiveness analysis supports the expectation that ivosidenib provides a cost-effective treatment option for patients with IDH1-mutated CCA in NHS England practice,

[redacted]

B.4 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ivosidenib for treating advanced cholangiocarcinoma with an *IDH1* mutation after at least 1 therapy [ID6164]

Summary of Information for Patients (SIP)

April 2023

File name	Version	Contains confidential information	Date
ID6164_Ivosidenib_CCA_NICE SIP_21Apr2023	1.0	Yes/no	21 April 2023

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

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

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

Ivosidenib (Tibsovo)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The population ivosidenib will be used by is adult patients with locally advanced (meaning the cancer has grown outside the body part it started in) or metastatic (meaning the cancer has spread to other parts of the body) cholangiocarcinoma with a specific gene mutation (known as IDH1 R132) who have received at least one prior line of 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.

Pending (See company submission table 2 page 12)

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:

Servier held a roundtable workshop with the patient organisation Alan Morement Memorial Fund (AMMF) to understand patient experience in Cholangiocarcinoma related to their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. Servier have paid Colabhealth (the communication agency) to organize the workshop and have compensated AMMF for their time but not the patients

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

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.
Cholangiocarcinoma (CCA) is often diagnosed at a late stage where curative surgery is no longer possible. Ivosidenib is for patients with advanced/metastatic cholangiocarcinoma with an IDH1 mutation and is also only for those reaching second-line therapy. 164 people per year are thought to be eligible in England During the course of the disease, patients experience aggravating and non-specific symptoms (e.g., jaundice, weight loss and abdominal pain). [1] The impact of CCA symptoms on the daily lives, work productivity, quality of life (QoL), mental health and sexual function of patients suffering from the disease is immense. In addition, patients potentially face the harmful side effects of systemic chemotherapy, which can be avoided with an oral targeted treatment. These harmful effects also extend beyond the physiological effects as, during the last months of a patient's life, they have to attend hospital for administration of a systemic treatment, which places a burden on the patient and their carers/family. The effect of a hospital visit especially during the post COVID-19 era can cause extreme anxiety, especially for those already suffering with a weakened immune system due to the effects of chemotherapy. [2] There are no other satisfactory treatment options, and ivosidenib offers significant additional benefit over existing treatment options. Half of all untreated patients do not survive beyond three to four months from presentation of symptoms[3], and current treatment only shows a median overall survival of 6.2 months[2]

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?
No specific screening methods are available to reliably detect CCA in its early stages, as most CCA cases are found only after the cancer has advanced to an incurable stage. Due to often late presentation and nonspecific symptoms, CCA may be detected incidentally as an isolated intrahepatic mass on imaging. Computed tomography (CT) and magnetic resonance imagining (MRI) are both helpful for the detection of the primary tumour in the first instance. The use of ivosidenib is conditional on the presence of IDH1 gene mutation. Therefore, diagnostic testing for

IDH1 gene mutation in people with advanced cholangiocarcinoma should be carried out through an NGS panel, which is already commissioned by NHS England

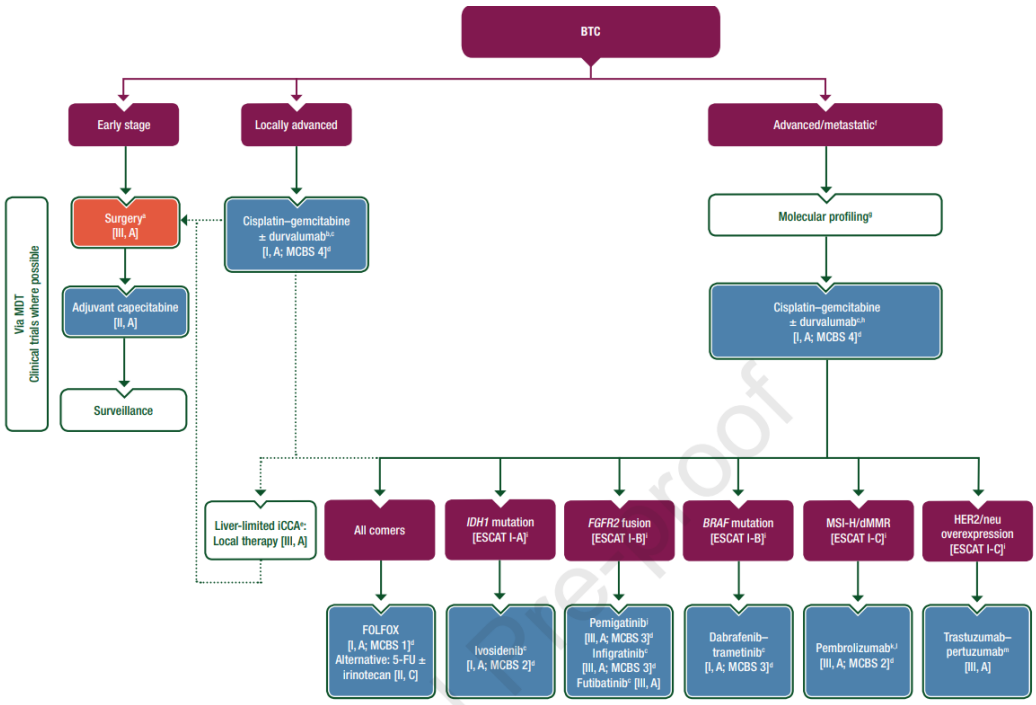
2c) Current treatment options:

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.

Current treatment is limited to either best support care (BSC) or modified folinic acid + fluorouracil + oxaliplatin (mFOLFOX). Whilst there appears to be small increases in overall survival (OS) with mFOLFOX vs BSC (median OS of 6.2 months in the ASC plus mFOLFOX group vs. 5.3 months in the ASC alone group) there is also a high incidence of AEs in this patient group. The efficacy of mFOLFOX in IDH1 mutation has not been studied.

The ESMO guidelines below highlight the current treatment pathway, and have already recognised ivosidenib within the treatment algorithm for biliary tract cancer (BTC)[4]



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.

Response:

Servier held a workskop organised with AMMF in April 2022, involving 6 patients and 2 family members from the UK.

Quality of life was affected due to side effects with current treatments such as pain and fatigue, as well as life threatening complications from chemotherapy such as portal hypertension, pneumonia and cellulitis. There was also social withdrawal due to anxiety around these side effects, and also the financial burden due to early retirement/stopping work[5]

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

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.

Ivosidenib is an oral innovative treatment with a first-in-class mode of action, which specifically targets and inhibits mutated *IDH1* activity, limiting cell proliferation for a small, underserved 2nd line patient population with *IDH1* mutation. It provides an option where there is a substantial unmet need for effective and well tolerated treatments which extend survival.

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.

N/A

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?

Ivosidenib has the advantage of being an oral treatment, which is especially pertinent in the post COVID-19 pandemic world. 500mg once daily (2x 250mg tablets) to be taken orally. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Under existing treatments, patients potentially face the harmful side effects of systemic chemotherapy, which can be avoided with an oral targeted treatment. This oral targeted treatment will mean patients and their carers will not have as many hospital treatments reducing the anxiety, time and cost pressures associated with this . For carers it may also mean less time off work.

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.

The only RCT in IDH1m population, ClarIDHy was a multicentre, randomized, double-blind, placebo-controlled phase III study to evaluate ivosidenib in patients with unresectable, locally advanced or metastatic CCA and an IDH1 mutation previously treated with a GEM- or 5-FU containing regimen, and provides the relevant efficacy and safety data in this population.[6] This has now completed. The ProvIDHe study will be a real world Phase 3b trial for advanced CCA patients with an mIDH1 mutation previously treated with 1 line of therapy.

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.

ClarIDHy is reflective of and generalisable to patients in UK clinical practice. Ivosidenib demonstrated a 63% reduction in risk of disease progression vs. placebo, corresponding to a higher median progression-free survival (PFS) of 2.7 months for patients who received ivosidenib vs. 1.4 months for patients who received placebo. The median OS in the placebo arm was 5.1 months vs 10.3 months in the ivosidenib arm[7]. Compared to mFOLFOX, ivosidenib improved survival by 42%

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.

Ivosidenib better maintained the patient's QoL vs. placebo, by limiting decline in mobility, usual activities and anxiety or depression, as measured by the EQ-5D-5L questionnaire. Clinically meaningful declines in physical and emotional functioning were observed via a cancer-specific questionnaire (EORTC QLQ-C30) in the placebo arm compared to the ivosidenib arm, and tiredness symptoms were significantly increased for placebo. The two advisors spoken to during an advisory board meeting held by Servier that had recruited patients into ClarIDHy both stated they had no idea which patients were on active treatment and normally you would have a sense of understanding.

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.

Safety data from ClarIDHy shows ivosidenib to have a favourable safety profile over placebo. Grade ≥3 TEAEs were reported in 89 patients (53.6%) in the ivosidenib arm vs. 22 patients (37.3%) in the placebo arm. Reported toxicities are manageable in patients with advanced CCA. TEAEs leading to discontinuation were less common in the ivosidenib arm when compared to the placebo arm (6.6% vs. 8.5%).

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
-

Ivosidenib increases OS and PFS compared to current treatments, while balancing this against potential toxicities

The cytotoxic side effects of current treatments are large and therefore, where there is a targeted treatment against an actionable mutation, this should always be preferred. Ivosidenib also has the advantage of being an oral treatment, which is especially pertinent in the post COVID-19 pandemic world. During the last months of a patient's life, they will not have to attend hospital for administration of a systemic treatment, easing the burden on the patient and their carers/family. In addition, the fact that a patient is worked up with biopsy to establish mutational status emphasises that if an alteration is found the expectation is to treat with the targeted agent

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

Ivosidenib can cause QTc interval prolongation which can cause irregular heartbeats. Therefore, you will need to have regular electrocardiograms to monitor your heartbeat

3i) 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.

There were no existing economic models which assessed the costs and effects of ivosidenib for second-line patients with IDH1-mutated CCA. A new cost-effectiveness model was therefore developed for the purposes of the economic modelling.

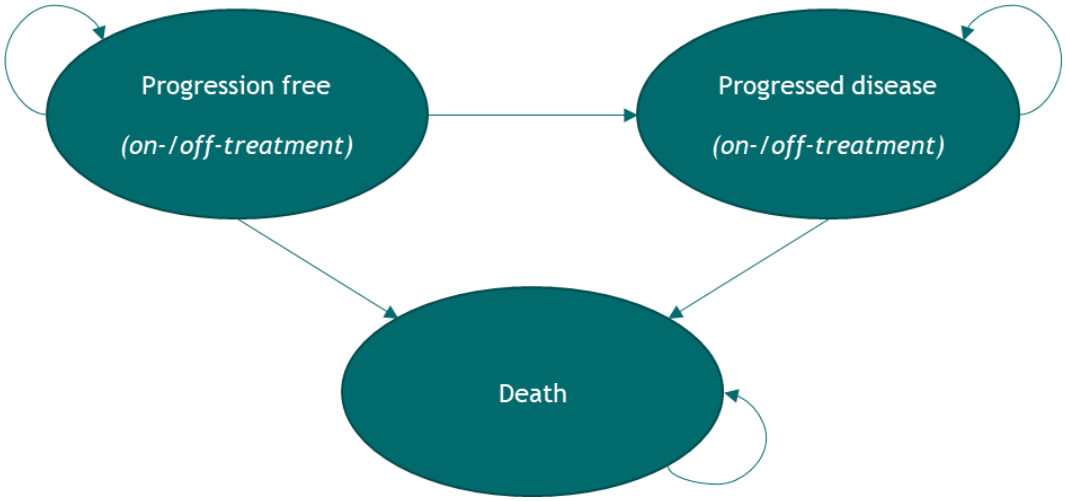
The model was structured using three 'health states' which help to capture both the costs to the NHS and the impact on quantity/length of life and quality of life, for the average patient with second line IDH1-mutated CCA.

The costs captured within the analysis include treatment costs, the cost of administering treatment, the costs of managing adverse events related to treatment, the costs of monitoring patients, and the costs of care at the end of life.

The health effects captured within the analysis are a combination of quantity of life and quality of life (known in economic modelling as quality-adjusted life years [QALYs]). A QALY of 1 is equivalent to a person living for 1 year while feeling in 'perfect health'.

The model 'health states' are progression free (or pre-progression), progressed disease (or post-progression), and death, as these show how the condition develops over time.

The trial outcomes of overall survival, progression-free survival and time on treatment feed into the model, and these outcomes are extrapolated out beyond the follow-up period of the trial, as is often necessary when estimating the lifetime costs and effects of a new treatment.



Ivosidenib increases the amount of time spent alive and time spent in the progression free state, and therefore extends life by delaying disease progression.

The model also shows that ivosidenib improves quality of life, by increasing time spent on treatment and free of progression, compared with BSC and chemotherapy (mFOLFOX). The model also shows ivosidenib improves quality of life due to fewer side effects (adverse events), compared with mFOLFOX. Furthermore, the model shows that ivosidenib improves quality of life compared with mFOLFOX, as ivosidenib is administered orally (2 tablets per day), compared to mFOLFOX chemotherapy which is administered through the veins (intravenously) every 2 weeks in a hospital setting.

The cost of treatment is increased with ivosidenib compared to current treatment, although cost reductions are seen compared with mFOLFOX in terms of administration costs (as ivosidenib does not need to be administered in hospital), and in terms of managing side effects.

Dose reductions of ivosidenib, the overall cost of ivosidenib, and the statistical method to indirectly compare ivosidenib and mFOLFOX across different clinical trials have the most effect on the cost-effectiveness estimate.

3j) 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)
Ivosidenib is an oral innovative treatment with a first-in-class mode of action. It represents a step change in treatment due to the focus now moving to targeted treatments

3k) 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
N/A

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.
Response: 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 • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • 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/ • 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

BSC, best supportive care
CCA, cholangiocarcinoma
ICER, incremental cost-effectiveness ratio
mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin
OS, overall survival
PFS, progression-free survival
QALY, quality-adjusted life year

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. American Cancer Society. Bile Duct Cancer Symptoms _ Bile Duct Cancer Signs. 2018.
2. 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;22:690–701. doi:10.1016/S1470-2045(21)00027-9.
3. Patel T. Cholangiocarcinomacontroversies and ch… Reviews Gastroenterology & Hepatology. Nat Rev Gastroenterol Hepatol. 2011;8:189–200.
4. Vogel A, Bridgewater J, Edeline J, Kelley RK, Klümpen HJ, Malka D, et al. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023;34:127–40. doi:10.1016/j.annonc.2022.10.506.
5. Servier. Workshop-impact of CCA. 2022.
6. Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2020;21:796–807. doi:10.1016/S1470-2045(20)30157-1.
7. Zhu AX, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With IDH1 Mutation: The Phase 3 Randomized Clinical ClarIDHy Trial. JAMA Oncol. 2021;7:1669–77. doi:10.1001/jamaoncol.2021.3836.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ivosidenib for treating advanced cholangiocarcinoma with an IDH1 mutation after at least 1 therapy [ID6164]

Clarification questions

May 2023

File name	Version	Contains confidential information	Date
Clarification questions to company	1	Yes	30/05/23

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.

Section A: Clarification on effectiveness data

Systematic literature review

A1. Document B, section B.2.5, p. 36; and Appendix D.4, Section 4.9, p. 35, Section 5.1, p. 141, and Section 8.6, p. 653. These sections of the company submission refer to the quality assessment of the ClarIDHy study and other studies identified in the SLR. Please clarify how many reviewers carried out the risk of bias assessment of these studies and whether they worked independently.

Servier response

For the SLR there were two independent reviewers:
All references/publications abstracts identified by the searches were reviewed independently by two reviewers for the SLRs, and a single reviewer for TLRs, based on the PICOS criteria. Additionally, 10% of the hits were quality checked by a third independent reviewer.
All publications where there was an uncertainty on including or any disagreements were resolved either through “reconciliation” (discussion between the two reviewers) or, through “arbitration” by a third independent reviewer for the SLRs or a second independent reviewer for the TLRs, where the “majority view” determined inclusion/ exclusion.

A2. Document B, Section B.2.2, Table 6: Clinical effectiveness evidence, p. 28. The last row of Table 6, regarding 'All other reported outcomes', appears blank in the copy of the document supplied by the company. Please provide a complete version of this table.

Servier response

Only other reported outcomes not previously mentioned are DOR and TTR

Study	AG120-C-005 ClarIDHy (Phase III-pivotal) [NCT02989857]
Study design	Multicenter, placebo-controlled, randomized, double-blind study
Population	mIDH1 nonresectable or metastatic CCA previously treated patients
Intervention(s)	Tibsovo® 500 mg QD orally in continuous 28-day cycles
Comparator(s)	Placebo (n = 61) Crossover permitted at radiographic disease progression
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	**PFS (per ICR)** **Safety, PFS (by investigator review), OS**, ORR, **QoL**, PK, pharmacodynamic.
All other reported outcomes	DOR, TTR

Analysis of ClarIDHy

A3. Document B, Section B.2.7, Subgroup analysis, p. 47. Please provide Appendix E mentioned in this section that provides a summary of the results for the subgroups. The EAG is unable to locate it in the reference pack.

Servier response

The following sensitivity analyses were performed:

• Subgroup analysis with unstratified log-rank test and unstratified Cox regression model. The HR (ivosidenib/placebo) with its 95% CI was displayed for all subgroups graphically in a forest plot. The subgroups included:

- o The actual number of prior line of therapies in advanced setting (1 vs. ≥ 2)
- o Gender (Female vs. Male)
- o Extent of disease at screening (Locally advanced vs. Metastatic). If subject had both Locally advanced and Metastatic, it was considered as Metastaticz
- o Intrahepatic vs. Extrahepatic. Perihilar was lumped into Extrahepatic category
- o ECOG at baseline (0 vs. ≥1)
- o Regions (North America vs. Europe vs. Asia

Servier have uploaded the file “CCA Subgroup Analysis ITT population”

A4. Document B, Section B.2.9, Indirect and mixed treatment comparison, p. 47. Please provide Appendix D mentioned in this section that provides full details of the methodology for the indirect comparison or mixed treatment groups. The current Appendix D appears to include the systematic literature review.

Servier response

Servier have uploaded the file “Ivosidenib_for_CCA_ITC report_16Sep22_v2”

A5. Document B, Section B.2.10, Adverse reactions, p.54. Please provide Appendix F mentioned in this section that provides details of additional adverse reactions. The EAG is unable to find it in the reference pack**.**

Servier response

The submission template states “In appendix F, provide details of any studies that report additional adverse reactions to those reported in the studies in section 2.2” There are no additional adverse reactions to report other than those reported in the studies in section 2.2. Servier apologises for not removing this box from the standard template

A6. **Document B, Section B.2.4.1, Statistical analysis, p.33.** Was inverse probability of censoring weighting also run as a method of adjusting for treatment crossover? If so, please provide the results from using this method.

Servier response

Results of the IPCW-adjusted Cox proportional hazards regression analysis and 95% CIs with treatment switching considering an informative censoring event are presented below. Baseline characteristics were included in the Cox model and the time-varying stabilised weights were applied. The model indicated that treatment with ivosidenib was associated with reduction in the risk of mortality, with [redacted]. However, this was not found statistically significant.

Table 1: IPCW-adjusted Cox proportional hazards regression analysis of OS

Covariate	Comparison	Hazard ratio	95% CI
Treatment arm	Ivosidenib vs placebo	[redacted]	[redacted]
Age (continuous)		[redacted]	[redacted]
Sex	Male vs Female	[redacted]	[redacted]
Geographic region	Asia vs North America	[redacted]	[redacted]
	Western Europe vs North America	[redacted]	[redacted]
Number of prior lines of treatment	2 vs 1	[redacted]	[redacted]
CCA subtype	Extrahepatic vs Intrahepatic	[redacted]	[redacted]
Extent of disease	Local/regional vs Metastatic	[redacted]	[redacted]
ECOG PS	≥1 vs 0	[redacted]	[redacted]
Liver function status	Mild/Moderate/Severe vs Normal	[redacted]	[redacted]
Renal function status	Mild vs Normal	[redacted]	[redacted]
	Moderate vs Normal	[redacted]	[redacted]
BMI (continuous)		[redacted]	[redacted]

Abbreviations: BMI, body mass index; CCA, cholangiocarcinoma; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group Performance status, IDH1, Isocitrate dehydrogenase 1; vs, versus

The IPCW-adjusted HR is presented alongside other approaches in the table 2. The approach of naïve censoring at switch improves the HR compared to the ITT analysis unadjusted for switching. However, differences in prognosis between switchers and non-switchers can lead to informative censoring bias in the naïve censoring approach. As shown in Table 3, switchers seem to have better prognostic factors than non-switchers, which would bias naive censoring results in favour of ivosidenib. Therefore, when the IPC weights are applied in combination with censoring in the IPCW adjusted analysis, the HR is closer to the unadjusted result. The difference between the IPCW-adjusted and naive censoring (patients are censored at time of switch) is [redacted] When compared to the unadjusted analysis the IPCW HR is slightly improved: HRs of [redacted]

Table 2: Ivosidenib vs Placebo HR of OS

Approach	Hazard ratio	95% CI	Events	Censored
Unadjusted (ITT analysis)	[redacted]	[redacted]	150	37
Naive censoring	[redacted]	[redacted]	117	70
IPCW adjusted	[redacted]	[redacted]	117	70

Abbreviations: CI. Confidence interval; IPCW, inverse probability of censoring weights; ITT, intention to treat

Table 3: Summary of patient demographic and baseline characteristics by switch status in the control arm (missing values have been imputed)

		Switchers	Non switchers
Number of patients (n)		[redacted]	
Age (mean (SD))			
BMI (mean (SD))			
Sex, n(%)	Female Male		
Geographic region n(%)	North America Asia Western Europe		

		Switchers	Non switchers
Number of prior lines of treatment n(%)	1	[redacted]	[redacted]
	2	[redacted]	[redacted]
CCA subtype n(%)	Extrahepatic	[redacted]	[redacted]
	Intrahepatic	[redacted]	[redacted]
Extent of disease n(%)	Metastatic	[redacted]	[redacted]
	Local/Regional	[redacted]	[redacted]
Renal function status n(%)	Normal	[redacted]	[redacted]
	Mild	[redacted]	[redacted]
	Moderate	[redacted]	[redacted]
Liver function status n(%)	Normal	[redacted]	[redacted]
	Mild/Moderate/Severe	[redacted]	[redacted]
ECOG PS n(%)	0	[redacted]	[redacted]
	≥1	[redacted]	[redacted]
EQ5D index (mean (SD))		[redacted]	[redacted]
Post-baseline characteristics			
Occurrence of any AE n(%)	No	[redacted]	
	Yes		
Occurrence of TEAE n(%)	No		
	Yes		
Documented progression event n(%)	No		
	Yes		

Abbreviations: AE, adverse event; BMI, body mass index; CCA, cholangiocarcinoma; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group Performance status, IDH1, Isocitrate dehydrogenase 1; SD, standard deviation; TEAE, treatment emergent adverse event; vs, versus. All percentages in the last two columns, are derived by switch status.

The IPC-weighted KM curve of the placebo arm survival represents a weighted version of the underlying data, i.e., the contributions that each patient makes to the curve at

each time point are weighted according to their baseline and time-dependent covariate values. In Figure 1, the ivosidenib arm is presented alongside the IPC-adjusted KM curve.

However, Servier would like to reiterate that the RPSFT model was prespecified, and ultimately used to preserve the trial randomization, especially as the crossover rates were relatively high (i.e., approximately 70% of the placebo patients ultimately crossed over after progression). Findings from a methodological review showed that in instances of a large proportion of crossover in small trials, the RPSFT method is preferable.

A7. Document B, Section B.2.6.1.1, Patient disposition, p.37. The EAG note that outcomes are presented at 3 different timepoints (31 January 2019, 31 May 2020, 21 June 2021). Progression free survival was analysed at 31 January 2019 but enrolment was completed on 1 March 2019. Please confirm the number of participants who were used in the analysis of progression free survival.

Servier response

The PFS was based on the data cut as of 31st Jan based on the analysis cut off date based on investigator-assessed progression free survival. At this point 185 patients were included in the analysis of PFS. The study recruitment did continue where 2 further patients were recruited and analysed in the May data cut for OS.

A8. Document B, Section B.2.6.1, Patient disposition and consort diagram. The numbers reported in the text for discontinuation of ivosidenib (and reasons) in the 43 patients who crossed over form the placebo arm, do not match those in the consort diagram (Figure 6). Please explain the differences or provide the correct numbers.

Servier response

The CONSORT diagram links to what appears in the Zhu publication. However, the text relates to the cut off date of 21 June 2021
The correct number of pts who discontinued treatment should be 43
Of the 61 subjects randomized to placebo, **43** (70.5%) subjects experienced progressive disease based on Investigator assessment and crossed over to receive open-label ivosidenib per the protocol. At the time of the database lock date, **all 43 of the crossover subjects had discontinued treatment**. The most common (≥5%) reason for treatment discontinuation among subjects who crossed over was progression of disease in **83.7%** of subjects.

A9. Document B, Section B.2.6.1.2, Baseline characteristics, table 9 p.39. The Ivosidenib column shows a total of 126 participants but tables 10 (p.42), 12 (p.49) and 14 (p.50) all show 124 participants randomised to Ivosidenib. Please explain the differences or provide the correct number.

Servier response

Servier apologises that Table 9 p.39 the reference should be updated to reflect the Zhu 2021 paper, which is where the data is taken from. Tables 10,12, and 14 where 124 participants are randomised to Ivosidenib are taken from January 31, 2019 data cut-off.

A10. Document B, Section B.2.6.3, Secondary efficacy outcomes, figure 8 p.41. Were further analyses of progression free survival and overall survival conducted at the final database lock date of 21 June 2021? If so, please provide these analyses.

Servier response

Servier can confirm that no further analyses of progression free survival and overall survival conducted at the final database lock date of 21 June 2021.

A11. Document B, Section B.2.6.4, Response outcomes, p.42. Please clarify which participants are referenced as the three and four patients in the following paragraph.

Servier response

The DOR for each of these three patients in the ivosidenib arm was 2.79, 2.73, and 11.07 months, respectively. The DOR for each of these four patients in the ivosidenib arm (before crossover) was 7.69, 4.27, 8.08, and 8.77 months, respectively, and 4.30 months for the responder in the placebo arm. The three patients referred to are those that had an ORR observed with IRC assessment. There were then 4 patients who had an ORR observed when assessed by the investigator

Indirect treatment comparison

A12. Priority question. Document B, Section B.2.9.1, Results Table 16, p.52. Please confirm the hazard ratios to be used in the Bucher analysis, as section B.2.6.3 p40 and p41 state [redacted] [adjusted] while the hazard ratios used in B.2.9.1 on p52 are [redacted]

Servier response

The detailed feasibility assessment carried out prior to evidence synthesis found differences in the trial eligibility criteria of ClarIDHy and ABC-06. Specifically, ABC-06 was limited to patients with one prior line of (chemo)-therapy, whereas ClarIDHy permitted patients with more than one prior line of therapy. In order address such between-study heterogeneity, the Bucher ITC used ClarIDHy evidence derived as follows:

	IVO+AZA (n)	PBO+AZA (n)
Original sample size	126	61

Per protocol population	124	61
1 prior LOT	66	33
ECOG PS 0-1	65	32

Using a Cox model, the HRs for IVO+AZA and PBO+AZA were estimated again for both unadjusted [redacted] and crossover-adjusted [redacted] scenarios prior to the Bucher ITC. Given these estimates are based on more comparable eligibility criteria between ClarIDHy and ABC-06, these hazard ratios should be used for the Bucher analysis.

Adverse events for mFOLFOX

A13. Document B, Section B.2.10 Adverse reactions, p.54. Is it possible to provide a table similar to Table 17 summarising the most common TEAE for the mFOLFOX trial so that a comparison of the relative safety profiles can be made?

Servier response

In The ABC-06 study, they reported AES regardless of causality by individual grades for both arms, and chemotherapy related events for the active arm.

Below is the table provided previously (Table 17) with the most common TEAEs reported from the ClarIDHy study. Below that we have included a table 17 .b. which includes the most common (≥ 15%) all grade AES and chemotherapy related AES reported in the ABC-06 trial

It is important to note the difference in types of AEs reported and the difference between study follow up from the ABC-06 trial and the June 2021 data cut from ClariDHY, where treatment emergent Adverse events of all grades were reported.

Table 1. ClarIDHy: most common (≥ 15%) TEAEs (21 June 2021 database lock)

Adverse Event, n (%)	ivosidenib (n=123)	Placebo (n=59)	After Crossover to ivosidenib (n=43)	Total ivosidenib (n=166)
Any TEAE	120 (97.6)	57 (96.6)	41 (95.3)	161 (97.0)
Most common TEAE, n (%)				
Nausea	52 (42.3)	17 (28.8)	12 (27.9)	64 (38.6)
Diarrhea	43 (35.0)	10 (16.9)	12 (27.9)	55 (33.1)
Fatigue	38 (30.9)	10 (16.9)	10 (23.3)	48 (28.9)
Abdominal pain	30 (24.4)	9 (15.3)	7 (16.3)	37 (22.3)
Cough	31 (25.2)	5 (8.5)	5 (11.6)	36 (21.7)
Decreased appetite	30 (24.4)	11 (18.6)	6 (14.0)	36 (21.7)
Vomiting	28 (22.8)	11 (18.6)	6 (14.0)	34 (20.5)
Ascites	28 (22.8)	9 (15.3)	5 (11.6)	33 (19.9)
Anemia	23 (18.7)	3 (5.1)	8 (18.6)	31 (18.7)
Edema peripheral	17 (13.8)	6 (10.2)	9 (20.9)	26 (15.7)
Constipation	20 (16.3)	11 (18.6)	5 (11.6)	25 (15.1)

[1]Total ivosidenib group includes 43 patients initially assigned to placebo who had crossed over to ivosidenib upon radiographic disease progression.
Source: AG120-C-005 – CSR Addendum. Database lock: June 21, 2021 [Data on file] (79), Zhu et al. 2021 (78).
Abbreviation: n, number; TEAE, treatment-emergent adverse event.

Table 2b ABCO6: most common (≥ 15%) all grade AES and/or Chemotherapy related events

n (%)	ASC (n = 81)	FOLFOX= ASC (n= 81)	FOLFOX + ASC (N=81) Chemotherapy related events
Any AE /CRAE	77 (95)	80 (99)	68 (84)
Neuropathy	8 (10)	56 (69)	53 (65)
Fatigue	53 (65)	73 (90)	56 (69)
Nausea	33 (41)	41(51)	31 (38)
Oral Mucositis	4(5)	30 (37)	29 (36)
Anorexia	37 (46)	48 (59)	26 (32)
Diarrhoea	14 (17)	29 (36)	24 (30)
Thromobocytopenia	1 (1)	18 (22)	18 (22)
Dysgeusia	12 (15)	23 (28)	16 (20)
Vomiting	20 (25)	23 (28)	16 (20)
Constipation	29 (36)	37 (46)	13 (16)
Neutropenia	1 (1)	23 (28)	22 (27%)
Infection	22 (27)	34 (42)	18 (22)
Anaemia	6 (7)	12 (15)	11 (14)
Dry Mouth	11 (14)	25 (26%)	
Pain	56 (69)	50 (62)	
Oedema	11(14%)	18 (22)	
Dyspnoea	7 (9)	14 (17%)	
Billary Events	18 (22)	19 (23)	
Hypertension	5 (6)	14 (17)	
Ascities	2 (2)	12 (15)	

Section B: Clarification on cost-effectiveness data

Clinical inputs

B1. Section B.2.9 and B.3.3.2.3. Reliance on the indirect treatment comparison with FOLFOX. The prognostic impact of IHD1 mutation has been discussed, but could you please comment more fully on the expected direction of any potential bias arising due to other differences in baseline characteristics and study design between the CLARIDHy and the ABC-06 trial.

Servier response

The EAG raises an important consideration with regards to the evidence base available to inform the comparison between ivosidenib and mFOLFOX. It is acknowledged that, as well as similarities, there are differences in study design and baseline characteristics between ClarIDHy and ABC-06. However, it is believed that the impact of any potential bias due to such differences are not exclusively in one direction, and on balance, there is no clear evidence that the results of the comparison would favour one treatment over the other. Furthermore, there are limited published data available which verify independent prognostic factors in advanced/metastatic CCA.

Both ClarIDHy and ABC-06 were phase III randomized controlled studies, and the sample size in ClarIDHy (n = 185) was comparable to that of ABC-06 (n = 162). ClarIDHy included patients with IDH1-mutated CCA only (of the included patients 91% had intrahepatic CCA [iCCA]). ABC-06 included a wider biliary tract cancer (BTC) population, including patients with cholangiocarcinoma (72% [iCCA 44%]), gallbladder cancer (21%) and ampullary carcinoma (7%). It is difficult to comment on the direction and magnitude of bias introduced by a wider BTC population in the ABC-06 study; however, Table 3 demonstrates that median OS and PFS were similar across tumour sites in ABC-06 (also taking into consideration a weighted average of survival estimates for gallbladder and ampulla tumour sites).

Table 3: ABC-06, median OS and PFS by tumour site subgroup

Tumour site	ASC alone		mFOLFOX + ASC		
	n	Median OS, months (95% CI)	n	Median OS, months (95% CI)	Median PFS, months (95% CI)
Intrahepatic	[redacted]			5.7 (4.1-7.4)	3.3 (2.5-5.2)
Extrahepatic				6.2 (4.0-7.9)	4.0 (2.9-5.9)
Gallbladder				5.1 (2.5-14.6)	3.9 (2.4-6.2)
Ampulla				10.4 (9.8-ne)	6.4 (4.1-ne)

Abbreviations: ASC, active symptom control; CI, confidence interval; mFOLFOX; modified folinic acid + fluorouracil + oxaliplatin; n, number of patients; ne, not estimable; OS, overall survival; PFS, progression-free survival.

Median age at baseline was lower in ClarIDHy (ivosidenib, 61 years; placebo, 63 year) than in the ABC-06 study (mFOLFOX 65 years; ASC, 65 years), and fewer patients in ClarIDHy patients were male (ivosidenib, 35%; placebo, 39%) versus ABC-06 (mFOLFOX 46%; ASC, 53%).

The ECOG PS 0-1 percentage was >99% across both ClarIDHy and ABC-06. With regards to treatment line, ClarIDHy included second- and third-line patients, while ABC-06 included patents receiving second-line treatment only. As such, ClarIDHy patients were more heavily pre-treated (on average). Furthermore, a higher proportion of patients in ClarIDHy had metastatic disease compared with local-regional disease (ivosidenib, 93%; placebo, 92%) than in ABC-06 (mFOLFOX, 83%; ASC, 81%).

Overall, between-study heterogeneity was low to moderate, with the extent of the disease generally well aligned across the studies. Furthermore, median age was well aligned between all studies with no major deviations, as well as ECOG PS with most patients having 0/1 status. There was more pronounced heterogeneity in terms of gender and lines of therapy. Median OS was similar for placebo in ClarIDHy (5.1 months; 95% CI: 3.8–7.6, when adjusted for crossover) compared to ASC in ABC-06 (iCCA: 5.2 months; 95% CI, 3.7–5.8; eCCA: 5.4 months; 95% CI, 3.9–6.4). PFS and complete response were not reported for the ASC arm of ABC-06.

As explained by the EAG in its question, the company submission discusses the prognostic impact of IDH1-mutations in patients with advanced/metastatic CCA, and although ClarIDHy provides comparative efficacy data for ivosidenib versus placebo (BSC) in an IDH1-mutation specific population, the ABC-06 study did not report the proportion of patients with IDH1-mutated CCA. As such, it is not possible to adjust for IDH1-status within an indirect treatment comparison.

In conclusion, although it is challenging to comment on the magnitude of bias, there appears to be no obvious direction of bias due to differences in study design and baseline characteristics between ClarIDHy and ABC-06.

B2. Section B.3.3.2.1. Please clarify why OS extrapolation for ivosidenib and BSC was based on the analysis of May 2020 data cut, if longer term survival data are available in a June 2021 final data lock.

Servier response

In ClarIDHy, two OS analyses were pre-planned – the first at the time of the primary PFS analysis, and the second after 150 OS events had been observed (final OS analysis). Although longer term treatment exposure data were available from a June 2021 data cut of the ClarIDHy study, as reported in Zhu *et al.,* (2021), the data cut-off date for the final OS analysis was 31 May 2020. As such, no further OS data are available beyond this data cut.

Health state utility

B3. Document B, Section 3.4.2. Is there a more detailed study report available on the analysis of the EQ-5D data to inform the economic model? If so, could it please be provided?

Servier response

Please find attached the utility analysis technical report (*"Ivosidenib in CCA_Utility analysis technical report_IQVIA_FINAL_v1.0_30092022"*), which was used to inform the economic model and company submission. As described in Section B.3.4.2, the best fitting model (as reported in the attached utility analysis report) was used to inform health state utility values in the cost-effectiveness analysis base case. However, as also described in Section B.3.4.2, additional utility models (beyond those included in the attached technical report) were run for consideration in scenario analysis. These additional models (which considered progression status only, and progression status and treatment status) were presented in scenario analysis in the company submission because the covariates and resulting utility values aligned directly with the cost-effectiveness model structure and definition of health states.

B4. Document B, Section 3.4.1 and B.3.4.2. Given the scheduled EQ-5D assessment times described in the text, and the fact that patients could cross over following radiographic progression on placebo, it seems surprising there are so few pre-progression observations and so many post-progression observations in the placebo arm (as indicated in the Table 30). Can you please provide a more detailed breakdown of the number of responses available by treatment arm, progression

status and treatment status at each of the scheduled assessment times (cycle 1 day 1, cycle 3 day1, end of treatment, cross over cycle day 1).

Servier response

The small number of pre-progression observations in the placebo arm of ClarIDHy is explained by the poor prognosis for patients with previously treated advanced/metastatic IDH1-mutated CCA. Due to rapid disease progression, more than 50% of the patients on the placebo arm experienced disease progression by the first post-baseline quality of life assessment.

The number of post-progression observations for the placebo arm were recorded as these data include pre-dose post-crossover observations in the placebo arm. That is, the analysis includes assessments that were conducted at “Crossover Cycle 1 Day 1”, before placebo patients that crossed over to ivosidenib had received any dose of ivosidenib. While the analysis only considered only EQ-5D assessment in the first analysis period (i.e., excluding the post-crossover assessments), this does not exclude pre-dose post-crossover assessments.

Additional details are available in the utility analysis report provided in response to clarification question B3. Furthermore, as requested, a more detailed breakdown of the number of responses by treatment arm, progression status and treatment status, by assessment visit is presented in Table 4 below.

Table 4: ClarIDHy, quality of life observations by treatment arm, progression status and treatment status, by assessment

Assessment	Ivosidenib						Placebo						Grand Total
	Baseline	Pre-progression		After-progression		Total	Baseline	Pre-progression		After-progression		Total	
	On tx	On tx	Off tx	On tx	Off tx		On tx	On tx	Off tx	On tx	Off tx		
Cycle 1 Day 1	107	-	-	-	-	107	55	-	-	-	-	55	**162**
Cycle 14 Day 1	-	-	-	1	-	1	-	-	-	-	-	-	**1**
Cycle 2 Day 1	-	3	-	-	-	3	-	-	-	-	-	-	**3**
Cycle 26 Day 1	-	-	-	2	-	2	-	-	-	-	-	-	**2**
Cycle 3 Day 1	-	38	-	12	-	50	-	6	-	6	-	12	**62**
Cycle 32 Day 1	-	-	-	1	-	1	-	-	-	-	-	-	**1**
Cycle 33 Day 1	-	-	-	1	-	1	-	-	-	-	-	-	**1**
Cycle 4 Day 1	-	1	-	1	-	2	-	-	-	-	-	-	**2**
Cycle 7 Day 1	-	1	-	-	-	1	-	-	-	-	-	-	**1**
End of Treatment 1	-	1	2	6	47	56	-	-	-	2	25	27	**83**
Safety Follow-up 1	-	-	-	-	4	4	-	-	-	-	-	-	**4**
Crossover Cycle 1 Day 1	-	-	-	-	-	-	-	-	-	-	38	38	**38**
Grand Total	**107**	**44**	**2**	**24**	**51**	**228**	**55**	**6**	**-**	**8**	**63**	**132**	**360**

Abbreviations: tx, treatment.

B5. Document B, Section B.3.4.2, Table 30. Please provide details on how the TRAE status was determined and coded in the regression. How were the patients judged to be currently experiencing a TRAE at the time of the EQ-5D assessment? And what grades of TRAEs did this capture?

Servier response

A TRAE was defined as any event with an onset date on or after the date of the first dose of study treatment or any ongoing event on the date of the first dose of study treatment that worsened in severity after the date of the first dose of study treatment. Grade 3 or higher TRAEs were considered.

The variable defined for TRAE status showed whether a patient had a TRAE Grade ≥3 or not at any point during the analysis. Thus, with respect to this variable, the regression shows the relationship between mean utility and the presence of a grade ≥3 TRAE irrespective of the timepoint of grade ≥3 TRAE occurrence. Only the presence of a Grade ≥3 TRAE at any point in time was considered (not the frequency of occurrence), so TRAE was a binary variable.

Additional details are available in the utility analysis report provided in response to clarification question B3.

Resource use and costs

B6. Priority question. Economic model, ivosidenib treatment acquisition costs. The model calculations do not appear to account for potential wastage of oral medication caused by patients discontinuing treatment before depleting their supply. Please justify this base case assumption and consider the impact of a scenario that accounts for expected wastage.

Servier response

Ivosidenib is administered orally at a dose of 500 mg once daily in continuous 28-day treatment cycles; however, ivosidenib is available in a pack size of 60 x 250 mg tablets. As such, at the recommended dose, an ivosidenib pack lasts for 30 days. In the company submission, it was assumed that packs could be split when dispensed (assuming the 4 x 250 mg tablets remaining at the end of a 28-day treatment cycle would be taken at the beginning of the next treatment cycle, before a subsequent pack is dispensed). As such, in the base case, the model assumes there are no wastage costs associated with oral therapies.

Nevertheless, an updated version of the economic model has been provided which includes the functionality to test the following scenarios for wastage associated with treatments administered orally:

- Apply the cost of ivosidenib each treatment cycle (every 28 days), rather than each 7-day model cycle ("cost every 28 days")
- Assume that an ivosidenib 60 x 250 mg pack lasts one treatment cycle (28 days), rather 30 days in line with the recommended dose ("cost full pack")

Probabilistic pairwise cost-effectiveness results for ivosidenib versus BSC, when testing the scenarios described above individually and in combination, are presented in Table 5. Pairwise results are presented versus BSC, as mFOLFOX remains extendedly dominated in each of the scenarios tested, in line with the model base case.

Table 5: Probabilistic results, oral wastage scenarios, ivosidenib versus BSC

Scenario	Cost every 28 days?	Cost full pack?	Incremental costs	ICER (£/QALY)	Change in ICER
Base case	[redacted]				
Apply the cost of ivosidenib every 28 days					
Assume each 60 x 250 mg pack lasts one treatment cycle (28 days)					
Apply the cost of ivosidenib every 28 days, and assume each 60 x 250 mg pack lasts one treatment cycle (28 days)					

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
Notes: ICER accounts for a x1.7 QALY weighting.

B7. Please provide details of any further lines of active treatment that patients in CLARIDHy received following progression on ivosidenib or placebo (other than ivosidenib following progression on placebo).

Servier response

Please see below information concerning further lines of active treatment for patients in the ClarIDHy study.

Subsequent systemic anti-cancer therapy was administered to 49 subjects (38.9%) randomized to ivosidenib. Fourteen subjects (32.6%) randomized to placebo received another anti-cancer therapy after crossing over to ivosidenib. One subject (5.6%) randomized to placebo who did not cross over to ivosidenib received 1 subsequent anti-cancer therapy following placebo. The median number of subsequent cancer therapies in all groups was 1.

Chemotherapy was the most common type of subsequent therapy (in 31.0% of subjects randomized to ivosidenib and 25.6% of subjects randomized to placebo with crossover to ivosidenib); gemcitabine + platinum and mFOLFOX were the most common chemotherapy regimens. Other subsequent therapies received were immunotherapy alone or in combination (in 7.9% of subjects randomized to ivosidenib and 7.0% of subjects randomized to placebo with crossover to ivosidenib), other targeted therapies alone or in combination (in 8.7% of subjects randomized to ivosidenib and 9.3% of subjects randomized to placebo with crossover to ivosidenib), and other investigational drugs alone or in combination (in 8.7% of subjects randomized to ivosidenib, 7.0% of subjects randomized to placebo with crossover to ivosidenib, and 5.6% of subjects randomized to placebo without crossover).

B8. If patients in the ivosidenib or placebo group did receive further lines of active treatment following radiographic progression of cancer (other than ivosidenib following progression on placebo), please consider implementing a scenario that captures the cost of these.

Servier response

As noted in response to clarification question B7, subsequent systemic anti-cancer therapy was administered to 49 patients randomized to the ivosidenib arm (39%) and 15 patients randomized to the placebo arm (25%) in ClarIDHy. The updated version of the cost-effectiveness model includes functionality to model subsequent treatment costs in scenario analysis, based on the proportions observed in ClarIDHy.

As it is not possible to track the patients entering the progressed disease health state from the progression-free health state each model cycle within a partitioned survival framework, a simplifying assumption is made using the proportion of PFS events that were deaths in ClarIDHy [redacted] In this approach, subsequent treatment costs are applied each cycle to the difference between the proportion of patients in PFS in the current cycle and previous cycle multiplied the additive inverse of the proportion of PFS events that were deaths (i.e., the proportion of patients entering the progressed state each cycle is approximated using the PFS curve and proportion of PFS events that were progressions).

As noted in response to clarification question B7, chemotherapy was the most common type of subsequent therapy. Gemcitabine-cisplatin is standard of care at first line for metastatic CCA; however, it is understood that gemcitabine-cisplatin is not recommended for use at later lines. Furthermore, as described in the company submission, ESMO guidelines position mFOLFOX in the later-line setting.

It is acknowledged that a smaller proportion of patients in ClarIDHy received subsequent immunotherapy, other targeted therapies, and investigational drugs (please see response to clarification question B7). EMSO guidelines now recommend the combination of cisplatin–gemcitabine with durvalumab in the first-line setting, although this regimen is not recommended at later lines. Additionally,

ESMO guidelines for BTC recommend pembrolizumab, but only for patients with microsatellite instability/mismatch repair deficiency status (MSI-H/dMMR), not those with IDH1-mutated CCA (relevant to this appraisal). Furthermore, pembrolizumab is not currently reimbursed by NICE or recommended by the MHRA in this indication. Finally, it is noted that 'other targeted treatments' and 'investigational therapies' cannot be appropriately costed in an economic model.

Therefore, taking into consideration the availability of treatments in UK practice, published guidelines, and based on the company's understanding of clinical practice, it is assumed that the cost mFOLFOX is representative of a 'typical' chemotherapy regimen that may be offered to patients at this line of therapy in NHS England practice, for all patients who receive subsequent therapy following ivosidenib or BSC. It is acknowledged that this is a simplifying assumption, but we consider it a suitable approach for the purpose for informing this exploratory scenario analysis within the cost-effectiveness model.

The cost subsequent mFOLFOX chemotherapy (including treatment acquisition and administration) is [redacted] based on the median number of cycles administered in the ABC-06 study (10 x 2-week cycles). We note that it may be the case that patients would receive fewer cycles of treatment in a later-line setting (on average), due to their expectedly poorer prognosis, though in the absence of data to inform this duration, the median from ABC-06 (which considers a second-line population) was applied without adjustment (which, as may be inferred from the results below, is likely biased against ivosidenib).

The resulting subsequent treatment costs, applied as a one-off upon progression each model cycle, were [redacted] and [redacted] in ivosidenib and BSC arms, respectively. Based on the median number of lines of subsequent therapy observed in ClarIDHy, it is assumed patients receive 1 line of subsequent mFOLFOX in both treatment arms. In this scenario, it is assumed that there are no subsequent treatment costs in the mFOLFOX arm of the model. The updated model includes additional functionality to apply subsequent treatment costs to the mFOLFOX arm (based on the average of the proportion of patients who received subsequent treatment in the ivosidenib and placebo arms of ClarIDHy in the absence of data) should the EAG wish to explore this subsequent treatment scenario. Furthermore, the updated model includes the

functionality to apply custom subsequent treatment costs in each of the model arms, should the EAG wish to explore such subsequent treatment scenarios further.

Probabilistic pairwise cost-effectiveness results for ivosidenib versus BSC, when exploring a scenario including subsequent treatment costs in the ivosidenib and BSC arms, are presented in Table 6.

Table 6: Probabilistic results, subsequent treatment scenario, ivosidenib versus BSC

Scenario	Incremental costs	ICER (£/QALY)	Change in ICER
Base case	[redacted]		
Apply subsequent treatment costs			

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
Notes: ICER accounts for a x1.7 QALY weighting.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ivosidenib for treating advanced cholangiocarcinoma with an IDH1 mutation after at least 1 therapy [ID6164]

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].

Information on completing this submission

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

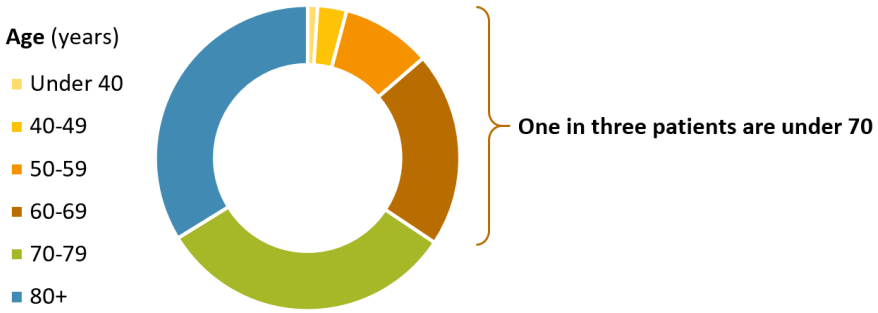
About you

1.Your name	[redacted]
2. Name of organisation	AMMF – The Cholangiocarcinoma Charity
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	AMMF is a charity, registered with the Charity Commission for England and Wales, registration no 1091915. It is the UK's only charity dedicated solely to cholangiocarcinoma. Funding is received via donations from members of the public, and a small amount of industry funding is received by way of sponsorship for AMMF's projects, such as the annual Cholangiocarcinoma Conference. 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 the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	**Date** / **Project** / **Sponsorship received from Servier** 24/05/2022 — AMMF European Website — € 20,000 (£16,638.04) 04/07/2022 — AMMF CCA Conference 2022 — £15,000.00 22/10/2022 — AMMF Patient Organisation CCA Information Project — € 25,000 (£21,272.97)

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
5. How did you gather information about the experiences of patients and carers to include in your submission?	AMMF supports patients with cholangiocarcinoma and their caregivers, providing them with information on treatments and clinical trials. We communicate with patients and their loved ones on a one to one basis by email and telephone, and face to face at our annual conference and with roundtable discussion groups, and many patients use AMMF's private discussion groups on social media. www.ammf.org.uk

Living with the condition

6. What is it like to live with the cholangiocarcinoma? What do carers experience when caring for someone with the condition?	The symptoms of cholangiocarcinoma (CCA) can be vague and easily attributed to a number of other causes and because of this, together with a lack of awareness at primary care level, this cancer is frequently diagnosed late. For the majority of patients, this late diagnosis will mean their cancer is inoperable and for them, this is a terminal diagnosis. For many patients this diagnosis and the prognosis can be truly shocking and they find it very difficult to assimilate the details. Patients struggle to accept that there really is so little treatment available to them, and that a diagnosis of inoperable CCA means their life will end soon – they have very little time left. Currently a resection is the only potentially curative treatment there is for CCA, so inoperable patients are left with very limited options. The standard first line treatment for those with inoperable CCA is the chemotherapy combination, Gemcitabine and Cisplatin – and this treatment has not been improved on for over a decade[1]. Undergoing this chemotherapy, which might or might not extend their life for a few months[2], is often at the expense of the quality of their life, and that of their families. For carers, understanding the diagnosis and its implications can be as difficult for them as for the patient. Many struggle to comprehend that there is no effective treatment for their loved one, and ask AMMF for advice on, 'treatments not available under the NHS'. Seeing loved ones enduring the side effects of chemotherapy, including repeated infections requiring hospitalisation which takes them away from their families when their life expectancy is so short, is very difficult. As is, of course, trying to come to terms to what is happening, not only to their loved one, but to their lives in general – especially as so many are in what should be the 'prime of their life'. Although CCA is considered a cancer affecting older people, at AMMF we hear from many in their 30s, 40s and up with this diagnosis. Information from the AMMF/PHE partnership for the project, "Incidence, mortality and survival for people diagnosed in England with cholangiocarcinoma between 2001-2017" shows that a considerable number of patients are under 70 at diagnosis. (Data has been QA'd by PHE, and will be published later in 2023.):



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

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

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

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

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

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

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

[2]ABC-02 trial 2010: “The median survival in the cisplatin–gemcitabine group was 11.7 months (95% confidence interval [CI], 9.5 to 14.3), as compared with 8.1 months (95% CI, 7.1 to 8.7) for the gemcitabine-only group (P<0.001).”

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	CCA patients and carers see other treatments and therapies, eg, SIRT, targeted therapies, immunotherapies, being adopted and available in other countries, particularly in the USA. They know that, following the approval by NICE of the first targeted therapy for CCA, molecular profiling should be available to all with a CCA diagnosis which could open the door to a targeted therapy or a trial – however, it seems to be available to only very few. Patients and carers find it very difficult to understand why there are no effective treatments available for CCA patients within the NHS. Many will search for treatments available privately or internationally.

8. Is there an unmet need for patients with this condition?	There are a number of unmet needs for cholangiocarcinoma patients: Effective treatments for CCA are desperately needed. The incidence of this disease is increasing year on year, with mortality mirroring incidence[3], and many younger adults being diagnosed. Currently resection is the only potentially curative treatment, but few are eligible for this. Standard of care 1st line chemotherapy for inoperable CCA patients hasn't changed in years and offers modest, if any, benefit. New and more effective treatments for CCA are desperately needed, both in 1st and 2nd line. Centres of Expertise for CCA patients are needed There seems to be no set pathway/guidance for the care of cholangiocarcinoma patients, many are never seen by those with specialist knowledge, and many are not considered for surgery nor for clinical trials. AMMF strongly believes that all CCA patients should be seen in 'centres of expertise' for confirmation of their diagnosis (operable/inoperable), and where their treatment pathway should be endorsed by an HPB multidisciplinary team, experienced in the care of CCA patients. Molecular profiling is needed for all CCA patients Molecular profiling should be available for all those diagnosed with CCA – at diagnosis or during 1st line treatment. With the advent of targeted therapies, such as pemigatinib and now ivosidenib, this is essential so that all those eligible for such treatments and/or trials can be considered in a timely manner. Currently it seems molecular profiling is available to only very few in the UK, via clinical trials, or privately. [3]*Incidence and Mortality rates of cholangiocarcinoma in England* *https://www.annalsofoncology.org/article/S0923-7534(19)30962-7/fulltext*

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients and their carers consider that ivosidenib offers a more personalised treatment for those with a certain 'molecular mutation', (IDH1), bringing with it the hope of extending survival over the more standard chemotherapies and/or best supportive care that might be offered following a 1st line treatment. Plus, as an oral therapy, this has certain quality of life advantages over an intravenous therapy, including spending less time in hospital receiving treatment. Patients and carers also see that this therapy was been approved by the FDA more than a year ago (August 2021) and has been available to eligible CCA patients in the USA since then.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients and carers do not see disadvantages in the treatment, but they see disadvantage in that it is not available to those who might otherwise be eligible to receive it.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those CCA patients have had first line chemotherapy and progressed, and are found to have the IDH1 mutation, could benefit from this targeted treatment. If a patient is found to have the IDH1 mutation, ivosidenib is a therapy which will specifically target that and so could have a positive impact on their cancer. Other, more general chemotherapies (Gemcitabine/Cisplatin, Capecitabine, etc) have been found to be effective for some with CCA, but not for all, and the effectiveness is not known until the patient has had several cycles of chemotherapy and may have endured a number of side effects and infections, only to find there has been no advantage for them in reducing or stabilising their cancer.

Equality

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

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission.	. In up to 5 bullet points, please summarise the key messages of your submission: • Incidence of CCA in increasing, mortality mirrors incidence. • Currently there is very little effective treatment for CCA patients. • Many CCA patients are not considered for surgery nor for clinical trials – 'centres of expertise' are needed for confirmation of diagnosis and treatment pathway, and for molecular profiling. • All CCA patients should receive molecular profiling at diagnosis or during 1st line treatment • For those found to have an IDH1 mutation, ivosidenib offers a realistic treatment, extending survival with modest toxicity and a better quality of life (over standard chemotherapies)

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ivosidenib for treating advanced cholangiocarcinoma with an IDH1 mutation after at least 1 therapy [ID6164]

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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- 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	**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** Other (please specify): **I AM ALSO CHAIR OF THE BRITISH SOCIETY OF GASTROENTROLOGY PANEL CURRENTLY WIRITNG AN UPDATE ON GUIDELINES FOR THE MANAGEMENT OF THIS CONDITION**
5a. Brief description of the organisation (including who funds it).	**CHOLANGIOCARCINOMA-UK IS A SPECIAL INTERST GROUP OF BASL – THE BRITISH ASSOCATION FOR THE STUDY OF THE LIVER**
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.**	**YES - THE COMPANY SERVIER WAS A SPONSOR FOR THE CHOLANGIOCARCINOMA-UK BASIC SCIENCE MEETING IN NOTTINGHAM, UK (6-7TH FEBRUARY 2023).** **SERVIER DONATED £10K TOWARDS THE RUNNING COSTS OF THE MEETING (VENUE HIRE, FOOD AND DRINKS)**
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 IMPROVE SURVIVAL IN A DISEASE WITH AN OTHERWISE POOR PROGNOSIS AND HIGH MORTALITY**
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.)	**IMPROVEMENT IN OVERALL SURVIVAL TIME**
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	**YES, WITHOUT DOUBT**

What is the expected place of the technology in current practice?

9. How is cholangiocarcinoma currently treated in the NHS?	**ADVANCED CHOLANGIOCARCINOMA IS TREATED WITH COMBINATION GEM-CIS CHEMOTHERAPY BUT OVERALL SURVIVA IS POOR AND THERE IS A LACK OF EFFECTIVE THERAPIES FOR PATIENT WHO ARE REFRACTORY TO FIRST LINE SYSTEMIC THERAPY.**

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	**BRITISH SOCIETY OF GASTROENTROLOGY – CURRENTLY BEING UPDATED**
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.)	**YES – WELL DEFINED AND GENERALLY AGREED NATIONALLY AND INTERNATIONALLY**
9c. What impact would the technology have on the current pathway of care?	**THISAGENT HAS BEEN SHOWN TO SIGNIFCANTLY IMPORVE SURVIVAL IN A SIB-COHORT OF PATIENTS WITH CHOLANGIOCARCINOMA – SPECIFCALLY CHEMOTHERAPY-REFRACTORY CHOLANGIOCARCINOMA WITH *IDH1* MUTATION.** **20% OF CHOLANGIOCARCINOMA PATIENTS ARE ESTIMATED TO HAVE THIS MUTATION**
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	**IT IS NOT ALREADY BEING WIDELY USED IN THE NHS**
10a. How does healthcare resource use differ between the technology and current care?	**A multicenter, randomized, double-blind, placebo-controlled, clinical phase 3 trial was conducted from February 20, 2017, to May 31, 2020, at 49 hospitals across 6 countries among patients aged 18 years or older with cholangiocarcinoma with IDH1 mutation whose disease progressed with prior therapy.** **Median OS was 10.3 months (95% CI, 7.8-12.4 months) with ivosidenib vs 7.5 months (95% CI, 4.8-11.1 months) with placebo (hazard ratio, 0.79 [95% CI, 0.56-1.12]; 1-sided *P* = .09). When adjusted for crossover, median OS with placebo was 5.1 months (95% CI, 3.8-7.6 months; hazard ratio, 0.49 [95% CI, 0.34-0.70]; 1-sided *P* < .001).**
10b. In what clinical setting should the technology be used? (For example,	**SECONDARY CARE: Adult patients with cholangiocarcinoma with IDH1 mutation whose disease has progressed with prior therapy.**

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	**MUTATION TESTING OF HISTOLGOY SPECIMENS**
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	**YES**
11a. Do you expect the technology to increase length of life more than current care?	**YES**
11b. Do you expect the technology to increase health-related quality of life more than current care?	**YES**
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	**Yes - Adult patients with cholangiocarcinoma with IDH1 mutation.**

The use of the technology

13. Will the technology be easier or more difficult to use for patients or	**NOT MORE DIFFICULT**

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?	**AS PER TRIAL FINDINGS MENTIONED ABOVE**
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?	**YES – IMPROVED SURVIVAL**
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	**YES**

way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	**YES**
16b. Does the use of the technology address any particular unmet need of the patient population?	**YES – THE HIGH MORTLAITY**
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?	**IN THE TRIAL, There were no treatment-related deaths. Patients receiving Ivosidenib reported no apparent decline in quality of life compared with placebo.**

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	**NO**
18a. If not, how could the results be extrapolated to the UK setting?	**IF APPLIED TO THE UK SETTING, UK PATIENTS WOULD BENEFIT BU A HIGHER LIFE EXPECTANCY**
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	**SURVIAL & SIDE EFFECTS – AND YES, THESE WERE MEASURED IN THE TRIAL**

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?	**NOT TO MY KNOWLEDGE**
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	**NOT TO MY KNOWLEDGE**
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 722. (Whilst TA722 was for a distinct subgroup to this appraisal this question is referring to any changes in the general cholangiocarcinoma pathway and treatments since TA722 was published)	**NOT TO MY KNOWLEDGE**
21. How do data on real-world experience	**AS EXPECTED, FROM ANECDOATAL EVIDENCE FROM COLLEAGUES IN OTHER COUNTRIES**

compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	**NOT TO MY KNOWLEDGE**
22b. Consider whether these issues are different from issues with current care and why.	**NOT TO MY KNOWLEDGE**

23. Do you consider IDH1 mutation testing in cholangiocarcinoma to be routine practice in the NHS at present? **Will most people having current clinical management for cholangiocarcinoma receive an IDH1 mutation test?** (If not already answered in questions 10c or 13)	**NOT YET BUT IT SHOULD BE – GETTING THERE** **GENOME HUIBS ARE SET UP AND WITH INCREASING AWARENESS, MUTATION TESTING SHOULD BECOME MORE ROUTINE**
24. Would you expect people who would be eligible for ivosidenib to also be candidates for stent insertion?	**NO - THIS IS UNLIKELY**

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• **CHOALNGIOCARCINOMA REFRACTORY TO CURRENT CHEMOTHERAPY HAS A DISMAL SURVIVAL** • **IVOSIDENIB IMPROVES THIS SURVIVAL SIGNIFICANTLY IN SELECTED PATIENTS (WITH IDH MUTATION)** • **IT IMPROVES SURVIVAL WITHOUT NEGATIVLY IMPACTING QOL** • **IVOSIDENIB SHOULD BE AVAILABLE**

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ivosidenib for treating advanced cholangiocarcinoma with an IDH1 mutation after at least 1 therapy [ID6164]

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.

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- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

About you

1. Your name	[redacted]
2. Name of organisation	RCP-ACP-RCR
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? A specialist in the clinical evidence base for this condition or technology?
5a. Brief description of the organisation (including who funds it).	RCP-ACP-RCR
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.**	The RCP received £426.00 in Contracted Services – Fees in 2022 from Servier Laboratories Ltd
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.)	Ivosidenib improves progression free and overall survival in patients with IDH1 mutation +ve cholangiocarcinoma.
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.)	Improvement of progression free survival by 2 months
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes

What is the expected place of the technology in current practice?

9. How is cholangiocarcinoma currently treated in the NHS?	Adjuvant capecitabine. 1st line cisplatin and gemcitabine (Valle 2010) 2nd line FOLFOX (Lamarca 2019)
9a. Are any clinical guidelines used in the	ESMO (Vogel 2022) and BSG (Khan 2023 in press)

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.)	Uptake of treatment significant regional variation and generally poor uptake of treatment with approximately 50% of patients not receiving treatment at all and a high proportion of patients presenting with advanced disease to A and E (Zain-Miller 2023)
9c. What impact would the technology have on the current pathway of care?	For the selected population, significant prolongation of life without significant toxicity (Abou-Alfa 2020).
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Used in addition to SoC described above.
10a. How does healthcare resource use differ between the technology and current care?	Addition.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics as advised in ESMO and BSG guidelines.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None: oral therapy. The testing for IDH1 mutation is already on national register.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Progression-free survival was significantly improved with ivosidenib compared with placebo (median 2·7 months [95% CI 1·6–4·2] vs 1·4 months [1·4–1·6]; hazard ratio 0·37; 95% CI 0·25–0·54). Median OS was 10.3 months (95% CI, 7.8-12.4 months) with ivosidenib vs 7.5 months (95% CI, 4.8-11.1 months) with placebo (hazard ratio, 0.79 [95% CI, 0.56-1.12]; 1-sided P = .09). When adjusted for crossover, median OS with placebo was 5.1 months (95% CI, 3.8-7.6 months; hazard ratio, 0.49 [95% CI, 0.34-0.70]; 1-sided P < .001).
11a. Do you expect the technology to increase length of life more than current care?	As above
11b. Do you expect the technology to increase health-related quality of life more than current care?	QoL maintained
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	IDH1 mutated intrahepatic cholangiocarcinoma

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	No significant issues

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?	Standard assessment of disease status
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?	QoL maintained.
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?	Personalised therapy for poor outcome cancers should be supported.
16a. Is the technology a 'step-change' in the management of the condition?	Yes

16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, improvement in survival for this population has been modest (Valle 2010 and Lamarca 2019)
op1ula7. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No significant side effects

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?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	As above
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	No

trials but have come to light subsequently?	
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 722. (Whilst TA722 was for a distinct subgroup to this appraisal this question is referring to any changes in the general cholangiocarcinoma pathway and treatments since TA722 was published)	No
21. How do data on real-world experience compare with the trial data?	Few data available

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None
22b. Consider whether these issues are different from issues with current care and why.	N/A

23. Do you consider IDH1 mutation testing in cholangiocarcinoma to be routine practice in the NHS at present? **Will most people having current clinical management for cholangiocarcinoma receive an IDH1 mutation test?** (If not already answered in questions 10c or 13)	Yes, on the national directory although uncertain whether routinely requested
24. Would you expect people who would be eligible for ivosidenib to also be candidates for stent insertion?	Not commonly

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Poor outlook cancer population with few SoC options • Targeted therapy for selected IDH1 mutated population • Improvement in PFS and OS • Minimal toxicity • Oral therapy

Thank you for your time.

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Ivosidenib for treating advanced cholangiocarcinoma with an *IDH1* mutation after at least 1 therapy [ID6164]

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

No competing interests to disclose.

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Rider on responsibility for report

The view 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.

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Contribution of authors

Mari Imamura and Moira Cruickshank reviewed and critiqued the clinical effectiveness evidence presented in the company submission and drafted the background section; David Cooper checked and critiqued the statistical analyses presented in the company submission; Graham Scotland and Abraham Getaneh reviewed and critiqued the cost-effectiveness evidence and economic model presented in the company submission; Paul Manson checked and critiqued the company's search strategies; Adnan Shaukat provided clinical guidance and comments on the draft report. Miriam Brazzelli acted as lead for the critique of the clinical effectiveness evidence. Graham Scotland lead for the critique of the health economic evidence, and coordinated all aspects of this appraisal. Graham Scotland and Miriam Brazzelli are the guarantors for the report. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

2-HG	2-hydroxyglutarate
5-FU	5-fluorouracil
α-KG	alpha- ketoglutarate
AE	Adverse event
AIC	Akaike information criterion
ASC	Active symptom control
BIC	Bayesian information criterion
BNF	British National Formulary
BOR	Best overall response
BSA	Body surface area
BSC	Best supportive care
BSG	British Society for Gastroenterology
BTC	Biliary tract cancer
C1D1	Cycle 1 day 1
CCA	Cholangiocarcinoma
CI	Confidence interval
CMPH	Committee for Medicinal Products for Human Use
CoS	Crossover Set
CR	Complete response
CT	Computed tomography
dCCA	Distal cholangiocarcinoma
DCR	Disease control rate
DNA	deoxyribonucleic acid
DoR	Duration of response
DSU	Decision Support Unit
EASL	European Association for the Study of the Liver
eCCA	Extrahepatic cholangiocarcinoma
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMIT	Electronic market information tool
ENS-CCA	European Network for the Study of Cholangiocarcinoma
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-BIL21	European Organisation for Research and Treatment of Cancer quality of life questionnaire cholangiocarcinoma and gallbladder cancer module

EOT	End of treatment
ESCAT	ESMO scale for clinical actionability of molecular targets
ESMO	European Society of Medical Oncology
ESMO-MCBS	ESMO magnitude of clinical benefit scale
EU	European union
FGFR	Fibroblast growth factor receptor
GBC	Gall bladder cancer
GI	Gastrointestinal
GLH	genomic laboratory hub
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCRU	health-care resource use
HR	Hazard ratio
HRQoL	Health related quality of life
HST	Highly specialised technology
iCCA	Intrahepatic cholangiocarcinoma
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ICR	independent central review
IDH1	isocitrate dehydrogenase 1
IDH2	isocitrate dehydrogenase 2
IDHM	isocitrate dehydrogenase mutation
INMB	incremental net-monetary benefit
IPCW	inverse-probability-of-censoring weighting
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
LVEF	Left ventricular ejection fraction
LYs	Life years
LYG	Life years gained
mFOLFOX	Modified folinic acid + fluorouracil + oxaliplatin
mGC	Metastatic gastric cancer
MMR	Mismatch repair
MMRM	Mixed Model for Repeated Measures

MRI	Magnetic resonance imagining
MSI	Micro-satellite instability
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not estimable
NGS	Next-generation-sequencing
NHB	Net health benefit
NHS	National Health service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute of Care and Excellence
NICE TA	NICE technology appraisal
NMB	Net monetary benefit
NTRK	Neurotrophic tyrosine receptor kinase gene fusion
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PartSA	Partitioned survival analysis
pCCA	Perhilar cholangiocarcinoma
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PGI-C	Patient Global Impressions of Change
PGI-S	Patient Global Impressions of Severity
PICC	Peripherally inserted central catheter
PK	Pharmacokinetic
PLD	Patient level data
PPS	Per-Protocol Set
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALYs	Quality-adjusted life years

QD	Once daily.
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors.
RMST	Restricted mean survival time
RPSFT	Rank preserving structural failure time model
SAE	Serious adverse events
SAS	Safety Analysis Set
SD	Stable disease
SE	Standard error
SLR	Systematic literature review
SoC	Standard of care
ToT	Time on treatment
TRAE	Treatment related adverse events
TSD	Technical Support Document
TTR	Time to recurrence
WTP	Willingness-to-pay

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. 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 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

The focus of the submission received from Servier Laboratories is ivosidenib for previously treated patients with advanced (non-resectable or metastatic) cholangiocarcinoma with an IDH1 mutation.

The clinical evidence submitted by the company consists of a phase-3, multi-centre, randomised, double-blind, placebo-controlled study, ClarIDHy. Participants received 500 mg oral ivosidenib or placebo once daily in continuous 28-day cycles. The primary efficacy endpoint was progression-free survival (PFS) as assessed by the Independent Radiology Centre (IRC).

At a median follow-up of 6.9 months (IQR 2.8, 10.9), PFS by IRC assessment was longer for the ivosidenib group compared with the placebo group (hazard ratio [HR] 0.37; 95% confidence interval [CI] 0.25, 0.54, p <0.001). The median PFS was 2.7 months (95% CI 1.6, 4.2) for participants receiving ivosidenib compared with 1.4 months (95% CI 1.4, 1.6l) for those receiving placebo.

The company carried out a Bucher indirect treatment comparison for OS of ivosidenib with folinic acid + fluorouracil + oxaliplatin + active symptom control (mFOLFOX). The HR from the ABC-06 trial comparing mFOLFOX to active symptom control (ASC) was 0.69; 95% CI 0.50, 0.97. To better match the populations from ClarIDHy and ABC-06, the

subgroup who had only received one prior line of chemotherapy from ClarIDHy were selected. The HR for this group is 0.40; 95% CI 0.23, 0.68 and this is used in the Bucher comparison to obtain the HR comparing ivosidenib to mFOLFOX as 0.58; 95% CI 0.31, 1.09 which is a hazard ratio favouring ivosidenib.

The cost-effectiveness evidence consists of a de Novo economic model, comparing ivosidenib with best supportive care (BSC) and mFOLFOX for patients with locally advanced or metastatic CCA with an IDH-1 mutation, who were previously treated with at least one prior line of systemic therapy. The model takes the form of a partitioned survival model, with states representing progression-free, progressed disease, and dead. Key efficacy inputs for ivosidenib and BSC are derived from parametric survival analysis of OS and PFS data from the ClarIDHy trial, and the comparison with mFOLFOX relies on the HR derived from the Bucher ITC for OS and a naïve comparison for PFS. The health states are further subdivided into on- and off-treatment sub-states, using time on treatment (ToT) data and assumptions. Health state utilities in the company base case are incorporated by treatment status rather than progression status, and one off QALY decrements are applied for adverse events. The company base case incorporates treatment acquisition and administration costs, health state costs, treatment related adverse event costs, and end of life costs. Costs of IDH1 testing, and costs of subsequent treatment are not included in the company base case but have been explored in sensitivity analysis.

The key issues identified by the EAG in the company's submission are summarised in Table 1.

Table 1 Summary of key issues

ID6164	Summary of issue	Report sections
1	Reporting of the indirect treatment comparison was not sufficiently transparent.	3.3, 3.4
2	Uncertainty in the extrapolation of overall survival for ivosidenib	4.2.6
3	Whether to allow for ivosidenib treatment beyond progression	4.2.6
4	Whether to include treatment wastage for ivosidenib	4.2.8
5	Modelling of time on treatment for mFOLFOX, and its acquisition and administration costs	4.2.8
6	Whether and how to include subsequent treatment costs	4.2.8

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are that the EAG: 1) apply a more conservative extrapolation of overall survival for patients receiving ivosidenib; 2) model ivosidenib treatment to continue as observed in the ClarIDHy trial, rather than assuming all treatment is stopped in line with the modelled disease progression; 3) assume a 30-day supply (one full pack) of ivosidenib will be dispensed to patients at a time, rather than the exact amount of tablets required each week; 4) assume a proportion of patients will receive subsequent mFOLFOX treatment following progression on ivosidenib, as opposed to assuming no subsequent treatment; and 5) apply lower treatment acquisition and administration cost for mFOLFOX compared to the company.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology (ivosidenib) is modelled to affect QALYs by:

- Increasing overall survival compared to other available treatments.
- Prolonging time on active treatment and/or delaying progression of disease.
- Having a different adverse event profile compared to other treatments.

Overall, the technology is modelled to affect costs by:

- Having higher acquisition costs compared to the other modelled treatments.
- Having lower administration costs relative to mFOLFOX
- Accumulating greater health care resource use over a period of extended survival
- Having a different adverse event profile compared to other treatments.

In scenario analyses, costs are also influence by

  - the addition of IDH1 testing to identify the eligible population.
  - different proportions moving on to have subsequent chemotherapy.

The modelling assumptions that have the greatest effect on the ICER are:

- The parametric survival curve selection for overall survival on ivosidenib
- The overall survival hazard ratio for ivosidenib versus mFOLFOX
- The decision to cap ivosidenib ToT with PFS, to exclude the possibility of treatment continuing beyond progression.
- Using PFS as a proxy for ToT with mFOLFOX, rather than deriving a separate ToT curve.
- Whether to account for potential wastage of ivosidenib in the treatment acquisition cost calculations.
- Whether and how subsequent treatment costs should be included in the different arms of the model.

1.3 The decision problem: summary of the EAG's key issues

In general, the company's decision problem is in line with the NICE final scope. The EAG, in consultation with their clinical advisor, considers the company's positioning of ivosidenib in the treatment pathway to be reasonable and in line with current clinical practice in the UK.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG reviewed the clinical effectiveness and safety evidence presented in the company's submission and identified the following issue for consideration.

Issue 1 Description of indirect treatment comparison

Report section	Section 3.3, 3.4
Description of issue and why the EAG has identified it as important	Clarity of reporting of the indirect treatment comparison method. To account for differences between the ClarIDHy and ABC-06 populations in terms of the number of prior lines of chemotherapy, it appears from the company's response to the clarification letter that a subgroup of ClarIDHy participants was used to obtain the overall survival hazard ratio used in the company's indirect treatment comparison (ITC) with mFOLFOX. This needed to be more transparent, as it only became apparent when the EAG queried the lack of consistency in the HR from the ClarIDHy trial and the HR used in the Bucher ITC. Further, the company have not fully justified the need for, or the selection criteria, for the subgroup used in the ITC.
What alternative approach has the EAG suggested?	While the EAG understands the company's reasoning for aligning the ClarIDHy and ABC-06 populations, the process of using a subgroup of ClarIDHy participants should have been made clearer and explained more thoroughly. It would have been useful to see the baseline characteristics and Kaplan-Meier curves for overall survival for the subgroup. It should have been made clear if the RPSFTM crossover adjustment was done on the whole population and the subgroup was subsequently selected or if the subgroup was selected first and the crossover adjustment was then made on the subgroup.
What is the expected effect on the cost-effectiveness estimates?	As there is lack of transparency in the methods used, this leaves uncertainty surrounding the overall survival hazard ratio for ivosidenib versus mFOLFOX, which is a key input in the economic model. This in turn leads to uncertainty in the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Detailed reporting of the subgroup analysis informing the ITC with mFOLFOX would be beneficial. This would ideally include evidence to support the need to align for prior treatment line and ECOG performance status as potential treatment effect modifiers, clarity on the data cut used and alignment of the available numbers with those reported elsewhere in the company submission, a summary of baseline characteristics in the selected subgroup, presentation of the Kaplan Meir curves before and after crossover adjustment, and details of the crossover adjustment in the selected subgroup.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

The EAG reviewed the cost-effectiveness evidence presented in the company's submission and identified the following issue for consideration.

Issue 2 Extrapolation of overall survival for ivosidenib

Report section	4.2.6
Description of issue and why the EAG has identified it as important	The company fit standard parametric survival distributions to the overall survival data from the ClarIDHy trial. They describe how, based on a combination of statistical and visual fit, and consultation with clinical experts (on the plausibility of extrapolations), they chose the log-normal curve for their base case analysis. The EAG note that: 1) there is little to choose between several parametric curves in terms of statistical fit; 2) the curve with lowest AIC provides the second most optimistic projection of OS, but the curve with lowest BIC provides the third most pessimistic projection; 3) there is no observed longer term data available against which to assess the plausibility of the extrapolations; and 4) all curves could be said to have acceptable visual fit to the observed data. The choice of curve for ivosidenib OS has substantial impact on the ICER versus both BSC and mFOLFOX, as illustrated by the company's scenario analysis.
What alternative approach has the EAG suggested?	The EAG has a tendency towards favouring the generalised gamma curve for modelling OS, on the basis that it has a good visual fit to the observed data and provides middle ground in terms of extrapolated survival landmarks compared with the lowest AIC, log-normal, and the lowest BIC, exponential, curve.
What is the expected effect on the cost-effectiveness estimates?	Selection of the generalised gamma has a modest upward impact on the ICER for ivosidenib versus both BSC and mFOLFOX.
What additional evidence or analyses might help to resolve this key issue?	It is unlikely that this issue can be resolved fully in the absence of longer-term data. It will be important for the committee to consider the uncertainty around the ICER driven by the OS curve selection.

Issue 3 Whether to allow for ivosidenib treatment beyond progression

Report section	4.2.6 and 4.2.8
Description of issue and why the EAG has identified it as important	The company have mature ToT data for ivosidenib (June 2021 data lock), and have selected a preferred parametric curve to model this. For their base case, however, they cap ToT at their preferred extrapolation of PFS, [redacted]. Their justification is that treatment would not continue beyond progression in routine NHS practice. This is an important assumption, because it reduces time on treatment in the model compared to that observed in the ClarIDHy trial, and consequently reduces the treatment acquisition costs. No corresponding adjustment is made to OS to reflect this reduction in ToT.
What alternative approach has the EAG suggested?	The EAG believe that ivosidenib ToT should be modelled as observed in ClarIDHy, using the best fitting parametric curve for the observed data, even if this does assume treatment continuing beyond progression for some. Clinical expert advice received by the EAG suggests that in some cases, clinicians may still treat beyond radiographic disease progression if they feel the patient may still be deriving benefit from it. Further, the chosen PFS extrapolation tends to underestimate PFS in the tail of the Kaplan Meier curve, which may further artificially reduce treatment costs. The summary of product characteristics (SmPC) states that "Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient".
What is the expected effect on the cost-effectiveness estimates?	The company have explored this in scenario analysis, and it results in a moderate upward shift in the ICER for ivosidenib versus BSC and mFOLFOX.
What additional evidence or analyses might help to resolve this key issue?	The EAG do not believe that further evidence is required. It is of the opinion that mature ToT data exists from the ClarIDHy trial, and that it should be used for consistency with the OS data applied in the model.

Issue 4 Inclusion of treatment wastage for ivosidenib

Report section	4.2.8
Description of issue and why the EAG has identified it as important	The company apply ivosidenib treatment costs on a per model cycle (weekly) basis, based on the calculated seven day cost (adjusted for dose intensity) multiplied by the proportion of the cohort remaining on treatment at the start of each cycle. This essentially assumes that packs can be split and that patients can be prescribed a seven-day supply for every week they remain on treatment. Ivosidenib comes in packs of 60 tablets, covering 30-days of treatment. The EAG believe it is more likely that patients on treatment will be supplied with a 30-day pack at a time, and a further pack will be dispensed when the supply runs low. If this is the case, the full pack cost will still be incurred for patients who discontinue before depleting their dispensed supply, as returned medication cannot be reused. These wastage costs are not included in the company's base case model, but scenarios were provided at the clarification stage.
What alternative approach has the EAG suggested?	The company offered three scenarios to capture potential wastage in response to the clarification letter (see section 4.8). However, the EAG believes that two of these may still underestimate wastage, and other may overestimate it. Therefore, the EAG has provided an alternative scenario that assumes patients on treatment are dispensed with one full pack of tablets (30 day supply) at a time, and that a new pack is dispensed in model cycles when the expected number of remaining tablets below the number required for the week.
What is the expected effect on the cost-effectiveness estimates?	The incorporation of wastage results in a moderate upward shift in the ICER for ivosidenib against both comparators.
What additional evidence or analyses might help to resolve this key issue?	It would be valuable to obtain expert opinion on how dispensing of ivosidenib would be implemented in routine practice; i.e. how frequently and in what quantity it would be dispensed to those on treatment, and, if any, what specific measures could be taken to minimise potential wastage.

Issue 5 Overestimation of mFOLFOX acquisition and administration costs

Report section	4.2.8
Description of issue and why the EAG has identified it as important	The company apply several assumptions which the EAG believe may overestimate the cost of providing mFOLFOX treatment in the given patient population: 1) They use PFS to model time on treatment up to maximum of 12 cycles, rather than estimating a separate time on treatment curve which would capture discontinuation due to reasons other than progression; 2) they model the cost of removing the peripherally inserted central catheter (PICC), required for prolonged fluorouracil infusion, after each treatment cycle, rather than upon treatment discontinuation. The company's model predicts a substantially greater number of mFOLFOX treatment cycles compared with that observed for patients enrolled in the ABC-06 trial – the source mFOLFOX efficacy data.
What alternative approach has the EAG suggested?	The EAG suggest that ToT for mFOLFOX should be modelled using an exponential distribution which aligns with the median number of treatment cycles observed for patients in the ABC-06 trial. The EAGs clinical expert also advised that patients would incur the cost of a district nurse visit to remove the chemotherapy pump during each treatment cycle, and that they would only return to hospital for PICC removal following completion (discontinuation) of their treatment course.
What is the expected effect on the cost-effectiveness estimates?	The above changes result in a modest upward shift in the ICER for ivosidenib versus mFOLFOX.
What additional evidence or analyses might help to resolve this key issue?	Further clinical expert opinion on the logistics of administering mFOLFOX treatment in patients with advanced or metastatic CCA may be informative for assessing the validity of different assumptions.

Issue 6 Inclusion of subsequent treatment costs

Report section	4.2.8
Description of issue and why the EAG has identified it as important	Following EAG request at the clarification stage, the company provided details of the percentage of patients in the ClarIDHy trial that went on to receive subsequent treatment following progression on ivosidenib or placebo (other than crossover to ivosidenib) and implemented a scenario in the economic model to capture these expected costs. However, it is not expected that patients receiving BSC in routine practice would go on to receive any active treatment upon progression, so the EAG believe that subsequent treatment costs should only be modelled as observed following progression on ivosidenib. The EAG also had some concerns with how the cost of subsequent treatment (with mFOLFOX) had been calculated in the company's scenario; by multiplying a median number of cycles by the acquisition and administration cost per cycle, and then applying this to smaller fraction of the cohort than observed to have received subsequent treatment in the ClarIDHy trial.
What alternative approach has the EAG suggested?	The EAG has implemented its own scenario for subsequent treatment, which involves recycling the expected discounted cost of mFOLFOX as an index treatment (from the comparator arm of the model) and applying it in the ivosidenib arm to the observed proportion of patients who received further treatment in the ivosidenib arm of the ClarIDHy trial.
What is the expected effect on the cost-effectiveness estimates?	The scenario produces a modest upward shift in the ICER for ivosidenib against both comparators.
What additional evidence or analyses might help to resolve this key issue?	It may be beneficial to have clinical experts comment on he expected subsequent treatment patterns for patient receiving the alternative treatments in the current decision problem. It would also be beneficial if the company could clarify if their approach to adjusting for crossover will have adjusted out the effect of any other subsequent treatment received by patients in the placebo arm of the ClarIDHy trial.

1.6 Other key issues: summary of the EAG's view

The EAG has not identified any other key issues which on their own materially affect decision making. However, it has preferences for several other minor changes, outline in 1.7, which taken together tend to push the ICER upwards. The company have made a case to

apply the higher severity weighting of x1.7 to incremental QALY gains in the model. The EAG agree that the threshold for the absolute and proportional QALY shortfall is met for this modifier to be considered in the current indication.

1.7 Summary of EAG's preferred assumptions and resulting ICER

The EAGs preferred base case modelling assumptions are summarised in Table 2 below.

The impact on the company base case results is displayed for each individual change for the comparison with both BSC and mFOLFOX. The results of the fully incremental deterministic and probabilistic analyses can be found in section 6.3 of this report. Modelling errors identified and corrected by the EAG are described in section 5.3. For further details of the exploratory and sensitivity analyses conducted by the EAG, see sections 6.2 and 6.3.

Table 2 Summary of the EAGs preferred modelling assumptions and ICER (deterministic)

Preferred assumption	Incremental versus BSC				Incremental versus mFOLFOX			
	Cost (£)	QALY (x1.7 modifier)	ICER (x1.7 modifier)	Change	Cost (£)	QALY (x1.7 modifier)	ICER (x1.7 modifier)	Change
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. Correct model code to cap mFOLFOX treatment cycles at a maximum 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. OS extrapolation (ivosidenib): generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Allow for ivosidenib treatment beyond progression (ivosidenib arm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. ToT extrapolation (ivosidenib): generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. ToT mFOLFOX: Exponential curve fitted to median number of treatment cycles in ABC-06	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. Ivosidenib acquisition costs: Account for wastage (EAG approach)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. Include a clinical examination and blood test every month for ivosidenib for the first three months of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8. mFOLFOX administration: District nurse visit (£51.84) to remove pump after each Tx cycle + Non-consultant led OP appointment (£190.59) to remove catheter at treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9. Apply weighted average HRG costs, inclusive of non-elective short stay and non-elective long stay, to adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10. Include subsequent treatment with mFOLFOX following progression on ivosidenib using the recycled discounted cost stream of mFOLFOX as an index treatment, and applying it to the proportion receiving further treatment from	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ClarIDHy. No subsequent treatment following progression on BSC or mFOLFOX.								
11. Include IDH testing for the ivosidenib arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12. Health state utility: By progression and treatment status (ClarIDHy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13. All changes 1-12 combined (EAG base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for the submission received from Servier is locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation previously treated with at least one gemcitabine or 5-fluorouracil-containing regimen. The company's description of this health condition in terms of prevalence, symptoms and complications appears generally accurate and in line with the decision problem. The relevant intervention for this submission is ivosidenib (Tibsovo®).

2.2 Background

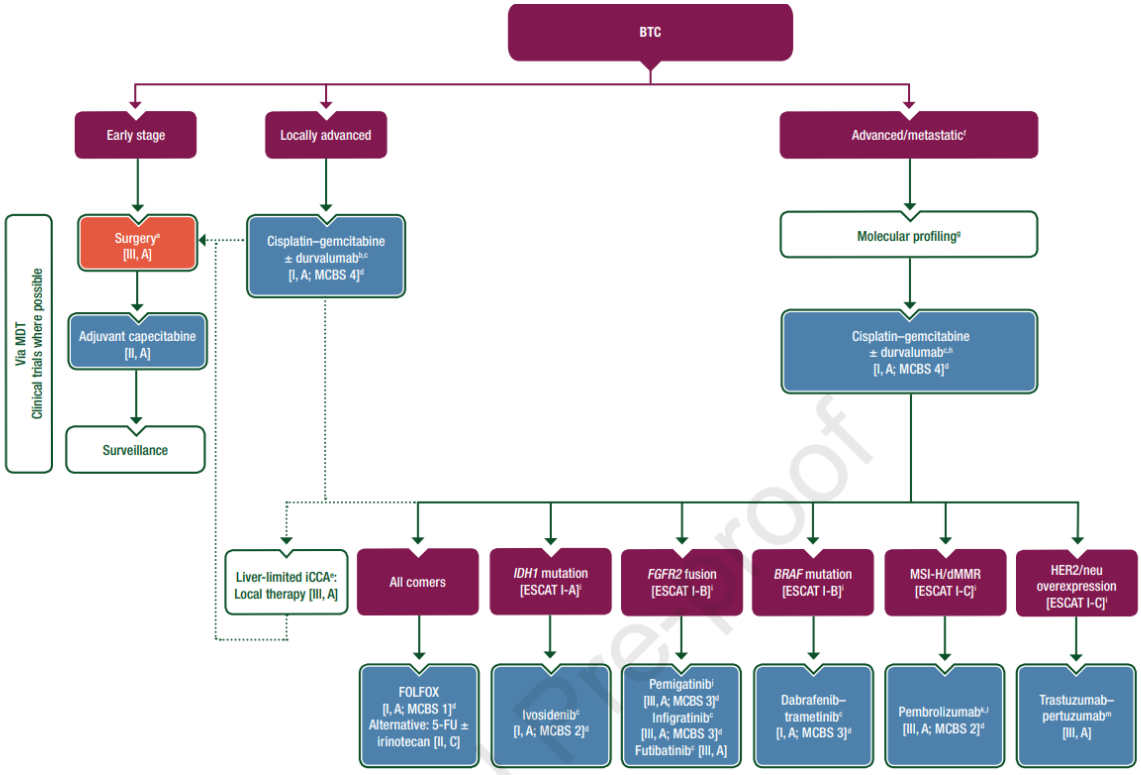
The company submission (CS) describes cholangiocarcinoma (CCA) as a biliary tract cancer with the following subtypes: intrahepatic CCA (iCCA; arising from the biliary tree), perihilar CCA (pCCA; originating in the hepatic ducts or their junction) and distal CCA (dCCA; arising from the bile duct region). The latter two subtypes are extrahepatic CCA (eCCA), albeit the current ESMO clinical practice guidelines for biliary tract cancer discourage the classification of pCCA and dCCA as eCCA due to lack of anatomical specificity.[1-4] Each subtype has specific risk factors, clinical and molecular characteristics, treatment options and prognosis.[4]

Risk factors for CCA differ between regions but chronic inflammation of the biliary epithelium is a common factor. Other risk factors for CCA include bile duct cysts, Caroli's disease, cholangitis, hepatolithiasis, cholelithiasis/choledocholithiasis and cirrhosis. Overall, around half of CCA cases are accounted for by known risk factors.[1, 5]

Incidence of CCA varies considerably across geographical regions, with higher incidence in the East (for example, age standardised incidence/100,000 in Thailand – North East: 85) as compared to the West (for example, age standardised incidence/100,000 in UK: 2.2). In addition, incidence of the disease varies within countries.[6] CCA is most common in the seventh decade of life and in slightly more males than females.[6, 7] In 2017, 2,187 people in England were diagnosed with CCA, giving an age standardised incidence rate of 4.3/100,000 (4.0 in females (95%CI 3.7-4.2); 4.6 in males (95%CI 4.3-4.9)).[8]

Cholangiocarcinoma is generally asymptomatic in the early stages and often not diagnosed until at an advanced stage. Such late diagnoses limit the available treatment options, and the prognosis tends to be poor.[6] It has been reported that five-year survival for people diagnosed with CCA in England in 2008 was 5%.[9]

The European Society for Medical Oncology (ESMO) has recently updated a clinical practice guideline for the diagnosis, treatment and follow-up of biliary tract cancer, including a treatment algorithm with the proposed positioning of ivosidenib (reproduced as Figure 1 below).[4]



Source: Adapted Vogel et al (2023).[4]

Abbreviations: 1st LOT, 1st line of therapy; 2nd LOT, 2nd line of therapy; BTC, biliary tract cancer; FOLFOX, folinic acid, fluorouracil and oxaliplatin; SoC, standard of care.

Figure 1 ESMO treatment algorithm for BTC [reproduced from Figure 4, Document B of the CS]

The algorithm recommends cisplatin-gemcitabine-durvalumab as first-line treatment for advanced/metastatic biliary tract cancer. The CS points out that this combination does not

have a current UK marketing authorization, with cisplatin-gemcitabine remaining as an approved option. Second-line treatment options include FOLFOX as standard of care, plus targeted treatments for specified genetic alterations, namely ivosidenib (IDH1 mutation), pemigatinib (FGFR2 fusion), dabrafenib-trametinib (BRAF mutation), pembrolizumab (MSI-H/dMMR) or trastuzumab-pertuzumab (HER2/neu overexpression). The CS notes that the ESMO guidelines recommend molecular testing at an early stage in advanced disease and that the gene panel should include IDH testing. The EAG clinical expert is of the opinion that the treatment algorithm published by ESMO reflects current clinical practice in the UK NHS. Guidelines published in 2012 by the British Society of Gastroenterology (BSG) also recommend cisplatin-gemcitabine for locally advanced or metastatic inoperable disease.[10]

Other European guidelines are also available. First-line cisplatin-gemcitabine is recommended by the European Network for the Study of Cholangiocarcinoma (ENS-CCA) consensus statement for metastatic CCA, but with no recommendation for second-line therapy.[6] The European Association for the study of the Liver (EASL) guidelines for management of intrahepatic CCA recommend surgical resection as the treatment of choice but there are no recommended first-line treatments for people with non-resectable disease.[11]

2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3 below. A critique of how the company's economic modelling adheres to the NICE reference case is provided in Chapter 3.

Table 3 Summary of the company's decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation, who were previously treated by at least one prior line of systemic therapy	People with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation, who were previously treated by at least one prior line of systemic therapy	R132 included to align with license	The EAG agrees with the company's approach. The EAG's clinical expert notes that R132 is the main targetable mutation in this context
Intervention	Ivosidenib	Ivosidenib	N/A	The intervention described in the CS matches that described in the NICE final scope. Ivosidenib monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH R132 mutation who were previously treated by at least one prior line of systemic therapy. Ivosidenib for the treatment of biliary tract cancer was authorised in the EU on 4th May 2023.[12]
Comparator(s)	• Chemotherapy (including fluorouracil and oxaliplatin) • Best supportive care (active symptom control, including stent insertion)	• Chemotherapy (including fluorouracil and oxaliplatin) • Best supportive care (active symptom control)	Servier do not consider stent insertion to be a relevant component of BSC at this line of therapy. In line with NICE TA722, stent insertion was not explicitly considered. As reported in NICE TA722, biliary stents are most likely to be used in patients with hilar or extrahepatic CCAs; however, >90% of patients in ClarIDHy presented with	The EAG agrees that the company's choice of comparators is appropriate for this appraisal and that stent insertion is not relevant in this context.

			intrahepatic CCA.[13] Furthermore, biliary stent insertion is primarily a treatment option in the earlier stages of disease and, although maintenance or replacement of stents may be required, insertion of a new stent is less likely to be considered after failure of previous lines of chemotherapy.	
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	N/A	The EAG agrees that the outcomes included in the CS are appropriate for addressing the topic of this appraisal
Economic analysis	The use of ivosidenib is conditional on the presence of IDH1 gene mutation. The economic modelling should include the costs associated with diagnostic testing for IDH1 gene mutation in people with advanced cholangiocarcinoma who would not otherwise have been tested. A sensitivity analysis	The scope states that the economic modelling should include the costs associated with diagnostic testing for IDH1 gene mutation in people with advanced cholangiocarcinoma who would not otherwise have been tested and a sensitivity analysis should be provided without the cost of the diagnostic test. However,		The company's economic analysis is broadly consistent with the final scope and aligns with the reference case. The EAG disagrees with the company's decision not to include IDH1 testing in their base case economic analysis, since there are no other IDH1 targeted treatments currently available for this population.

	should be provided without the cost of the diagnostic test.	IDH1 testing is already part of the genetic test directory so funding should be in place. Therefore, Servier believes the base case should not include cost of testing		
Subgroups	None	None	N/A	The company conducted analyses of PFS and OS of the following subgroups: number of prior lines of therapy (1 vs ≥2); gender (male vs female); extent of disease at screening (locally advanced vs metastatic); CCA type (intrahepatic vs extrahepatic), ECOG at baseline (0 vs 1), regions (North America vs Europe vs Asia)
Special considerations including issues related to equity or equality	N/A	No equality issues to be considered	N/A	The EAG is satisfied that there are no relevant equality issues

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D of the CS. The EAG's appraisal of the company's systematic review methods is summarised in Table 4 below.

Table 4 EAG's appraisal of the systematic review methods presented in the CS

Review process EAG	EAG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details provided in Appendix D of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included Embase, Medline, and CENTRAL for primary research, and Cochrane Database of Systematic Reviews for secondary research. Relevant conference proceedings and trial registers were also searched. Bibliographies of recent SLRs were examined to identify relevant studies not captured by the literature searches Full details are provided in Appendix D of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	Searches were not restricted by any eligibility criteria, so all results were discovered and only those relevant to the scope were selected.
Was study selection conducted by two or more reviewers independently?	Yes	Appendix D, Section D.4.7: *"All references/publications abstracts identified by the searches were reviewed independently by two reviewers for the SLRs [systematic literature reviews], and a single reviewer for TLRs [targeted*

		literature reviews], based on the PICOS criteria. Additionally, 10% of the hits were quality checked by a third independent reviewer."
Was data extraction conducted by two or more reviewers independently?	No	Appendix D, Section D.4.8: *"Data extraction was performed by one researcher and checked by another independent researcher. Any disagreements were resolved by consulting with the third reviewer.*" The EAG considers this strategy to be adequate.
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	Appendix C, section D.4.9: *"The quality of RCT studies retained for data extraction was assessed using the Cochrane Risk of Bias tool".*
Was the risk of bias assessment conducted by two or more reviewers independently?	Yes	From clarification response: *'All references/publications abstracts identified by the searches were reviewed independently by two reviewers […], based on the PICOS criteria. Additionally, 10% of the hits were quality checked by a third independent reviewer. All publications where there was an uncertainty on including or any disagreements were resolved […] through "reconciliation" (discussion between the two reviewers) or, through "arbitration" by a third independent reviewer ….'*
Was identified evidence synthesised using appropriate methods?	Partially	As the SLR identified only one RCT, meta-analysis was not conducted. While the method used for the indirect treatment comparison was probably correct, the EAG had some concerns that the process of using a subgroup of ClarIDHy participants for the overall survival estimation was not sufficiently transparent.

The EAG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria. The results are presented in Table 5. Overall, *the EAG considers the methods used by the company for the systematic review of clinical effectiveness evidence adequate.* However, it is the opinion of the EAG that the indirect treatment comparison should have been made clearer and explained more thoroughly. In particular, more information should have been provided on the process of using a subgroup of ClarIDHy participants to estimate the OS effect size used in the economic model and where in the process the RPSFTM crossover adjustment was made. Summary statistics for this subgroup should have been provided.

Table 5 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Partially
5. Are the primary studies summarised appropriately?	Partially

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

Details of the key clinical effectiveness evidence are presented in Document B, Section B.2 of the CS. The main clinical evidence for the clinical effectiveness and safety of ivosidenib consisted of one multicentre, randomised, double-blinded, placebo-controlled phase III study, ClarIDHy. *The EAG has no major concerns about the design and conduct of this trial.*

The participant flow in the ClarIDHy study is presented in Document B, Figure 6 of the CS. An overview of the study is presented in Document B, Table 6 of the CS and reproduced as Table 6.

Table 6 Clinical effectiveness evidence [Reproduced from Table 6, Document B of the CS; supplemented by clarification response]

Study	AG120-C-005 ClarIDHy (Phase III-pivotal) [NCT02989857]
Study design	Multicenter, placebo-controlled, randomized, double-blind study
Population	mIDH1 nonresectable or metastatic CCA previously treated patients
Intervention(s)	Tibsovo® 500 mg QD orally in continuous 28-day cycles
Comparator(s)	Placebo (n = 61) Crossover permitted at radiographic disease progression
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in the model	N/A
Reported outcomes specified in the decision problem	**PFS (per ICR)** **Safety** **PFS (by investigator review)** **OS** ORR **QoL** PK Pharmacodynamic
All other reported outcomes*	DOR TTR

* The information regarding 'All other reported outcomes' was supplemented by the company's response at clarification.
Abbreviations: CCA, cholangiocarcinoma; DOR, duration of response; ICR, independent central review; ORR; objective response rate; N/A, not applicable; OS, overall survival; PFS, progression-free survival; PK pharmacokinetic; TTR, time to recurrence; QD, once daily.

The methods used by the ClarIDHy study are reported in Document B, Section 2.3 of the CS. The primary objective of ClarIDHy was to demonstrate the efficacy of ivosidenib based on progression-free survival (PFS) per Independent Radiology Centre (IRC) assessment

compared to placebo in patients with nonresectable or metastatic CCA with an IDH1 mutation. Key eligibility criteria for ClarIDHy are reported in Document B, Table 7 of the CS.

The study, funded by Servier Pharmaceuticals, was done in 49 centres across six countries (France, Italy, South Korea, Spain, UK and the USA). At the time of primary analysis (31 January 2019 data cut-off), 185 patients were randomly assigned in a 2:1 ratio to ivosidenib (n = 124) or placebo (n = 61). At the time of secondary analysis (31 May 2020 data cut-off), 187 patients were randomised (invosidenib, n = 126, or placebo, n = 61). Randomisation was by a block size of 6 and stratified by number of prior systemic treatment regimens for advanced disease (one or two).

Eligible participants were aged 18 years or older with histologically confirmed, advanced CCA with IDH1 mutation. Participants were required to have at least one but no more than two prior systemic regimens for advanced disease (nonresectable or metastatic), including one gemcitabine- (GEM) or 5-fluorouracil- (5-FU) based chemotherapy regimen, and received no prior IDH-variant inhibitor therapy.

The study's ivosidenib dosing regimens are in line with the anticipated licensed posology for ivosidenib for adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy (Summary of Product Characteristics [SmPC] in Appendix C of the CS). In ClarIDHy, ivosidenib 500 mg (2 x 250 mg tablets) or matched placebo were taken orally once daily in continuous 28-day cycles. Treatment should be continued until disease progression or until treatment is no longer tolerated by the participant. All participants continued to receive best supportive care according to institutional practice throughout the study, regardless of treatment arm.[14] Upon radiographic disease progression, participants in the placebo group who continued to meet eligibility criteria were permitted to cross over to receive open-label ivosidenib. During the study period, 43 of the 61 participants (70.5%) originally randomised to the placebo group were crossed over to the ivosidenib group.

The company performed a quality appraisal of the ClarIDHy study in Table 8, Section B.2.5 of the CS. The CS referenced the revised version of the Cochrane risk-of-bias tool.[15] The assessment criteria in the CS observed by the EAG suggest that the original version of the

Cochrane tool may have been used. *Overall, the EAG generally agrees with the company's assertion that risk of bias was low in this study.*

Details of the baseline demographic and disease characteristics of ClarIDHy are reported in Table9, Section B.2.6.1.2 of the CS and reproduced as Table 7, below. As of May 31 2020 (data cut-off date for secondary analysis), around two thirds of participants were female and the median age was 61 years in the ivosidenib group and 63 years in the placebo group. Most participants had metastatic disease (ivosidenib, 117/126 [93%]; placebo, 56/61 [92%]). The most common IDH1 mutation was R132C (ivosidenib, 86/126 [68%]; placebo, 45/61 [74%]).

In an associated publication for the ClarIDHy study by Zhu et al., it is also reported that among all 187 participants, most (106 [57%]) participants were White and 23 [12%] were Asian.[16] Around half (88 [47%]) had received two previous lines of therapy, while the others (99 [54%]) received one previous line of therapy.[16]

The baseline characteristics for the ivosidenib and placebo groups appear to be similar. In general, the EAG's clinical expert is satisfied that the baseline characteristics of ClarIDHy are representative of patients with CCA who would be eligible for this treatment in the UK.

Table 7 ClarIDHy: patient demographics and baseline characteristics (31 May 2020 data cut-off) [reproduced from Table 9, Document B of the CS]

Parameter	Ivosidenib (n = 126)	Placebo (n = 61)
Age (years)		
Median (range)	61 (33 to 80)	63 (40 to 83)
Sex, n (%)		
Male	44 (35)	24 (39)
Female	82 (65)	37 (61)
ECOG PS score at baseline, n (%)		
0	50 (40)	19 (31)
1	75 (60)	41 (67)
2	0	1 (2)

3	1 (1)	0
IDH1 mutation, n (%)		
R132C	86 (68)	45 (74)
R132L	21 (17)	7 (11)
R132G	17 (14)	6 (10)
R132S	2 (2)	1 (2)
R132H	0	2 (3)
Cholangiocarcinoma subtype		
Intrahepatic	113 (90)	58 (95)
Extrahepatic/perihilar	5 (4)	1 (2)
Unknown	8 (6)	2 (3)
Extent of disease at screening		
Local/regional	9 (7)	5 (8)
Metastatic	117 (93)	56 (92)

Source: Abou-Alfa (2020)[17]

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IDH1, isocitrate dehydrogenase 1; PS, performance status

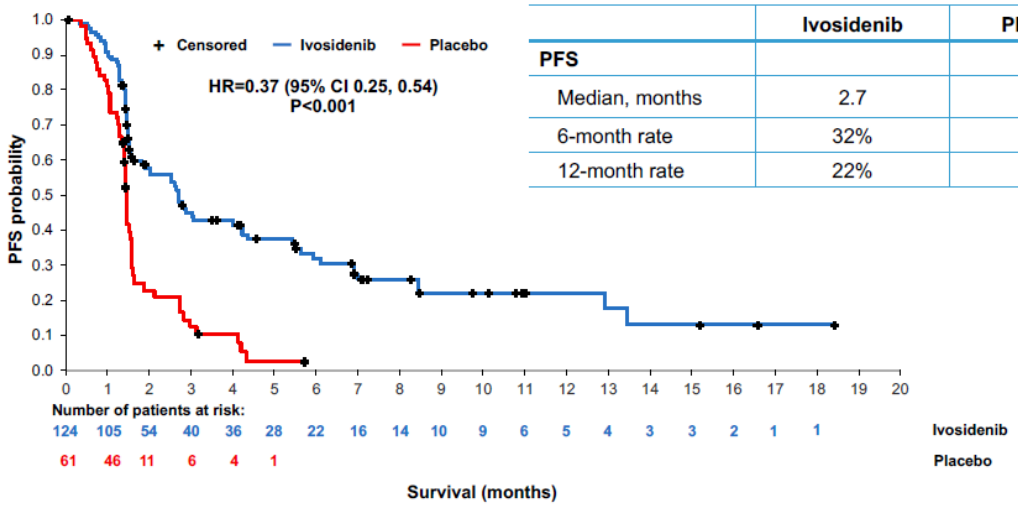
3.2.2 Primary and secondary efficacy endpoints

The outcome measures listed in the NICE final scope for this appraisal were: overall survival (OS), progression-free survival (PFS), response rates, adverse effects of treatment and health-related quality of life (QoL).

The PFS by Independent Radiology Centre (IRC) assessment was the primary outcome of the ClarIHDy study and was analysed based on the primary analysis data cut as of 31st January 2019, including 185 participants (ivosidenib, 124 participants; placebo, 61 participants). Secondary analysis for OS was based on a data cut-off date of 31st May 2020, including 187 participants (126 participants in the ivosidenib arm and 61 participants in the placebo arm.

Primary endpoint: PFS by IRC assessment

The primary endpoint of ClarIDHy was achieving PFS, defined as the time from date of randomization to date of first documented disease progression as assessed by the IRC per response evaluation criteria in solid tumours (RECIST) v1.1,[18] or date of death due to any cause. The median follow-up for PFS by IRC assessment was 6.9 months (interquartile range [IQR] 2.8, 10.9). A Kaplan-Meier plots is presented by the company in Document B, Figure 7 of the CS, reproduced as Figure 2 below. There was an improvement in PFS by IRC assessment for participants receiving ivosidenib compared with those receiving placebo (HR 0.37; 95% confidence interval [CI] 0.25, 0.54, p <0.001), with median PFS of 2.7 months (95% CI 1.6, 4.2) for ivosidenib compared with 1.4 months (95% CI 1.4, 1.6) for placebo. The PFS rate for ivosidenib was 32% (95% CI 23, 42) at 6 months and 22% (95% CI 13. 32) at 12 months. No patients in the placebo group were free from progression for 6 months or more. A summary of these outcomes is presented in Table 8.



	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE

Source: Abou-Alfa 2020[17]

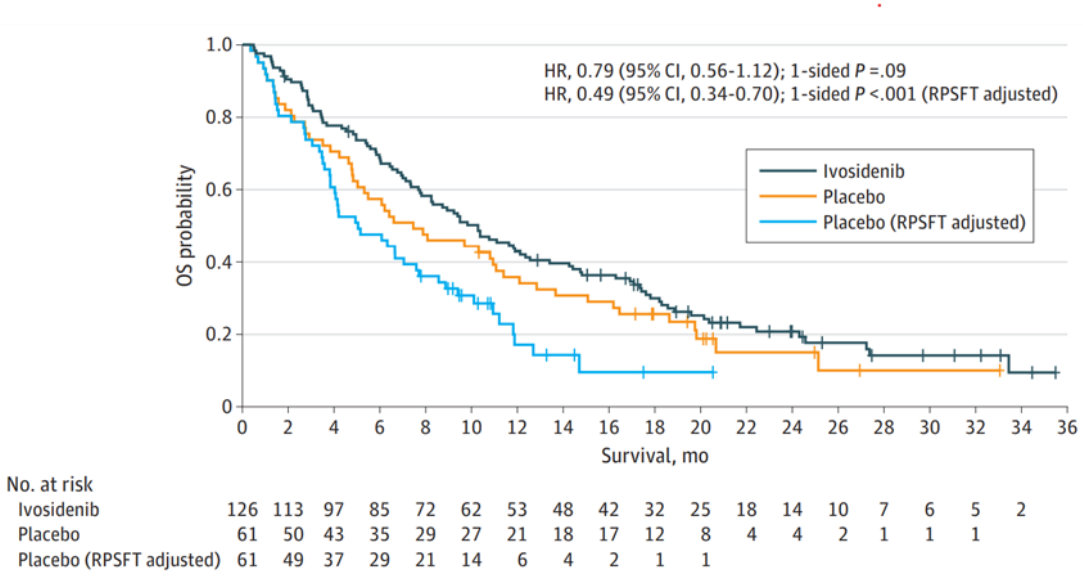
Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival.

Figure 2 ClarIDHy: ivosidenib vs. placebo – PFS (overall) (31 January 2019 data cut-off) [Reproduced from Figure 7, Document B of the CS]

Secondary endpoints: OS and objective response rate (ORR)

The secondary endpoints of ClarIDHy included overall survival (OS) and objective response rate (ORR). A summary of secondary outcomes is presented in Table 8.

- **Overall survival** (OS; defined as the time from date of randomisation to date of death)**:** Based on the secondary analysis data cut-off (31st May 2020), before adjusting for crossover the median OS was 10.3 months (95% CI 7.8, 12.4) in the ivosidenib group compared with 7.5 months (95% CI 4.8, 11.1) in the placebo group (HR 0.79, 95% CI 0.56, 1.12, p = 0.093). Forty-three of the 61 participants (70.5 %) in the placebo group crossed over to receive open-label ivosidenib. After adjusting for crossover using the RPSFT (rank preserving structural failure time model) method, the median OS in the placebo group was 5.1 months (95% CI 3.8, 7.6) compared with 10.3 months in the ivosidenib group (HR 0.49, 95% CI 0.34, 0.70, p < 0.0001). The 12-month OS rate for ivosidenib was 43% (95% CI 34%, 51%), compared with 36% (95% CI 24%, 48%) for placebo. A Kaplan-Meier plots is presented by the company in Document B, Figure 8 of the CS, reproduced as Figure 3 below.



Source: Zhu 2021[16]

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; RPSFT, rank-preserving structural failure time.

Figure 3 ClarIDHy: ivosidenib vs. placebo – OS (31 May 2020 data cut-off) [reproduced from Figure 8, Document B of the CS]

- **Objective response rate** (ORR; defined as the proportion of patients with a best overall response (BOR; defined as complete response [CR] or partial response [PR]) as assessed by the Investigator and by the IRC per RECIST v1.1.[18] Response outcome was analysed at the time of primary analysis (31 January 2019 data cut-off). The ORR as assessed by IRC was 2.4%, with three of 124 participants in the ivosidenib group achieving PR (3/124 [2.4%]). No participant in the placebo group achieved CR or PR. The treatment duration reported for the three patients achieving PR in the ivosidenib group was 11.0, 6.0 and 17.1 months, respectively. The duration of response (DOR) in these patients was 2.79, 2.73 and 11.07, respectively. Additionally, a BOR of stable disease (SD) was achieved in 50.8% of ivosidenib participants, compared with 27.9% of placebo participants before crossover. The ORR assessed by the investigator was akin to that obtained by the IRC assessment.

Table 8 Summary of clinical effectiveness [adapted from Figures 7 and 8 and Table 10, Document B of the CS]

Endpoint	**Outcome**	**Primary analysis data cut-off (31 January, 2019)**	
		Ivosidenib (n = 124)	**Placebo (n = 61)**
Progression-free survival (PFS) by IRC assessment	Median, months (95% CI)	2.7	1.4
	Rate at 6 months	32%	NE
	Rate at 12 months, % (95% CI)	22%	NE
	HR (95% CI; p-value)	0.37 (0.25, 0.54), p < 0.001	
ORR by IRC assessment	Confirmed BOR, n (%): PR	3 (2.4%)	0 (0%)
	SD	63 (50.8%)	17 (27.9%)
	PD	41 (33.3%)	35 (57.4%)
	UNK/NE	3 (2.4%)	1 (1.6%)
	Confirmed ORR (CR or PR), n (%)	3 (2.4%)	0 (0%)
	ORR Odds ratio (95% CI)	NE (0.29, NE)	
Endpoint	**Outcome**	**Secondary analysis data cut-off (31 May, 2020)**	
		Ivosidenib (n = 126)	**Placebo (n = 61)**
OS	Median, months (95% CI), unadjusted	10.3	7.5
	Rate at 6 months, % (95% CI)	69%	57%
	Rate at 12 months, % (95% CI)	43%	36%
	HR (95% CI, p-value), unadjusted	0.79 (0.56, 1.12), p = 0.093	

Endpoint	Outcome	Primary analysis data cut-off (31 January, 2019)	
		Ivosidenib (n = 124)	Placebo (n = 61)
	Median, months (95% CI), adjusted for crossover using RPSFT method	10.3	5.1
	HR (95% CI; p-value), adjusted for crossover using RPSFT method	0.49 (0.34, 0.70), p < 0.0001	

Abbreviation: CI, confidence interval; CR, complete response; IRC, independent radiology centre; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RPSFT, rank preserving structural failure time model; SD, stable disease; UNK, unknown;

Health-related quality of life (HRQoL)

HRQoL was reported using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire cholangiocarcinoma and gallbladder cancer module (EORTC QLQ-BIL21) and EQ-5D-5L. QoL analysis was generally limited by a small sample size and limited data beyond Cycle 2, Day 1, as participants tended to have short treatment duration.[16]

- **EORTC QLQ-C30:** At the time of secondary analysis (31st May 2020 data cut-off), EORTC QLQ-30 change scores from baseline were available for 67 (53%) of 126 participants in the ivosidenib group and 21 (34%) of 61 participants in the placebo group at Day 1 of Cycle 2 (C2D1), and 50 (40%) and 9 (15%), respectively, at Day 1 of Cycle 3 (C3D1).[16, 19] At C2D1, the EORTC QLQ-C30 physical functioning subscale showed a larger decline in the placebo group compared with the ivosidenib group with a least square mean difference in change from baseline for ivosidenib vs. placebo of 11.0 points (95% CI 4.23, 17.71; p = 0.001). This difference in physical functioning persisted at C3D1 (12.3 points, 95% CI 3.88, 20.76; p = 0.004). Ivosidenib was also favoured on the EORTC QLQ-C30 emotional functioning subscale at C2D1 (13.8 points, 95% CI 6.08, 21.43; p =< 0.001) and at C3D1 (18.8 points, 95% CI 8.82, 28.74; p =< 0.001).
- **EORTC QLQ-BIL21:** At the time of secondary analysis (31st May 2020 data cut-off), EORTC-BIL21 change scores from baseline were available for 65 (52%) of 126 participants in the ivosidenib group and 20 (33%) of 61 participants in the placebo group at C2D1, and 48 (38%) and 9 (15%) at C3D1.[16, 19] The CS focuses on the

tiredness symptoms subscale of EORTC QLQ-BIL21. At C2D1, the results showed that tiredness symptoms declined more slowly in the ivosidenib group compared with the placebo group (difference for ivosidenib vs. placebo of 13.2 points, 95% CI -22.67, -3.77; p = 0.006), although this difference did not reach statistical significance at C3D1 (3.9 points, 95% CI -16.20, 8.38; p = 0.532).

- **EQ-5D-5L:** Based on the January 31, 2019, data cut-off, 107 (86%) of 124 participants in the ivosidenib group and 51 (84%) of 61 participants in the placebo group completed the EQ-5D-5L baseline assessment. At Day 1 of Cycle 3, EQ-5D-5L data were available for 42 (34%) and 10 (16%) participants receiving ivosidenib and placebo, respectively (Figure 9, Document B of the CS).[8] The results showed that, at C3D1, higher proportions of participants receiving ivosidenib compared with placebo reported 'no' or 'slight' problems on the domains of mobility (ivosidenib: 81.0%, placebo: 60.0%), anxiety or depression (ivosidenib: 92.9%, placebo: 60.0%), and usual activities (ivosidenib: 76.2%, placebo: 70.0%).[8]

3.2.3 Subgroup analyses

The company conducted analyses of PFS and OS of the following subgroups: number of prior lines of therapy (1 vs ≥2); gender (male vs female); extent of disease at screening (locally advanced vs metastatic); CCA type (intrahepatic vs extrahepatic), ECOG at baseline (0 vs 1), regions (North America vs Europe vs Asia). Details of subgroup analyses of PFS and OS are presented in Figure 10 and Figure 11, respectively, in Section B.2.7 of the CS.

Results from the subgroup analyses show that achievement of PFS and OS was broadly consistent across most specified sub-groups, favouring ivosidenib. The results should be interpreted with caution due to small sample size and not accounting for crossover adjustment.

3.2.4 Adverse events

The company presents details of adverse events in the ClarIDHy trial at the time of the June 2021 database lock in Document B, Section B.2.10 of the CS. The safety analysis set (SAS) consisted of all patients who received at least one dose of the study drug: ivosidenib (n=123) and placebo (n=59). Median treatment duration was 2.8 months (range 0.1-45.1) in the

ivosidenib group and 1.6 months (range 0.0-6.9) in the placebo group. An overview of treatment-emergent adverse events (TEAEs) is presented as Table 9 below.

Table 9 Summary of TEAEs in ClarIDHy (SAS; 21 June 2021 database lock) [adapted from Table 6 of the ClarIDHy CSR, Second Addendum]

TEAEs, n (%)	Ivosidenib (n=123)	Placebo (n=59)	After crossover to ivosidenib (n=43)	Total ivosidenib (n=166)
Any TEAE	120 (97.6)	57 (96.6)	41 (95.3)	161 (97.0)
Any Grade ≥3 TEAE	63 (51.2)	22 (37.3)	26 (60.5)	89 (53.6)
Any treatment-related TEAE	81 (65.9)	23 (39.0)	23 (53.5)	104 (62.7)
Any serious TEAE	43 (35.0)	14 (23.7)	23 (53.5)	55 (33.1)
TEAE leading to study drug discontinuation	9 (7.3)	5 (8.5)	2 (4.7)	11 (6.6)
TEAE leading to study drug dose reduction	5 (4.1)	0	0	5 (3.0)
TEAE leading to death	6 (4.9)	0	2 (4.7)	8 (4.8)

Abbreviation: TEAE, treatment-emergent adverse event

Almost all participants experienced a TEAE with around one-third to two-thirds experiencing Grade ≥3 TEAEs and treatment-related TEAEs. Serious TEAEs were less common, occurring in around one-quarter to one-half of participants. Around 5% of participants receiving ivosidenib, including those who crossed over from placebo, experienced a TEAE leading to death. None were related to ivosidenib treatment, according to the investigator assessment.

The company presents a summary of the most common (≥15%) TEAEs at the June 2021 database lock as Document B, Table 17 of the CS, reproduced as Table 10 below.

Table 10 ClarIDHy: most common (≥ 15%) TEAEs (SAS; 21 June 2021 database lock) [reproduced from Table 17, Document B of the CS]

Adverse Event, n (%)	ivosidenib (n=123)	Placebo (n=59)	After Crossover to ivosidenib (n=43)	Total ivosidenib (n=166)
Any TEAE	120 (97.6)	57 (96.6)	41 (95.3)	161 (97.0)
Most common TEAE, n (%)				
Nausea	52 (42.3)	17 (28.8)	12 (27.9)	64 (38.6)
Diarrhoea	43 (35.0)	10 (16.9)	12 (27.9)	55 (33.1)
Fatigue	38 (30.9)	10 (16.9)	10 (23.3)	48 (28.9)
Abdominal pain	30 (24.4)	9 (15.3)	7 (16.3)	37 (22.3)
Cough	31 (25.2)	5 (8.5)	5 (11.6)	36 (21.7)
Decreased appetite	30 (24.4)	11 (18.6)	6 (14.0)	36 (21.7)
Vomiting	28 (22.8)	11 (18.6)	6 (14.0)	34 (20.5)
Ascites	28 (22.8)	9 (15.3)	5 (11.6)	33 (19.9)
Anaemia	23 (18.7)	3 (5.1)	8 (18.6)	31 (18.7)
oedema peripheral	17 (13.8)	6 (10.2)	9 (20.9)	26 (15.7)
Constipation	20 (16.3)	11 (18.6)	5 (11.6)	25 (15.1)

[1]Total ivosidenib group includes 43 patients initially assigned to placebo who had crossed over to ivosidenib upon radiographic disease progression.
Source: AG120-C-005 – CSR Addendum. Database lock: June 21, 2021,[19] Zhu et al. 2021.[16]
Abbreviation: n, number; TEAE, treatment-emergent adverse event.

The most common TEAEs reported by patients who received ivosidenib (including those who crossed over from placebo) were nausea (38.6%), diarrhoea (33.1%), fatigue (28.9%) and abdominal pain (22.3%). These TEAEs also occurred in over 15% of participants in the placebo group including those who crossed over to ivosidenib .

Table 8 of Document B presents a summary of Grade ≥3 TEAEs occurring in at least 5% of participants in any arm of ClarIDHy (CSR, Second Addendum) and is reproduced as Table 11 below. The company maintain that the reported toxicities are manageable in this patient group. *The EAG's clinical expert agrees with the company's assertion.*

Table 11 Summary of Most Common (≥5%) Grade 3 or Higher Treatment-Emergent Adverse Events by Preferred Term (SAS; 21 June 2021 database lock) [adapted from Table 8 of the ClarIDHy CSR, Second Addendum]

Preferred term, n (%)	Ivosidenib (n=123)	Placebo (n=59)	After crossover to ivosidenib (n=43)	Total ivosidenib (n=166)
Any Grade ≥3 TEAE	63 (51.2)	22 (37.3)	26 (60.5)	89 (53.6)
Ascites	11 (8.9)	4 (6.8)	4 (9.3)	15 (9.0)
Anaemia	9 (7.3)	0	4 (9.3)	13 (7.8)
Blood bilirubin increased	7 (5.7)	1 (1.7)	3 (7.0)	10 (6.0)
Hyponatraemia	7 (5.7)	6 (10.2)	1 (2.3)	8 (4.8)
Hypophosphataemia	4 (3.3)	3 (5.1)	2 (4.7)	6 (3.6)
Hypertension	2 (1.6)	1 (1.7)	3 (7.0)	5 (3.0)
Blood alkaline phosphatase increased	3 (2.4)	3 (5.1)	0	3 (1.8)

Source: Table 14.3.1.1, Table 14.3.1.6. Database lock date: 21 June 2021.[19]
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PD, progressive disease; PT, Preferred Term; TEAE, treatment-emergent adverse event.
Note: Safety Analysis Set was defined as all subjects who received at least one dose of study drug (ivosidenib or Placebo). 'After Crossover to ivosidenib' column is for the placebo subjects who crossed over to ivosidenib upon radiographic PD. 'Total ivosidenib' column includes all the subjects who have ever been dosed with ivosidenib. TEAEs presented in the summary tables include the AEs that begin or worsen on or after the start of study drug through 28 days after the last dose of study treatment. Most common TEAEs include TEAEs reported by ≥5% in any column. PTs are sorted in descending frequency by Total ivosidenib column. A subject with multiple occurrences of an AE under one treatment is counted only once in the PT for that treatment. Preferred Terms are coded from MedDRA Version 23.1. Percentages are calculated with the number of subjects in the Safety Analysis Set in each column as the denominator.

Treatment-emergent adverse events of Grade ≥3 reported in at least 5% of participants in all participants who received ivosidenib included ascites (9.0%), anaemia (7.8%) and blood bilirubin increased (6.0%). Incidence of these TEAEs was similar in placebo-group participants who crossed over to ivosidenib but lower in the placebo-only group, in which hyponatraemia was the most frequently reported TEAE (10.2% as compared to 4.8% of the total ivosidenib group).

One type of TEAE of special interest was reported in the CS: prolonged QTc ECG was experienced by 13/166 participants (7.8%) who received ivosidenib and 2/59 (3.4%) who received placebo.

In the 55 participants who received ivosidenib and experienced a serious TEAE, ascites, cholangitis, pneumonia and sepsis were most commonly reported, in four participants (2.4%) each.

Overall, the EAG clinical expert is satisfied that the adverse events reported in the CS are as expected from clinical use of ivosidenib in these patients and has no concerns.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company identified the ClarIDHy and ABC-06 trials as eligible for evidence synthesis in this context. Both trials are summarised in Document B, Section B.2.9 of the CS and ClarIDHy is described in Section 3.2.1 above. ABC-06 was a phase 3, randomised, open-label trial comparing folinic acid, fluorouracil and oxaliplatin chemotherapy (FOLFOX) plus active symptom control (referred to in the CS as mFOLFOX or FOLFOX. The EAG clinical expert notes that the doses described in the Lamarca 2020[20] publication are that of modified FOLFOX 6, also referred to as FOLFOX) with active symptom control alone in adults with locally advanced or metastatic biliary tract cancer and progression to previous first-line cisplatin and gemcitabine chemotherapy. The primary outcome was overall survival. The trial was conducted in 20 sites in the UK between March 2014 and January 2018 and randomised a total of 162 patients to ASC plus FOLFOX (n=81) or ASC alone (n=81), of which the primary tumour sites were intrahepatic CCA in 72/162 (44.4%; 34 in FOLFOX group and 38 in ASC group) or extrahepatic CCA in 45/162 (27.8%; 26 in FOLFOX group and 19 in ASC group). The proportion of participants with IDH1 mutations was not reported. Summaries of baseline participant and disease characteristics of ClarIDHy and ABC-06 are presented in Tables 12 and 13 below.

Table 12 Baseline participant and disease characteristics of ClarIDHy and ABC-06 [adapted from Tables 9, 12-14, Document B of the CS]

	ClarIDHy		ABC-06	
	Ivosidenib (n=126)	**Placebo (n=61)**	**FOLFOX + ASC (n=81)**	**ASC (n=81)**
Participant characteristics				
Sex, n (%)				
Male	44 (34.9)	24 (39.3)	43 (53.1)	37 (45.7)
Female	82 (65.1)	37 (60.7)	38 (46.9)	44 (54.3)
Age, years, median (range)	61 (33-80)	63 (40-83)	65 (26-84)	65 (26-81)
ECOG PS score at baseline, n (%)				
0	50 (39.7)	19 (31.1)	25 (30.9)	28 (34.6)
1	75 (59.5)	41 (67.2)	55 (67.9)	52 (64.2)
2	0	1 (1.6)	0	0
3	1 (<1)	0	0	0
Missing	0	0	1 (1.2)	1 (1.2)
Disease characteristics				
CCA subtype, n (%)				
Intrahepatic	113 (89.7)	58 (95.1)	34 (42.0)	38 (46.9)
Extrahepatic/perihilar	5 (4.0)	1 (1.6)	26 (32.1)	19 (23.5)
Unknown	8 (6.3)	2 (3.3)	0	0
Not CCA	0	0	21 (25.9)	24 (29.6)
Extent of disease at screening, n (%)				
Local/regional	9 (7.1)	5 (8.2)	14 (17.3)	15 (18.5)
Metastatic	117 (92.9)	56 (91.8)	67 (82.7)	66 (81.5)
Prior lines of therapy				
1	66 (52.4)	33 (54.1)	81 (100)	81 (100)
2	60 (47.6)	28 (45.9)	0	0

Abbreviation: ASC, active symptom control; CCA, cholangiocarcinoma; FOLFOX, folinic acid, fluorouracil and oxaliplatin chemotherapy

Table 13 summarises the most common adverse events in the ABC-06 trial. Adverse events were experienced by 77 of the 81 participants in the active symptom control group and 80 out of the 81 participants in the FOLFOX + ASC group. The most observed AE in the FOLFOX + ASC group were fatigue (90%), neuropathy (69%), pain (62%), anorexia (59%) and nausea (51%).

Table 13 ABC-06: most common (≥ 15%) all grade AEs and/or Chemotherapy related events [reproduced from Table 17b of the Company's Clarification Response]

n (%)	ASC (n = 81)	FOLFOX+ ASC (n= 81)	FOLFOX + ASC (N=81) Chemotherapy related events
Any AE /CRAE	77 (95)	80 (99)	68 (84)
Neuropathy	8 (10)	56 (69)	53 (65)
Fatigue	53 (65)	73 (90)	56 (69)
Nausea	33 (41)	41(51)	31 (38)
Oral Mucositis	4 (5)	30 (37)	29 (36)
Anorexia	37 (46)	48 (59)	26 (32)
Diarrhoea	14 (17)	29 (36)	24 (30)
Thromobocytopaenia	1 (1)	18 (22)	18 (22)
Dysgeusia	12 (15)	23 (28)	16 (20)
Vomiting	20 (25)	23 (28)	16 (20)
Constipation	29 (36)	37 (46)	13 (16)
Neutropenia	1 (1)	23 (28)	22 (27)
Infection	22 (27)	34 (42)	18 (22)
Anaemia	6 (7)	12 (15)	11 (14)
Dry Mouth	11 (14)	25 (26)	
Pain	56 (69)	50 (62)	
Oedema	11(14)	18 (22)	
Dyspnoea	7 (9)	14 (17)	
Biliary Events	18 (22)	19 (23)	
Hypertension	5 (6)	14 (17)	
Ascites	2 (2)	12 (15)	

Abbreviation: AE, adverse events; CRAE, chemotherapy related adverse events

3.4 Critique of the indirect comparison and/or multiple treatment comparison

As progression-free survival was not reported in the control arm of ABC-06, the only indirect comparison made was of overall survival. As the comparison was only between the ClarIDHy and ABC-06 trials the Bucher method was used and this is considered appropriate by the EAG.

In the ClarIDHy study, 43 out of the 61 participants in the placebo group crossed over to receive ivosidenib upon disease progression and the rank-preserving structural failure time

model (RPSFT) was used to adjust for crossover. The company also considered using the inverse probability of censoring weighting as the crossover adjustment.

The unadjusted and adjusted effect sizes are presented in Table 14.

Table 14 Overall survival effect sizes (ivosidenib vs placebo) [reproduced from Figure 8 and Table 16, Document B of the CS and Table 2 of the company's clarification response]

Method	HR (95% CI)
unadjusted	0.79 (0.56,1.12)
RPSFT adjusted	0.49 (0.34,0.70)
IPCW adjusted	0.74 (0.31,1.56)
unadjusted subgroup	0.87 (0.54,1.40)
RPSFT adjusted subgroup	0.40 (0.23,0.68)

Due to there being 70.5% of participants who crossed over, *the EAG agrees with the company that the RPSFT adjustment is the more appropriate method to use*. The IPCW censors participants at crossover and reweights the participants who do not crossover. This will result in large weights being applied to the participants remaining on placebo and explains why the effect size is less favourable towards ivosidenib. The RPSFT assumes a common treatment effect in that participants will receive the same benefit from receiving a treatment regardless of when they start. *The EAG clinical expert thinks this assumption is reasonable.*

There were differences between the ClarIDHy and ABC-06 populations and specifically ABC-06 was restricted to patients with one prior line of chemotherapy while ClarIDHy allowed for more than one prior line. To take account of this it appears from the company's clarification response that a subset of the ClarIDHy population (65 ivosidenib and 32 placebo participants) was used to obtain the estimated overall survival used to compare ivosidenib to mFOLFOX via the Bucher method. The EAG notes that these numbers are inconsistent with those shown in Figure 11, Document B (70 and 36 participants, respectively, in the subgroup with 1 prior line of therapy). The EAG also highlights that figure 11, Document B does not

show a difference between prior lines of therapy in the effect of ivosidenib and this questions whether it was necessary to obtain the estimate from the subgroup.

It is the opinion of the EAG that this process of using a subgroup of ClarIDHy participants should have been made clearer and explained more thoroughly. It would have been useful to see the baseline characteristics and KM plots for this subgroup. It should have been made clear if the crossover adjustment was done on the whole population and the subgroup was subsequently selected or if the subgroup was selected first and the crossover adjustment was then made on the subgroup. The method used is probably justified, but it needed to be made considerably clearer.

The EAG believes that in the absence of any method to make a formal comparison on progression-free survival, the company's approach of naïve comparison using the method suggested by Guyot et al. is appropriate.[21]

3.5 Additional work on clinical effectiveness undertaken by the EAG

The EAG were able to replicate the Bucher method calculations to compare overall survival between ivosidenib and FOLFOX+ASC.

3.6 Conclusions of the clinical effectiveness section

The EAG have reviewed the reported progression free and overall survival presented in the company submission for ivosidenib compared to placebo from the ClarIDHy trial and the reported overall survival of FOLFOX compared to ASC from the ABC-06 trial. All these analyses show the two respective treatments as superior to standard care or control and the EAG agrees with the company's statement that the ClarIDHy trial shows a benefit to patients from receiving ivosidenib.

In addition, the EAG has reviewed the safety profiles of both ivosidenib and FOLFOX. Ivosidenib and FOLFOX show 97.6% and 99% of participants, respectively, experiencing a treatment-emergent adverse event though adverse events of Grade 3 and above are less common. It is the opinion of the EAG that the safety profile of ivosidenib is favourable in comparison to FOLFOX.

The EAG broadly agrees that the indirect treatment comparison shows a greater benefit on overall survival from ivosidenib compared to FOLFOX. Using the RPSFTM as the adjustment for crossover is appropriate and as there are only two studies. The EAG also believes the Bucher comparison to be the correct method. The EAG, however, wishes to stress that while it may be justified to align the ClarIDHy and ABC-06 populations, more information should have been provided on the subgroup from the ClarIDHy study used in the ITC. It would have been useful to see the baseline characteristics and KM curves for the subgroup and establish where in the process the crossover adjustment was made.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company started by searching for published economic evaluations, cost studies, and health care resource use studies related to interventions of relevance to the decision problem in unresectable advanced or metastatic CCA. Due to the lack of data, the search scope was expanded to include all interventions (except surgery) for advanced CCA and advanced or metastatic BTC. This broadened inclusion criterion was used for the final screening. The two-step literature search conducted by the company identified 30 studies, eleven of which were economic evaluations. However, only one of the economic evaluations was deemed relevant to the current appraisal (Table 15); this being the partitioned survival analysis used in the NICE STA of Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement (TA722).[13] Details of the systematic literature review of economic evidence was provided in appendix D of the company submission.

Since CCA patients with IDH1 mutation currently have no option other than unlicensed cytotoxic chemotherapy, the lack of economic evaluations of direct relevance to the decision problem is expected. The EAG is satisfied with the company's search strategy and approach and is reasonably confident that the company did not miss any relevant published articles. However, according to the search strategy described in the main submission document and Appendix D of the company submission, the company does not appear to have undertaken searches of the unpublished literature, which means we cannot rule out the possibility that relevant unpublished studies have been missed. The EAG is broadly supportive of the company's use of the model from TA722 to help inform assumptions in their de novo economic model for the current appraisal but acknowledge the company's point regarding population differences.

Table 15: Summary list of published cost-effectiveness studies (Source: Table 18, Document B of CS)

Study	Year	Summary of model	Patient population (average age in years)	LYs / QALYs	Costs (£)	ICER (per QALY gained)
NICE TA722[13]	2021	Cohort-level PartSA model, informed using independently modelled OS, PFS, and ToT curves	Adult patients with previously treated, unresectable, locally advanced, or metastatic CCA with FGFR2 fusions/rearrangements (55.3 years; SD = 12.02)	• ASC: 0.51 / NR • mFOLFOX: 0.60 / NR • Pemigatinib: 2.34 / NR	• ASC: NR • mFOLFOX: NR • Pemigatinib: NR	• mFOLFOX extendedly dominated by pemigatinib • Pemigatinib versus ASC: £61,084 • Pemigatinib versus mFOLFOX: £57,315

Abbreviations: CCA, cholangiocarcinoma; ICER, incremental cost-effectiveness ratio; LY, life years; NICE, National Institute for Health and Care Excellence; NR, not reported; OS, overall survival; PartSA, partitioned survival analysis; PFS, progression-free survival; QALYs, quality-adjusted life years; SD, standard deviation; TA, technology appraisal; ToT, time on treatment.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 16 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Aligns with the reference case. Focussed on direct health effects for patients.
Perspective on costs	NHS and PSS	Aligns with reference case
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Aligns with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Aligns with reference case
Synthesis of evidence on health effects	Based on systematic review	Aligns with reference case – but uncertainty exists with respect to the extrapolation of certain efficacy inputs and an indirect treatment comparison with mFOLFOX
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the	Aligns with reference case, but uncertainty exists with respect to the chosen statistical model for

	preferred measure of health-related quality of life in adults.	incorporating health state utility values in the economic model.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Aligns with reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Aligns with reference case (EQ-5D-5L responses mapped to EQ-5D-3L values using the NICE DSU preferred algorithm).[22]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Aligns with reference case
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	Aligns with reference case, but uncertainty exists with respect to the estimation of certain elements of resource use and cost in the model.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Aligns with reference case
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company developed a de novo economic model. It is a partitioned survival model with three discrete health states: progression free, progressed disease, and death. The pre progression and progressed disease health states are further divided into on and off treatment substates using time on treatment (ToT) data for ivosidenib and mFOLFOX. The model was developed in Microsoft Excel with a one-week cycle length, reducing the importance of a half cycle correction which has been omitted. Section B.3.2.2 of the company submission provides a more comprehensive description of the model structure.

The health states in the model reflects the outcomes measured within the ClarIDHy trial. The health state occupancy or distribution of patients across health states is determined in the model based on progression free and overall survival curves derived from the ClarIDHy and ABC-06 trials.[16, 17, 20]

The EAG agrees that the structure of the model is suitable for the decision problem. The layout of is clear and transparent. The modelling approach is consistent with the previous

NICE appraisal in CCA. It is worth noting that the partitioned survival structure does not explicitly capture transitions to progressive disease or the structural relationship between progression and mortality. This necessitates certain assumptions when modelling subsequent treatment in the progressive disease state, which the company included in several scenario analyses in response to the clarification letter.

4.2.3 Population

Patients with locally advanced or metastatic CCA with an IDH1 mutation who have undergone at least one prior line of systemic therapy are the target population in the company's economic evaluation. The population is in line with the anticipated marketing authorization for ivosidenib and the population studied in the ClarIDHy trial.

The EAG has no concern with the proposed target population. It may be noted, however, that its identification requires IDH1 gene testing. The company argue that this is routinely available in NHS England. The relevance of including costs for this in the model is discussed further in section 4.2.8 below.

4.2.4 Interventions and comparators

The intervention is ivosidenib, as described in section.1.2 and B.3.2.3.1 of the company submission. The dose is 500mg once daily (2 x 250mg tablets) to be taken orally.

The company noted in their submission that there is currently no clearly established standard of care for patients with CCA with an IDH1 mutation. Whilst pemigatinib was recommended in NICE TA722[13] as an option for patients with locally advanced or metastatic CCA with an FGFR2 fusion or rearrangement, the company note that pemigatinib is not a relevant treatment option for patients considered in their submission since FGFR2 fusion/rearmaments and IDH1 mutations are mutually exclusive. mFOLFOX, based on evidence from the ABC-06 trial study, and BSC are the comparators included in the company's submission.

The EAG agrees with the comparators included in the company's economic evaluation, and these are consistent with the final scope issued by NICE. The EAG's clinical expert also corroborated the choice of comparators.

4.2.5 Perspective, time horizon and discounting

The perspectives used in the company's economic model are the NHS and personal social service (PSS) for costs, and direct health effects for patients for outcomes.

The company argue that 20 years is sufficient for representing a lifetime horizon in the model as more than 99% of the cohort experience death across treatment arms by 20 years.

The company apply a 3.5% discounting rate for both costs and health benefits.

The EAG is satisfied that the perspective and discounting method used by the company are in line with the NICE reference case. The EAG also concurs that the time horizon used in the economic model is long enough to capture all relevant differences in costs and outcomes between treatments.

4.2.6 Treatment effectiveness and extrapolation

The clinical data used for Ivosidenib and BSC care in the company's economic model are obtained directly from the ClarIDHy study, using the May 2020 data cut for OS and the January 2019 data cut for PFS.[16, 17] Overall survival in the BSC arm of the model is informed by Kaplan Meier data from the placebo arm from ClarIDHy, adjusted for crossover to ivosidenib using the rank preserving structural failure time (RPSFT) approach (see section 3.3.3.2 of the company submission). Median OS was 10.3 months and 5.1 months for the ivosidenib and placebo arms (after crossover adjustment), respectively. Median PFS was 2.7 months for the ivosidenib arm and 1.4 months for the placebo arm. Overall survival for mFOLFOX was derived by applying a hazard ratio from a Bucher indirect treatment comparison (ITC). This relied on OS hazard ratios for ivosidenib versus placebo, and mFOLFOX versus active symptom control from the ClarIDHy[16] and the ABC-06 trials,[20] respectively. This assumes that the placebo arm of the ClarIDHy trial and the active symptom control (ASC) arm of the ABC-06 trial can be considered a common comparator. Since there was no PFS data reported for the active symptom control arm of the ABC-06 trial, an ITC was not possible for this outcome and so the modelling of PFS for mFOLFOX relied on a naïve comparison.

The company also refer to a June 2021 final data lock in their submission but clarified that this was for treatment exposure and that no further PFS or OS data were available beyond

their respective pre-planned final analysis data cuts. The June 2021 data cut was used to inform adverse event rates and time on treatment for ivosidenib.

The summary of clinical data used in the model is provided in Table 20 of the company submission (document B), reproduced as Table 17 below.

Table 17: Summary of clinical data sources used in the model (Source: Table 20, Document B of CS)

Component	Application within the model	Source(s) for ivosidenib	Source(s) for BSC	Source(s) for mFOLFOX
Baseline characteristics	Used to estimate age- and sex-matched general population mortality and utility values, and used in weight-based dosing calculations	ClarIDHy (baseline patient characteristics of the modelled cohort are not treatment specific)		
OS	Parametric survival curves to estimate lifetime OS outcomes and determine health state occupancy	ClarIDHy PLD	ClarIDHy PLD (placebo)	ABC-06 (Bucher comparison)
PFS	Parametric survival curves to estimate lifetime PFS outcomes and determine health state occupancy	ClarIDHy PLD	ClarIDHy PLD (placebo)	ABC-06 (naïve comparison [base case] and exploratory RMST analysis [scenario analysis])
ToT	Parametric survival curves to estimate lifetime ToT outcomes and capture cost and HRQoL consequences	ClarIDHy PLD	N/A	ABC-06 (and necessary assumptions in the absence of reported KM data)
AEs	Inform the proportion of patients who incur AE management costs and utility decrements	ClarIDHy PLD	N/A	ABC-06

Abbreviations: AE, adverse event; BSC, best supportive care; HRQoL, health-related quality of life; KM, Kaplan-Meier; N/A, not applicable; OS, overall survival; PFS, progression-free survival. PLD, patient-level data; RMST, restricted mean survival time; ToT, time on treatment.

The company extrapolate the OS, PFS and time on treatment (ToT) data beyond the trial follow-up period to estimate outcomes over the lifetime of patients. For this, six standard parametric survival models were fitted for each outcome, following NICE Decision Support Unit (DSU) guidance.[23] The visual fit of the parametric curves to the Kaplan Meier (KM) data, the statistical goodness of fit (AIC and BIC), and clinical plausibility of extrapolations

based on clinical expert opinion was taken in to consideration to select from the six fitted models for each outcome.

OS Ivosidenib

From the six standard parametric curves fitted to the ClarIDHy trial data, the company selected the log normal curve for their base case analysis. The exponential and log logistic curves were tested in scenario analysis. As shown in Figures 14 and 15 of the company's main submission (Document B), all six curves exhibit a reasonable visual fit to the trial data but start to diverge in the tail of the Kaplan Meier curve. The AIC and BIC estimates are presented in Table 18 below. Of three NHS clinical experts interviewed by the company, the company noted that one found it challenging to comment on the long-term plausibility of different curves in the absence of long-term data, one was in favour of the log-normal curve but also indicated this was difficult to ascertain, and a third concluded that none of the curves appear to be clinically implausible.

Table 18: Ivosidenib OS, survival estimates and statistical fit (Source: Table 22, Document B of CS)

Model	Median OS	AIC	BIC	OS landmarks (years)				
	Months			1	2	5	10	20
KM	10.28	-	-	42.8%	20.7%	-	-	-
Exponential	10.35	248.10	**250.93**	45.3%	20.5%	1.9%	0.0%	0.0%
Generalized gamma	9.89	247.13	255.64	43.7%	20.3%	3.6%	0.5%	0.0%
Gompertz	10.58	250.05	255.72	45.7%	20.3%	1.5%	0.0%	0.0%
Log-logistic	9.89	246.59	252.27	43.0%	20.9%	6.2%	2.3%	0.8%
Log-normal	9.66	**246.19**	251.86	42.6%	21.5%	5.6%	1.4%	0.3%
Weibull	10.81	248.69	254.37	46.5%	19.2%	1.1%	0.0%	0.0%

Abbreviations: AIC; Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan-Meier; OS, overall survival. Note: Bold text indicates lowest AIC/BIC.

Given that the three NHS experts were unsure of which specific curve to select, the visual fit was similar for each of the six curves, and the statistical goodness of fits fell within a narrow range (table 18 above), care is required when selecting the OS curve for ivosidenib. For example, selection of the exponential curve (with the lowest BIC) or the Weibull curve instead of the log-normal (which was used in the base case), increases the ICER by almost 30

and 36 percent respectively. The company selected the second most optimistic (log-normal). They did, however, also assess the more pessimistic exponential curve as a scenario analysis. The EAG are of the opinion that the log-normal and log-logistic curves may provide a slightly less satisfactory visual fit to the tail of the Kaplan Meier data than some of the alternatives. The generalised gamma perhaps demonstrates a better visual fit and provides a middle ground in terms of the extrapolated survival landmarks.

OS BSC

Similarly, six standard parametric curves were fitted to the OS data from the placebo arm of the ClarIDHy trial. Figures 16 and 17 in the company submission (document B) show the Kaplan Meier curve (after adjusting for crossover) and the six fitted parametric curves. Visually, all the six curves appear to have an acceptable fit to the trial data. The AIC/BIC and the extrapolated proportion of patients alive at different survival landmarks (in years) are presented below (Table 19). The company selected the Weibull curve for the base case and Gompertz curve for their scenario analysis. The company noted that the curve selection was guided by clinical expert opinion (very few patients expected to be alive at 2 years and close to 0% at 5 years).

Table 19: BSC OS (RPSFT crossover adjusted), survival estimates and statistical fit (Source: Table 22, Document B of CS)

Model	Median OS	AIC	BIC	OS landmarks (years)				
	Months			1	2	5	10	20
KM	5.05	-	-	17.1%	-	-	-	
Exponential	5.29	59.45	**61.56**	22.2%	4.9%	0.1%	0.0%	0.0%
Generalized gamma	5.29	59.81	66.14	21.4%	6.6%	0.6%	0.0%	0.0%
Gompertz	5.52	61.31	65.54	21.6%	3.6%	0.0%	0.0%	0.0%
Log-logistic	5.29	58.78	63.00	21.6%	8.5%	2.1%	0.7%	0.2%
Log-normal	5.06	**58.00**	62.22	22.1%	8.0%	1.2%	0.2%	0.0%
Weibull	5.75	60.13	64.35	20.4%	2.9%	0.0%	0.0%	0.0%

Abbreviations: AIC; Akaike information criterion; BIC, Bayesian information criterion; BSC, best supportive care; OS, overall survival; RPSFT, rank preserving structural failure time.

Note: Bold text indicates lowest AIC/BIC.

The company noted that their selection of the Weibull curve for OS on BSC was based on clinical long-term plausibility. Based on their discussions with clinical specialists (Appendix

N of the company submission), they were advised that close to 0% of patients receiving BSC would be expected to be alive at 5 years. The Weibull curve predicts that 2.9% and 0.0% of patients are alive at 2 and 5 years, respectively. The EAG agrees that the most optimistic curves (log-logistic, log-normal and generalized gamma) should be excluded from the selection. However, based on statistical and visual fit, and clinical plausibility of extrapolations, the exponential and Gompertz curves provide valid options. According to table 19 (above), the exponential curve has the lowest BIC and projects only 0.1% of patients alive at 5 years. The EAG acknowledge that the company have explored the use of these more optimistic BSC extrapolations in scenario analysis, and they have limited impact on the ICER given the maturity of the OS data for BSC.

OS mFOLFOX

The company utilised a Bucher ITC, treating the placebo arm of the ClarIDHy trial and ASC arm from the ABC-06 trial as a common comparator, to compare the OS between ivosidenib and mFOLFOX. As the company note, the Bucher analysis assumes that the trials included in the indirect treatment comparison are comparable in terms of study population, study design, outcome measurements, and the distribution of treatment effect modifiers; and that there is no 'closed loop' of evidence that may introduce inconsistencies in effect measures. The outcome of the company's Bucher analysis is presented below (Table 20). Section B.3.3.3.3 of the company submission contains more description.

Table 20: Results of the Bucher analysis for OS, crossover adjusted (Source: Table 16 and 24, Document B of CS)

Analysis	HR	95% CI
Unadjusted		
ClarIDHy (ivosidenib vs placebo)[16, 17]	[redacted]	[redacted]
ABC-06 (FOLFOX + ASC vs ASC)[20]	[redacted]	[redacted]
Ivosidenib vs FOLFOX +ASC	[redacted]	[redacted]
Crossover adjustment		
ClarIDHy (ivosidenib vs Placebo)[16, 17]	[redacted]	[redacted]
ABC-06 (FOLFOX + ASC vs ASC)[20]	[redacted]	[redacted]
Ivosidenib vs FOLFOX +ASC	[redacted]	[redacted]

Abbreviations: ASC, Active symptom control; CI, Confidence interval; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HR, Hazard ratio; OS, Overall survival.

It was initially unclear to the EAG why the unadjusted and adjusted hazard ratios for ivosidenib versus placebo (BSC) employed in the company's Bucher analysis were different to those reported for main clinical effectiveness results; [redacted] and [redacted], respectively compared to 0.79 (95% CI: 0.56, 1.12) and 0.49 (95% CI: 0.34, 0.7), respectively. The company's original submission had no explanation of this but following a clarification question, the company explained that the Bucher ITC had used data from a subgroup of ClarIDHy to better align with the population included in the ABC-06 trial. The company noted that whilst ClarIDHy included patients with more than one line of prior therapy, the ABC-06 trial inclusion criteria only allowed patients with one prior line of chemotherapy. To address between-study heterogeneity in the eligibility criteria, the company explained that the Bucher ITC had used data for a ClarIDHy subgroup derived as outlined in Table 21.

Table 21. Derivation of ClarIDHy subgroup used for the indirect comparison with mFOLFOX (Source: company response to the clarification letter, QB6)

	Ivosidenib (n)	Placebo (n)
Original sample size	126	61
Per protocol population	124	61
1 prior LOT	66	33
ECOG PS 0-1	65	32

IVO, ivosidenib; PBO, placebo; LOT, line of therapy.

A Cox model in this restricted subgroup generated the HRs for ivosidenib versus placebo that were employed in the Bucher ITC (Table 20 above).

Although the company acknowledge the presence of heterogeneity between the ClarIDHy and ABC-06 trials and discussed the prognostic impact of one of these differences (IHD1 mutation), the original submission did not discuss the expected direction of any potential bias resulting from other population differences and baseline patient characteristics. This was asked for at the clarification stage. The company argued in their response that the impact of any potential bias due to differences are not exclusively in one direction, and on balance, there is no clear evidence that the results of the comparison would favour one treatment over the other (see company response to the clarification letter, QB1 for further details). It was

somewhat reassuring to note that, except for ampulla tumours, OS and PFS were similar across tumour sites in the wider BTC population included in ABC-06, and that OS for ASC was well aligned with the OS for the placebo arm of ClarIDHy after adjustment for crossover. Based on this response, the EAG accept that the extent and direction of any bias arising from between study heterogeneity is unclear.

Perhaps in contrast to the above response, it did become clear at the clarification stage that the company had used a restricted subgroup of patients from ClarIDHy (Table 21) in their Bucher ITC; those who received study treatment as per protocol, had exposure to only one prior line of therapy, and had an ECOG of 0 or 1. Based on clinical expert advice, the EAG accept the company's reasoning for removing those with two prior lines of therapy and those with ECOG score >1. However, the company have not presented strong evidence that these are treatment effect modifiers for ivosidenib which need to be aligned for comparability. Furthermore, the EAG are less clear on the justification for focussing on the per protocol population of ClarIDHy; the HR from the ABC-06 trial is based on an ITT analysis. In general, there is a lack of transparency in the reporting of the subgroup analysis that has fed through into the Bucher ITC. Since it is informing such a key input in the economic model, the EAG would expect a greater level of justification and detailed reporting of the analysis. For instance, the number with one prior line of therapy reported in table 21 above does not appear to be consistent with the number reported in Figure 11 of the company submission (document B).

PFS Ivosidenib

For extrapolation of PFS, the company selected the log normal curve for their base case based on statistical goodness of fit and clinical plausibility of the extrapolation. The log-logistic and generalized gamma curves were tested in scenario analysis. Based on AIC and BIC, the generalised gamma provided the best statistical fit to the observed PFS data. However, the company noted that it, along with the Gompertz curve, provided implausibly high long-term survival projections that crossed the modelled OS curve. The company noted from their interviews with clinical experts, that 1-3% was a plausible estimate of 2-year PFS. Details are provided in section B.3.3.4.1 of the company submission document.

PFS BSC

The company selected a Weibull curve in their base case and tested the log logistic curve in a scenario analysis. Given the maturity of the Kaplan Meier PFS data for BSC, only small differences exist between the fitted survival projections. Section B.3.3.4.2 of the company submission paper has a detailed description.

PFS mFOLFOX

Since no PFS data were available for the active symptom control group of the ABC-06 trial, the company conducted a naive comparison using unadjusted PFS data for mFOLFOX in their base case. They extracted data points from the published Kaplan Meier curve and used the published algorithm from Guyot et al. to reconstruct pseudo individual patient survival and censoring times.[21] They then fitted parametric models to the reconstructed data. The log-normal curve, which had the lowest AIC and BIC out of the six standard parametric curves fitted, was chosen for the base case. Section B.3.3.4.3 of the company submission provides more detail, including the description of a scenario analysis in which PFS for mFOLFOX is estimated by applying adjustment hazard ratios versus the selected OS curve for mFOLFOX.

The EAG has no major concerns regarding the PFS extrapolations made by the company. However, the EAG would note that the company's base case projection of two-year PFS for ivosidenib is towards the upper end of what one of their clinical experts felt was plausible (1-3%). Yet, the company have only tested more optimistic curves in their scenario analysis and have ignored the Weibull and exponential curves which satisfy this range of clinical plausibility. Therefore, the EAG suggest that these alterative curves should also be explored in scenario analysis.

Time on treatment (ToT) ivosidenib

To extrapolate ToT for Ivosidenib, six parametric curves were fitted to the ClarIDHy trial data (cut off June 2021). Considering statical goodness of fit, the log normal curve was selected for the base case. [redacted].
The company noted that treatment beyond progression is unlikely to occur in NHS practice. Therefore, in the model base case the ivosidenib ToT curve was capped by the PFS curve. Section B. 3.3.5.1 of the company submission has further details.

The EAG has some concerns regarding the company's decision to cap ivosidenib ToT with PFS. It is apparent that some participants in ClarIDHy did receive treatment beyond

progression (Figure 4) and this is may have influenced the observed OS of patients. Whilst two of three clinical experts consulted by the company said it was reasonable to stop treatment on progression, with one expert stating it was now "standard practice", the other expert noted that discontinuing treatment may depend on the type of advancement and the reasons why there would be a perception of continuing benefit (Company submission, appendix N). The expert added that it can be challenging to accurately determine progression from a radiological scan or to compare to baseline in some circumstances; in these situations, treatment may continue past progression. The EAGs clinical expert corroborated this view. Given the above, it is possible that some patients may be treated beyond progression in NHS practice, and they may potentially derive benefit from it. The EAG is of the opinion that mature ToT data exists from the ClarIDHy trial, and that it should be used for consistency with the OS data applied in the model. Further, the chosen PFS extrapolation (Figure 4) tends to underestimate PFS in the tail of Kaplan Meier data, which may further artificially reduce treatment costs if used to cap ToT.

Figure 4 Kaplan Meir curves and preferred parametric extrapolations of PFS and ToT for ivosidenib (adapted from the company model)

TOT mFOLFOX

Noting the absence of reported ToT data for mFOLFOX, the company didn't explore parametric survival curves for ToT extrapolation. The ToT for mFOLFOX was instead assumed to follow PFS up to the maximum number of treatment cycles.

The EAG acknowledge the lack of Kaplan Meier data for ToT for mFOLFOX. However, using PFS to approximate TOT will neglect the percentage of patients that discontinue treatment before progression due to adverse events, treatment intolerance or patient or physician choice. This may increase costs in the mFOLFOX arm above what would be expected in routine practice, reducing the ICER in favour of ivosidenib. In the report of the ABC-06 trial of FOLFOX in BTC, it is noted that a substantial proportion of patients discontinued treatment early for reasons other than progression, and that the median number of cycles was 5 (IQR:2-6).[20] This is substantially lower than the median number of cycles predicted by the mFOLFOX PFS curve used in the model. Given these concerns, the EAG suggest aligning mFOLFOX ToT with the median number of cycles observed in the ABC-06 trial, using an exponential distribution. The company model in fact provides the functionality to do this, and the company explored the impact of this in their scenario analysis.

4.2.7 Health related quality of life

For the base case the company derived the utility values from the ClarIDHy trial EQ-5D data to inform the economic model. Consistent with the NICE reference case, the EQ-5D-5L data was converted to a EQ-5D-3L score using the NICE preferred mapping approach reported by Hernandez-Alva et al.[24] The company fitted a Mixed Model for Repeated Measures (MMRM) to the EQ-5D-3L scores. The covariates considered included:

I. Treatment status at the time of EQ-5D assessment (on/off treatment)
II. Progression status (pre/post progression)
III. Arm of treatment (Ivosidenib/BSC)
IV. TRAEs at the time of EQ-5D assessment

The company chose a final model based on AIC predictions after employing a stepwise process. As a result, the chosen model simply included treatment status and TRAEs as independent variables (see Table 22 below). Thus, health state utility in the model was assumed to vary only by treatment status with decrements applied for adverse events. The company's submission did not include the AIC estimates for each model used in the selection

process. In the scenario analysis, utility values from Tables 33 and 34 of the company submission (document B), by progression status and progression and treatment status, were also assessed.

Table 22 Final MMRM model coefficients (base case) [Source: Table 32, Document B of CS]

Coefficient	Value	SE	95% CI	p-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Off treatment	[redacted]	[redacted]	[redacted]	[redacted]
TRAE grade ≥3	[redacted]	[redacted]	[redacted]	[redacted]

The company also conducted a systematic literature review to identify relevant published HRQoL data for previously treated patients with advanced or metastatic CCA. The search turned up a single article (a cost effectiveness analysis) that used health state utility values in CCA. The company chose not to include it in their analysis because the study's country setting was not the UK. Additionally, the company assessed health utility values that had been reported in earlier NICE appraisals for similar diseases. The only prior NICE submission the company found for the underling target population was TA722.[13] However, the utility values were redacted from this appraisal, and so could not be used. Therefore, the company looked for other NICE submissions on other types of cancer (see Table 23 below). From the submissions identified, the company selected utility values from TA474 (HCC) to test in scenario analysis.[25]

Table 23 Summary of final utility values in previous submissions (Source: Table 35, Document B of CS)

NICE appraisal (indication)	Treatment	Progression-free	Post-progression
TA722 (CCA)[13]	Pemigatinib	Not reported	Not reported
TA474 (HCC)[25]	Sorafenib	0.6900	0.7100
TA208 (mGC)[26]	Trastuzumab	0.7292	0.5770
TA669 (mGC)[27]	Trifluridine-tipiracil	0.7644	0.6522

Abbreviations: HCC, hepatocellular carcinoma; mGC, metastatic gastric cancer; NICE, National Institute for Health and Care Excellence.

In the base case economic model, adverse event-related disutility values were mainly sourced from a prior NICE appraisal in CCA (TA722).[13] The company used the utility decrement coefficient from their preferred MMRM model (Table 22 above) in a scenario analysis. The MMRM model took account of TRAEs of grades 3 and higher, but the company clarified that this indicator variable took the value of 1 for individuals who had experienced this grade of adverse event at any time after the date of first dose of study treatment. It is, therefore, unclear for what duration it should be applied. Section B.3.4 of the company submission contains detailed information on health-related quality of life inputs to the economic model.

The health state utility values included in the company base case are linked only to treatment status and not progression status. Progression status is assumed to have no independent effect on health state utility. Thus, health state utility in the progression free and progressive disease states differs only according to proportion on treatment in each state for each comparator. The EAG has concerns regarding the plausibility of this assumption and its potential for biasing against BSC and FOLFOX. It precludes any health state utility benefit from remaining progression free in the BSC arm of the model, and it limits the benefit for remaining progression free for mFOLFOX to the fixed duration treatment period. There is no discussion of the clinical plausibility of these assumptions in the company's submission, and the measures of statistical fit for the alternative models have not been provided for the EAG to be able to verify the company's claims. Given these concerns, the EAG prefer the approach of applying health state utility values by progression status or progression and treatment status. which the company have explored in scenarios analysis. The EAG believe these approaches fits better with the model structure, are more clinically credible, and more consistent with the approach taken in previous relevant NICE TAs identified by the company (TA474, TA208, TA669)[25-27] (see Table 23 above).

The company chose to present only the utility values from TA474 (HCC)[25] as an additional scenario analysis from the list of prior NICE submissions identified, citing clinical expert opinion that advanced hepatocellular carcinoma provided a relevant proxy condition. However, the presented values appear to lack face validity and were a source of controversy in TA474, as they suggest health state utility improves upon progression of disease (Table 23 above).[25] This will potentially bias in favour of ivosidenib since most of its survival benefit against the comparators accrues on the progressive disease state.

Only including adverse events of grade 3 and above, occurring in 5% or more patients in each treatment arm, may lead to an underestimation of treatment-related utility loss, although any impact on the ICER would be expected to be small.

4.2.8. Resources and costs

The following costs and resource use were included in the company's original economic model:

i. Treatment acquisition costs
ii. Treatment administration costs
iii. Health states resource use
iv. Adverse event costs
v. Miscellaneous costs (end of life costs and IDH1-mutaion testing)

The company added functionality to include subsequent treatment costs in response to a clarification question.

Treatment acquisition costs

Ivosidenib is supplied as a pack of 60 x 250mg tablets. It is administered orally at a dose of 500mg once daily, a pack providing 30 days' worth of treatment. A proposed simple patient access scheme (PAS) discount of [redacted] was applied to the ivosidenib list price in the company's economic analysis, giving a pack price of [redacted]. The company apply the costs of ivosidenib on a weekly basis in their economic model and they also apply a relative dose intensity (RDI) adjustment ([redacted]) to account for dose interruptions as observed in ClarIDHy. Thus, the per model cycle cost comes to [redacted]. The application of this cost per model cycle assumes that packs can be split and that patients can be dispensed the exact quantity of medicine required on weekly basis.

The comparator mFOLFOX is administered intravenously every two weeks for up to 12 cycles, at a calculated price of [redacted] per two-week treatment cycle. Prices were taken from the eMIT database, and doses based on body surface area (BSA) were calculated using an average BSA based on the average height and weight of patients ClarIDHy. To incorporate wastage, the company used a methods of moments approach, whereby they fitted a normal distribution to BSA and calculated the average number of vials required per patient (assuming no vial sharing). The estimated cost per two-week treatment cycle is applied to the

proportion of the cohort in the progression free health state at the start of the model and then every second model cycle up to the maximum number of treatment cycles (12). The BSC arm in the model does not incur drug acquisition costs. Section B.3.5.1.1 of the company submission contains further details.

The company's original model calculations did not account for potential wastage of oral medication caused by patients discontinuing treatment before depleting their supply. During the clarification stage, the company were asked to justify their base case assumption and consider the impact of a scenario that accounts for expected wastage. The company responded that their base case assumes packs can be split, and that the 4 x 250 mg ivosidenib tablets remaining at the end of a 28-day treatment cycle would be taken at the beginning of the next treatment cycle, before a subsequent pack is dispensed. The company did, however, also perform scenario analyses which impacted the base case probabilistic ICER moderately (Table 24 below). The first scenario assumed that the 28-day cost of ivosidenib is applied every 28 days to the proportion on treatment at the start of the corresponding model cycle; the last one assumes that a whole pack cost is applied every 28 days in the model. The EAG believe that these scenarios may be more realistic than the company base case and that wastage should be factored into ICERs used for decision making. The EAG offer an alternative wastage scenario, that assumes ivosidenib is dispensed to patients in packs of 30, and that a new pack is dispensed at the begging of model cycles when less that a week's supply of tablets remains (accounting for average relative dose intensity). This lies between the company's more optimistic and more pessimistic wastage scenarios.

Table 24 Probabilistic results, oral wastage scenarios, ivosidenib versus BSC (source: company response to the clarification letter, QB6)

Scenario	Cost every 28 days?	Cost full pack?	Incremental costs	ICER (£/QALY)	Change in ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply the cost of ivosidenib every 28 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assume each 60 x 250 mg pack lasts one treatment cycle (28 days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply the cost of ivosidenib every 28 days, and assume each 60 x	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

250 mg pack lasts one treatment cycle (28 days)					

Concerns regarding the use of PFS to model time on treatment with mFOLFOX have been raised in section 4.2.6. In addition, there appears to a minor error in the model code which results in the number of FOLFOX treatment cycles being capped at 13 rather than 12. The EAG believe this should be corrected in the economic model.

Treatment administration costs

Costs of treatment administration are described in section B.3.5.1.2. of the company submission. Ivosidenib, administered orally, is assumed to incur no administration costs. The mFOLFOX regimen incurs the NHS reference cost for delivering complex chemotherapy (SB14Z). In addition, the company assume the cost of a non-consultant led oncology outpatient follow-up attendance to remove the catheter required for the prolonged (46-hour) fluorouracil infusion.

The EAG identify a potential issue with the administration assumptions for mFOLFOX. Based on its clinical expert advice, it is the EAGs understanding that patients should not incur the cost of having their peripherally inserted central catheter (PICC) removed after each treatment cycle. Rather, they would be expected to incur the cost of a district nurse visit after each cycle to remove the chemotherapy pump and flush the catheter, and then only incur the cost of PICC removal upon treatment discontinuation. The EAG assess the impact of incorporating these alternative assumptions in Chapter 6.

Health states resource uses

Health state resource use was derived from the previous NICE submission of pemigatinib for previously treated advanced or metastatic CCA with FGFR2 alteration. Table 25 below summarizes the monitoring strategy.

Table 25 Healthcare resource use estimates (Source: Table 43, Document B of CS)

Resource item	Resource usage, annual frequency (every X months)	
	Progression free	**Progressed disease**
Clinical examination	4 (every 3 months)	4 (every 3 months)
CT scan	4 (every 3 months)	1 (every 12 months)
Blood test	4 (every 3 months)	4 (every 3 months)
Daily morphine sulphate	0	365.25 (daily)

Abbreviations: CT, computerized tomography; ECG, electrocardiogram; NICE, National Institute for Health and Care Excellence.

The corresponding costs were presented in Table 44 of the company submission (Document B).

Based on NICE TA722, the company assumed a frequency of every three months for clinical examination and blood tests in patients in the progression free health state.[13] However, in appendix N of the company submission, it is reported that one of the clinical experts consulted by the company, stated that they would see patients in the PF state once every treatment cycle (once a month) and would also conduct blood tests once per treatment cycle. Similarly, another expert stated that it is realistic to anticipate patients be seen more regularly for clinical examinations and blood tests when in the progression-free state; this might be up to monthly rather than quarterly (quarterly for scans). The EAGs clinical expert was of the view that monthly clinical examination may be typical during the first three months of ivosidenib treatment, before moving to quarterly monitoring. Therefore, the EAG suggest testing these alternative clinical monitoring frequencies in scenario analysis.

Adverse event costs

Unit cost related to the management of treatment related adverse events (>= grade 3) are presented in Table 45 of the company submission (Document B). The sourced unit costs are combined with data on the incidence of adverse events for each comparator, taken from the relevant trials, and applied as a one-off AE management cost in the first model cycle.

The EAG note that the company selected the NHS reference cost for non-elective short stay (< 2 days) for adverse events that were assumed to require hospitalisation. This may

underestimate the cost of adverse events, as some patients with grade 3 adverse events will incur longer stays in hospital. Furthermore, the company only included medicine costs for hyponatremia and hypophosphatemia. This may underestimate the costs of health care resource use for managing grade 3 AEs. The EAG suggest a scenario analysis that uses the weighted average of the NHS reference cost for non-elective long-stay and non-elective short-stay for each HRG based cost applied to adverse events in the model.[28]

Consistent with the critique made of the modelling of QALY losses from treatment related adverse events, incorporating only grade 3 adverse events occurring in 5% or more of patients may underestimate adverse event management costs. However, broader inclusion of adverse events would likely have a similar impact across the treatment arms and, therefore, have limited impact on the ICERs.

Miscellaneous costs

Costs related to end of life and IDH1-mutation testing are described in section B.3.5.4 of the company submission. There was no inclusion of subsequent treatment costs in the company original submission, but scenarios were provided at the clarification stage.

The company didn't include the cost of IDH1 gene testing in their base case economic analysis. Given that identification of the population requires IDH1 testing, and there are no other IDH1 targeted treatments for advanced CCA, the EAG is of the opinion that this cost should be applied in the ivosidenib arm of the model.

At the clarification stage, the EAG asked the company to provide details of any further lines of active treatment that patients in the ClarIDHy trial received following progression on ivosidenib or placebo (other than ivosidenib following progression on placebo). The company was also asked to consider implementing a scenario that captures the cost of subsequent therapy. The company gave a detailed response to this, noting that 38.9% of patients randomised to ivosidenib went on to receive further anticancer therapy. They also noted that 24.6% of patients randomised to placebo received further anticancer therapy other than ivosidenib (after crossing over to ivosidenib except for one patient). Chemotherapy was noted to be the most common subsequent treatment in both arms, although a range of treatment types were received (see company response to the clarification letter, QB7). The company implemented a scenario whereby they assumed all subsequent treatment would be

mFOLFOX, calculated the once off excepted cost of this, and multiplied it by the proportions observed to have received subsequent treatment indicated above. The resultant expected costs of subsequent therapy of [redacted] *and* [redacted] *for the ivosidenib and placebo arms were then applied to the percentage of patients expected to transition to progressive disease in each model cycle. For the last step, they used the proportion of PFS events in ClarIDHy that were disease progression (*[redacted]*).*

The EAG has several concerns with the company's implementation of this scenario:

(1) The calculated proportions receiving subsequent treatment from ClarIDHy are from the whole ITT population, not those making the transition to progressive disease. Multiplying these by the assumed proportion transitioning to progressive disease in each model cycle will underestimate the proportion receiving subsequent therapy in the model compared to that observed in the trial.

(2) The estimated cost of FOLFOX per patient commencing subsequent treatment was based on the median number of cycles observed in the ABC-06 trial, multiplied by the acquisition and administration cost per treatment cycle, rather than a distribution of expected ToT. This will tend to underestimate subsequent treatment costs, because the mean number of cycles is expected to be greater than the median.

(3) There was an error in the calculation of (2), whereby the company multiplied treatment cycle costs by the median number of treatment weeks (n=10) rather than the median number of treatment cycles (n=5). This will overestimate subsequent FOLFOX treatment costs.

In addition to the above, the EAGs clinical expert advisor confirmed that it is not a common practice to treat patients with chemotherapy following progression on BSC. Therefore, the observed subsequent treatment proportion in the placebo arm of ClarIDHy may not be appropriate for application in the BSC arm of the model. The EAG, therefore, suggests a scenario whereby subsequent chemotherapy costs are added only to the Ivosidenib arm of the model. Whilst this might not be consistent with what happened in the ClarIDHy trial, the RPSFT crossover adjustment, used to remove the effect of crossover to ivosidenib from the OS curve for BSC, should also have adjusted out any potential benefits that patients in the placebo arm received form subsequent chemotherapy following crossover to ivosidenib.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

Table 26 below shows the deterministic base case results reproduced from the company's main submission (document B). Considering a × 1.7 QALY weight and including the PAS price for ivosidenib, the base case result indicates that mFOLFOX is extendedly dominated by ivosidenib, and the ICER versus best supportive care is [redacted]. The probabilistic results for the company base case are reproduced in Table 27 below. These indicate a similar pattern of results, but it may be noted that the QALYs accruing for mFOLFOX are greater than in the deterministic analysis, resulting in lower ICER for mFOLFOX versus BSC. It remains, however, extendedly dominated.

5.2 Company's sensitivity analyses

In addition to their probabilistic analysis, the company ran one way sensitivity analysis (OWSA). For the BSC comparison, the incremental net monetary benefit (iNMB) was most sensitive to the relative dose intensity (RDI %) of ivosidenib, this impacting on drug acquisition costs. For the mFOLFOX comparison, the iNMB was most sensitive to variation in the OS HR for Ivosidenib vs mFOLFOX derived from the Bucher ITC. Figures 34 and 35 in the company submission (document B) provide the tornado diagrams of the OWSA for the BSC and mFOLFOX comparisons respectively.

The company also conducted a range of scenario analyses, which are described in Table 57 and the results presented in Table 58 of their main submission document. Based on the scenarios explored, the following parameter choices and assumptions generated the greatest increases in the ICERs:

1. Applying an exponential curve for Ivosidenib overall survival instead of log-normal
2. Simultaneously testing alternative survival models for ivosidenib OS, PFS, and TOT (particularly applying generalised gamma curves for all outcomes).
3. Allowing for treatment beyond progression for ivosidenib, using the best fitting lognormal curve to extrapolate ToT.

Table 26 Base-case results (deterministic) [Source: Table 54, Document B of CS]

Technologies	Total			Incremental (versus BSC)			ICER versus BSC (£/QALY) (x1.7 modifier)	ICER incremental (£/QALY) (x1.7 modifier)
	Costs	LYG	QALYs	Costs	LYG	QALYs (x1.7 modifier)		
BSC	[redacted]	[redacted]	[redacted]					
mFOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

Table 27 Base-case results (probabilistic) [Source: Table 53, Document B of CS]

Technologies	Total			Incremental (versus BSC)			ICER versus BSC (£/QALY) (x1.7 modifier)	ICER incremental (£/QALY) (x1.7 modifier)
	Costs	LYG	QALYs	Costs	LYG	QALYs (x1.7 modifier)		
BSC	[redacted]	[redacted]	[redacted]					
mFOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

The EAG agrees that the economic model used by the company is relatively robust to most of the variations explored in sensitivity analysis. However, there are some parameters to which the cost effectiveness results are sensitive. The importance of the OS HR for ivosidenib versus mFOLFOX, which was discussed in in section 4.2.6 above, is confirmed by the OWSA (Fig 35 of the company main submission). There is substantial uncertainty in this input arising from limitations of the indirect treatment comparison on which it is based.

The EAG acknowledge that the company performed many relevant scenario analyses around the cost effectiveness base case results. However, based on issues identified in chapter 4, the EAG believe that there are several further uncertainties that have not been addressed by the company's scenario analyses. These are further discussed and presented chapter 6.

5.3 Model validation and face validity check

The company indicated that prior to submission the model was quality assured by an economist who was not involved in the development of the model. The company also performed their own internal validation by comparing the median OS and median PFS from the model with the published clinical trial data that were used to inform the model inputs (Table 28 and 29 below). The model appears to slightly underpredict median OS for ivosidenib and FOLFOX compared to data reported in their respective trials, and slightly overpredicts median OS for BSC.

Table 28 Internal validation, comparison of median OS (Source: Table 59 of the CS, document B)

Treatment	Median OS (months)		
	Literature	Source	Model
Ivosidenib	10.3	ClarIDHy[16, 17]	[redacted]
BSC	• 5.1 • 5.3	• ClarIDHy (crossover adjusted)[16, 17] • ABC-06[20]	[redacted]
mFOLFOX	6.2	ABC-06[20]	[redacted]

Abbreviations: BSC, best supportive care; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; PFS, progression-free survival.

Table 29 Internal validation, comparison of median PFS (Source: Table 60 of the CS, document B)

Treatment	Median PFS (months)		
	Literature	Source	Model
Ivosidenib	2.7	ClarIDHy[16, 17]	[redacted]
BSC	• 1.4 • NR	• ClarIDHy[16, 17] • ABC-06[20]	[redacted]
mFOLFOX	4.0	ABC-06[20]	[redacted]

Abbreviations: BSC, best supportive care; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; OS, overall survival.

In addition, the EAG conducted its own internal consistency checks, using a combination of formula checking and black box tests suggested by Tappenden and Chilcott (2014).[29] The results of these checks are summarized in Table 30 below. No major issues were identified. However, the EAG did identify several minor inconsistencies in model, which are outlined below:

1. The formula to cap the time on treatment with mFOLFOX at 24 weeks, equating to a maximum of 12 treatment cycles, appear to allows up to 25 weeks of treatment and captures the cost of 13 treatment cycles.
2. The company's calculation of expected subsequent treatment costs (applied only in scenario analysis) multiplies the treatment cycle cost by a median number of treatment weeks (n=10) rather than the median number of treatment cycles (n=5).

The impact of correcting/ revising these is assessed in Chapter 6 below.

Table 30 Summary of "black box" checks of the model carried out by the ERG

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	Equalizing the survival curve parameters, changing all survival curves to the log normal distribution, equalizing the QALY decrement for adverse events, removing IV administration disutility and equalizing the on and off treatment utility values led to equal LYG and QALYs for the treatment arms.
	Sum expected health state populations at any model timepoint (state transition models)	Total probability equals 1.0	No issues found.
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	No issues found
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	No issues found.

	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	No issues found
Cost estimation	Set intervention costs to 0	ICER is reduced	No issues found.
	Increase intervention cost	ICER is increased	No issues found.
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	No issues found.
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	No issues found.
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter.	-
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	No issue found

Abbreviations: ICER, incremental cost-effectiveness ratio; IV, intra venous; LYG, life year gain; QALY, quality adjusted life year.

It is worth noting that the life year and QALY gains with Ivosidenib occur primarily in the progressed disease state of the model. This is most pronounced for comparison with mFOLFOX, where there is little difference in terms of time spent in the progression free state, but a gain of [redacted] life years in the progressed disease state. This is consistent with the model inputs for PFS and OS (Figures 5 and 6 below). In figure 5, the PFS curves for ivosidenib and mFOLFOX are very close and overlap. Whereas, in Figure 6 there is a clear gain in OS for ivosidenib versus mFOLFOX. The EAGs clinical expert advised that this pattern of benefit is quite commonly seen with biologics and is consistent a with longer-term benefit being conferred compared to mFOLFOX. It may also be partly explained by the reliance on a naïve comparison of PFS between ClarIDHy and ABC-06 (which included less heavily treated patients). It is, however, also possible that it partly reflects an optimistic OS extrapolation for ivosidenib.

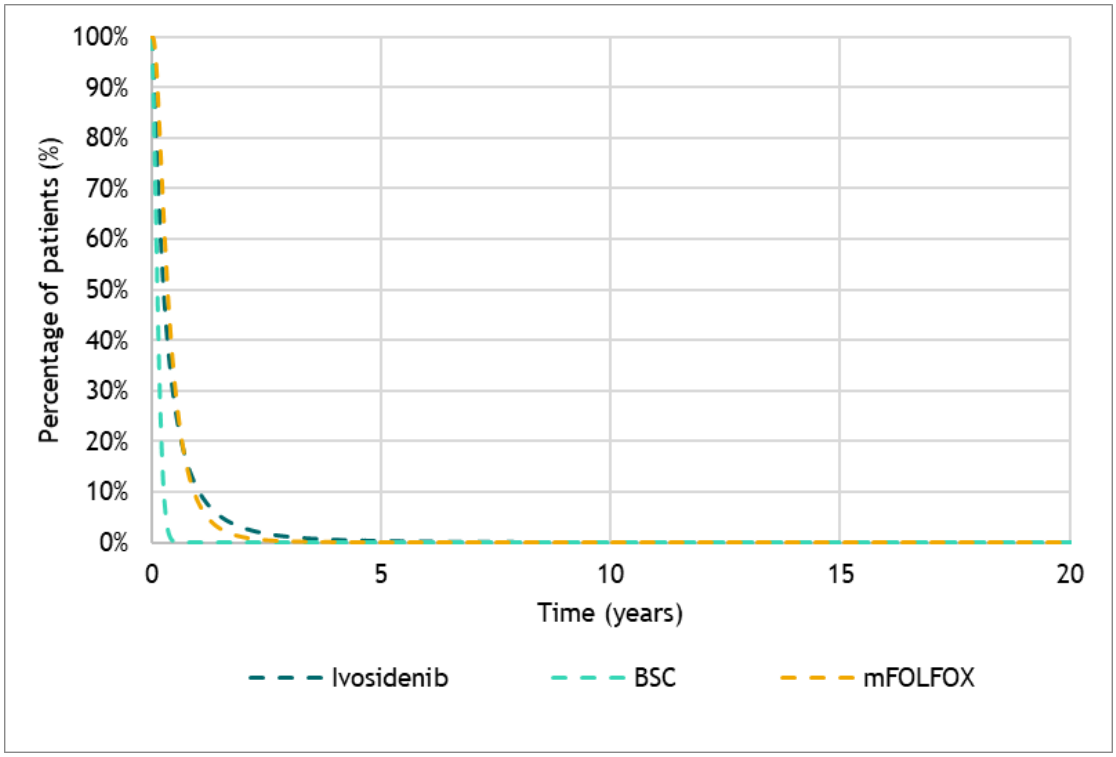


Figure 5: Summary of selected PFS curves (Source: Figure 27, Document B of CS)

Figure 6: Summary of selected OS curves ((Source: Figure 18, Document B of CS)

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

To address uncertainties that the company had not fully explored, the EAG conducted further scenario analyses as described and justified in Table 31 below.

In summary, based on the critiques made in section 4.2.6 to 4.2.8 above, the EAG performed scenario analyses around a selection of key inputs and assumptions. These included several efficacy and ToT inputs as outlined in scenarios 1-10 (Table 31). Given limitations in the available health state utility data from ClarIDHy, and questions over the clinical plausibility of estimates available from NICE TA474 in HCC[25], the EAG also performed further scenario analysis (Table 31, scenarios 13-14) using health state utility values from NICE TA669 and TA208 (mGC) (see Table 23).[26, 27]

Further, the EAG explored scenarios to address various uncertainties around the resource use and costing assumptions in the model (scenarios 11-12 and 15-25). These included scenarios around the acquisition and administration costs for mFOLFOX, the frequency of clinic visits for patients on ivosidenib, the unit costs applied for adverse events, the inclusion of subsequent treatment costs, and the incorporation of wastage of ivosidenib. The latter scenarios include deterministic implementation of the scenarios around subsequent treatment and wastage that the company provided in response to the clarification letter. Further details of each scenario are provided in Table 31, and the corresponding results by scenario number are provided in Table 32. As per the company's scenario analysis, Table 32 provides the incremental results for ivosidenib versus each comparator for each scenario. In any scenario where the ICER for ivosidenib is higher versus mFOLFOX than it is against BSC, mFOLFOX would no longer be extendedly dominated in the full incremental analysis.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Table 32 shows the cost-effectiveness results to be moderately sensitive to some of the changes introduced in the individual scenarios. The greatest impact for the comparison against mFOLFOX is observed in scenario 1; When the OS hazard ratio for ivosidenib versus mFOLFOX is based on a Bucher ITC between the ITT population of ClarIDHy and the ITT population of ABC-06 trial, the relative treatment effect is smaller and correspondingly the expected QALY gain for ivosidenib is substantially lower. This leads to a substantial increase in the ICER against mFOLFOX.

Other scenarios that have a sizable upward impact on the ICERs include those that allow for treatment beyond progression on ivosidenib (scenarios 5-7), reduce ToT for mFOLFOX (mFOLFOX comparison only) (scenarios 9-10), apply health state utility values from TA208 (mGC)[26] (scenario 14), incorporate subsequent treatment costs (18-21), and incorporate ivosidenib wastage (22-25).

Interestingly, the scenarios that incorporate more pessimistic extrapolations of PFS for ivosidenib result in a lower ICER for ivosidenib against each comparator. This is driven by reductions in ivosidenib treatment costs arising from the assumption that ToT is capped by PFS in the company base case model.

Table 31. Details of further scenario analysis conducted by the EAG

EAG scenario number	Setting	Company base case	Scenario	Justification
1	1. OS mFOLFOX	HR from Bucher ITC (using ClarIDHy subgroup data to align with ABC-06 inclusion criteria)	HR from a Bucher ITC (using the ITT data from ClarIDHy); HR= 0.71	Whilst ideally it makes sense to align the inclusion criteria of the trials in the Bucher analysis, the reliance on a small post hoc subgroup of ClarIDHy generates uncertainty. Further, the company have not identified number of prior treatments as a significant effect modifier for ivosidenib (section 4.2.6).
2	2. PFS extrapolation (Ivosidenib)	Log normal	Exponential	The exponential and Weibull distributions satisfy the range of clinically plausible projections (1-3%) provided by clinical experts for PFS at 2 years (Section 4.2.6).
3			Weibull	
4	3. PFS extrapolation (BSC)	Weibull	Log-logistic	The log-logistic provide the best statistical fit to the observed Kaplan Meir data (section 4.2.6)
5	4. ToT (ivosidenib)	Log-normal (capped at PFS to remove treatment following progression)	Enable treatment beyond progression (log-normal)	One of three clinical experts consulted by the company, and the EAGs clinical expert, believed that ivosidenib may be used beyond progression in some cases. And the OS data for ivosidenib may reflect the fact that some patients did receive treatment beyond progression in ClarIDHy. The generalized gamma and exponential curves may provide more plausible long-term projections of ToT (section 4.2.6).
6			Enable treatment beyond progression (generalised gamma)	
7			Enable treatment beyond progression (exponential)	
8	5. ToT (mFOLFOX)	Follows PFS to a maximum of 12 treatment cycles	Correct model code to limit mFOLFOX to maximum 12 rather than 13 cycles.	The model code appears to allow up to 13 treatment cycles with mFOLFOX rather

EAG scenario number	Setting	Company base case	Scenario	Justification
9			Model ToT using HR versus PFS, to match the median number of treatment cycles observed in ABC-06	than 12. And the assumption of using PFS to approximate ToT overestimates the median number of treatment cycles (n=5) that patients in ABC-06 received (section 4.2.6 and company model).
10			Apply exponential distribution through the median number of treatment cycles observed in in the ABC-06 trial	
11	6. mFOLFOX administration costs	Complex chemotherapy (SB14Z) + non-consultant led OP appointment to remove their peripherally inserted central catheter (PICC) after each treatment cycle	District nurse visit (N02AF) at £51.84 to remove chemotherapy pump after each Tx cycle[28]	Based on its clinical advice, the EAG understand that patients should not incur the cost of having their PICC removed after each treatment cycle. Rather, they may incur the cost of a district nurse visit after each cycle (to remove the pump) and incur the cost of PICC removal upon treatment discontinuation (section 4.8).
12			Community nurse visit to remove pump after each Tx cycle + non-consultant led OP appointment to remove catheter at treatment discontinuation	
13	7. Utility source	ClarIDHy model 1 (treatment status and Grade ≥3 TRAEs)	NICE TA669 by progression status	The company identified several alternative utility values from previous relevant NICE TAs in proxy conditions. However, they only tested one set, which lacked face validity, in their own scenario analysis (section 4.2.7).
14			NICE TA208 (mGC) by progression status	
15	9. Frequency of clinical examination and blood tests in PF state (ivosidenib)	Every 3 months	Every month	Clinical expert advice to the company appears to suggest that some clinical experts would choose to monitor patients on ivosidenib every month. The EAGs clinical expert was of the view that monthly clinical examination may be typical during the first three months of ivosidenib treatment (section 4.2.8).
16			Every month for the first three months of treatment	

EAG scenario number	Setting	Company base case	Scenario	Justification
17	10. Adverse event costs	Applies non-elective short stay costs for hospital admissions	Apply weighted average of non-elective short stay and non-elective long-stay to hospital admissions.[28]	Based on its clinical advice, the EAG understand that the duration of hospital admissions for grade three adverse events to be variable, and for some will require long stay admissions (section 4.2.8).
18*	11. Subsequent treatment costs following progression	No subsequent treatment costs	Include subsequent treatment following progression on ivosidenib and BSC	In line with the company scenario at clarification, the cost of subsequent treatment should be modelled for the proportion that received subsequent treatment in ABC-06. However, subsequent treatment would not be considered for those receiving BSC in routine NHS practice (section 4.8). The effect of further treatment received by patients in the placebo arm of ClarIDHy should also have been adjusted out by the RPSFT analysis (section 4.6 and 4.2.8).
19*			Include subsequent treatment following progression on ivosidenib only	
20*			Apply the expected cost of subsequent FOLFOX treatment to all transitions out of the PFS state, to avoid over adjusting for proportion who progress from the PF state.	
21			Recycle the discounted cost stream of mFOLFOX as an index treatment, to model its cost as a subsequent treatment	
22	12. Wastage of ivosidenib	No wastage assumed	Apply the cost of ivosidenib every 28 days	The EAG find it implausible that there would be no wastage of ivosidenib with routine prescribing/dispensing. Scenarios that account for wastage may be more realistic.
23			Assume each 60 x 250 mg pack lasts one treatment cycle (28 days)	
24			Apply the cost of ivosidenib every 28 days, and assume each 60 x 250 mg pack lasts one treatment cycle (28 days)	
25			EAG: assume ivosidenib is dispensed to patients in packs of 30, and that a new pack is dispensed at the begging of model cycles when less than a week's supply of tablets remains (accounting for average relative dose intensity)	

*Scenarios that use the company's estimate of expected subsequent FOLFOX treatments costs are corrected to reference the median number of treatment cycles (n=5) from the ABC-06 trial, rather than median number of treatment weeks (n=10), to calculate expected cost of subsequent mFOLFOX treatment

Table 32 Results of the ERG's further scenario analysis

Scenario number	Incremental versus BSC				Incremental versus mFOLFOX			
	Cost (£)	QALY (x1.7 modifier)	ICER (x1.7 modifier)	Change	Cost (£)	QALY (x1.7 modifier)	ICER (x1.7 modifier)	Change
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

19*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

*Scenarios that use the company's estimate of expected subsequent FOLFOX treatment costs are corrected to reference the median number of treatment cycles (n=5) from the ABC-06 trial, rather than median number of treatment weeks (n=10), to calculate expected cost of subsequent mFOLFOX treatment

6.3 EAG's preferred assumptions

Based on the critiques made in chapters 4 and 5, and the justification for scenarios outlined in Table 31, the EAG prefers the modelling assumptions laid out in Table 33. These are applied sequentially and cumulatively in Table 33, with their cumulative impact on incremental costs, effects, and the ICER provided against both BSC and mFOLFOX. It can be noted that the major impacts on the ICERs come through:

(1) Changing the OS extrapolation for ivosidenib (step 2)
(2) Allowing for ivosidenib treatment beyond progression (step 3)
(3) Revising the modelling of ToT for mFOLFOX, to align with the ABC-06 trial (step 5)
(4) Incorporating wastage of ivosidenib, by applying the EAGs prescribing/dispensing assumptions (step 6).
(5) Incorporating the cost of subsequent FOLFOX treatment following progression on ivosidenib (ivosidenib arm only) (step 11)
(6) Applying health state utility values by progression and treatment status (step 15)

The full deterministic incremental analysis for the resultant EAG base case is provided in Table 34. The corresponding probabilistic results are found in Table 35, with corresponding cost-effectiveness scatter plots and the acceptability curves provided in Figures 7-9. In both the deterministic and probabilistic analyses, mFOLFOX ceases to be extendedly dominated by the combination of BSC and ivosidenib, and there is a substantial upward shift in the ICER for ivosidenib against both mFOLFOX and BSC. These analysis incorporate the severity weighting of 1.7 on incremental QALY gains, as the EAG agree that the absolute and relative QALY shortfall thresholds are met based on the expected QALYs under BSC and mFOLFOX.[30] The results of selected scenario analyses, from the reference point of the EAG base case, are provided in Table 36. These confirm the following parameters/assumptions to be important sources of uncertainty in the economic case: the choice of parametric curve for ivosidenib overall survival; the source of utility values; whether to include ivosidenib treatment beyond progression; and whether to incorporate ivosidenib wastage.

Table 33 ERG's preferred base case model assumptions – cumulative impact of changes on the ICER

Preferred assumption	Incremental versus BSC				Incremental versus mFOLFOX			
	Cost (£)	QALY (x1.7 modifier)	ICER (x1.7 modifier)	Change	Cost (£)	QALY (x1.7 modifier)	ICER (x1.7 modifier)	Change
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1. Correct model code to cap mFOLFOX treatment cycles at a maximum of 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. OS extrapolation (ivosidenib): generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Allow for ivosidenib treatment beyond progression (ivosidenib arm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. ToT extrapolation (ivosidenib): generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. ToT mFOLFOX: Exponential curve fitted to median number of treatment cycles in ABC-06	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. Ivosidenib acquisition costs – incorporate wastage using EAG method (Table 31, scenario 25)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. Include a clinical examination and blood test every month for ivosidenib for the first three months of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8. mFOLFOX administration: District nurse visit (£51.84) to remove pump after each Tx cycle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9. mFOLFOX administration: Non-consultant led OP appointment (£190.59) to remove PICC at treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10. Apply weighted average HRG costs, inclusive of non-elective short stay and non-elective long stay, to adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11. Include subsequent treatment with mFOLFOX following progression on ivosidenib only*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

12. Recycle the discounted cost stream of mFOLFOX as an index treatment, to model its cost as a subsequent treatment (ivosidenib arm only)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13. Apply the expected cost of subsequent FOLFOX treatment to all transitions out of the PFS state, to avoid over adjusting for the proportion who progress from the PF state (ivosidenib arm only).	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14. Include IDH testing for the ivosidenib arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15. Health state utility: By progression and Tx status (EAG base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

*Scenarios that use the company's estimate of expected subsequent FOLFOX treatments costs are corrected to reference the median number of treatment cycles (n=5) from the ABC-06 trial, rather than median number of treatment weeks (n=10), to calculate expected cost of subsequent mFOLFOX treatment

Table 34 EAG deterministic base case (full incremental analysis)

Technologies	Total			Incremental (versus BSC)			ICER versus BSC (£/QALY) (x1.7 modifier)	ICER incremental (£/QALY) (x1.7 modifier)
	Costs	LYG	QALYs	Costs	LYG	QALYs (x1.7 modifier)		
BSC	[redacted]	[redacted]	[redacted]					
mFOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

Table 35 EAG probabilistic base case (full incremental analysis)

Technologies	Total			Incremental (versus BSC)			ICER versus BSC (£/QALY) (x1.7 modifier)	ICER incremental (£/QALY) (x1.7 modifier)
	Costs	LYG	QALYs	Costs	LYG	QALYs (x1.7 modifier)		
BSC	[redacted]	[redacted]	[redacted]					
mFOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

Figure 7 Incremental cost-effectiveness scatter plot (EAG base case - Ivosidenib versus BSC)

Figure 8 Incremental cost-effectiveness scatter plot (EAG base case - Ivosidenib versus mFOLFOX)

Figure 9 Cost-effectiveness acceptability curves (EAG base case)

Table 36 Selected scenario analysis around the EAG base case (deterministic)

Parameter/ assumption	EAG base case	Scenario	Incremental versus BSC				Incremental versus mFOLFOX			
			Cost (£)	QALY (x1.7 modifier)	ICER (x1.7 modifier)	Change	Cost (£)	QALY (x1.7 modifier)	ICER (x1.7 modifier)	Change
EAG base case			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS extrapolation (ivosidenib)	Generalised gamma	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility source	ClarIDHy (Progression and Tx status	ClarIDHy (progression status)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ClarIDHy (Treatment status)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		NICE TA208 (mGC) by progression status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib ToT	Allow beyond progression	Cap and PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib wastage	Included	No wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

6.4 Conclusions of the cost effectiveness section

The de novo economic model provided by the company is reliable, transparent, and populated using data relevant to the decision problem. The comparator and population included are in line with the final scope issued by NICE. A key strength in the economic case relates to the maturity of the clinical effectiveness data used to inform the model, which limits the uncertainty associated with extrapolation of several outcomes. Nevertheless, there are remaining uncertainties in the company's economic case that could have a material impact on decision making and warrant scrutiny and discussion. These include:

1. The validity and reliability of the hazard ratio for the comparison of OS with ivosidenib versus mFOLFOX, derived from the Bucher ITC. This is a key driver of the ICER for ivosidenib versus mFOLFOX, and the ITC informing it has several limitations and has not been transparently reported. \AZ B
2. The choice of parametric curve for extrapolating OS for ivosidenib. Whilst the data are mature, the alternative curves still produce substantial changes in the ICER for ivosidenib against both comparators. No individual curve offers a clearly superior fit to the observed data, and there are no longer-term data against which to assess the plausibility of extrapolations.
3. Whether to allow for ivosidenib treatment to continue as observed in the ClarIDHy trial, or cap it using the selected PFS curve in the model.
4. The assumptions related to the extrapolation of the TOT for mFOLFOX. This was approximated in the company base case using the selected PFS curve for mFOLFOX. This, however, overestimates the number of treatment cycles in the model compared to observed number in the trial informing mFOLFOX efficacy.
5. Whether to incorporate ivosidenib wastage in the model. This relates to how ivosidenib will be dispensed in clinical practice, and what steps might be taken to minimise the potential for wastage.
6. Whether to incorporating the cost of subsequent mFOLFOX treatment following progression on ivosidenib (ivosidenib arm only).
7. Whether to incorporate health state utility values in the model by progression status, treatment status, or a combination of both.

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Appendices

Single Technology Appraisal

Ivosidenib for treating advanced cholangiocarcinoma with an IDH1 mutation after at least 1 therapy [ID6164]

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 7 July** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.1 – incorrect company stated. Page 14 EAG writes "The focus of the submission received from **Agios Pharmaceuticals**"	"The focus of the submission received from **Servier Laboratories**"	The company is Servier Laboratories (ivosidenib), per the final stakeholder list	The text has been amended accordingly

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.4 Issue 3, Page 20 Whether to allow for ivosidenib treatment beyond progression EAG writes "The EAG believe that ivosidenib ToT should be modelled as observed in ClarIDHy, using the best fitting parametric curve for the observed data, even if this does assume treatment continuing beyond	The summary of product characteristics states that treatment should be continued until disease progression or until treatment is no longer tolerated by the patient.	Amendment to Summary of product characteristics that now does only allow for treatment up until disease progression	The EAG report has been amended to indicate the wording to reflect the updated SmPC.

progression for some. Clinical expert advice received by the EAG suggests that in some cases, clinicians may still treat beyond radiographic disease progression if they feel the patient may still be deriving benefit from it. The draft summary of product characteristics does not preclude this. Servier would like to point out that the summary of product characteristics does now preclude this. An update to the SpC has been made since the submission was sent in and the SpC updated on 4/5/2023 now reads Cholangiocarcinoma: Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient. This has been specifically altered from the draft SpC which stated: Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.			

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6 Page 40 ToT Ivosidenib EAG writes: "According to one of the clinical experts the company spoke with (Company submission, appendix N), discontinuing treatment may depend on the type of advancement and the reasons why there would be a perception of continuing benefit. The expert added that it can be challenging to accurately determine progression from a radiological scan or to compare to baseline in some circumstances; in these situations, treatment may continue past progression" Servier believes that although this was mentioned by one	The majority of experts opinion gained by the company said it was reasonable to stop on progression, with one expert stating it was now "standard practice" to stop on progression	Expert opinion gained by the company states that it is reasonable to stop treatment on progression	The passage has been expanded to include the views of the two other experts, as per the company's request. The EAG has also aligned the wording for justifying its treatment beyond progression scenarios in Table 31, to indicate that "one of three experts consulted by the company…." believed ivosidenib may be used beyond progression in some cases.

expert, the remaining experts who disagreed with this have been left out of the report. The majority of experts opinion gained by the company said it was reasonable to stop on progression, with one expert stating it was now "standard practice" to stop on progression			

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.4 Issue 3, Page 20 EAG writes "Whether to allow for **iopidine** treatment beyond progression	"Whether to allow for **ivosidenib** treatment beyond progression"	Correction of typographical error (incorrect intervention)	The text has been amended accordingly

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6, page 66 ToT mFOLFOX It is stated that the company submission does not explore the functionality to fit an exponential ToT curve using the median number of cycles observed in ABC-06 for mFOLFOX. "The company model in fact provides the functionality to do this but its impact was not explored in the company submission."	Suggest instead noting that the company explored the impact of testing this approach in scenario analysis (See CS Section B.3.10.3, Table 57, scenario #22). For example: "The company explore the impact of this in scenario analysis"	The company explored this functionality in their submission through a scenario analysis	Text has been amended accordingly. This was an oversight by the EAG.

(please cut and paste further tables as necessary)

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ivosidenib for treating advanced cholangiocarcinoma with an *IDH1* mutation after at least 1 therapy [ID6164]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **16th August 2023**. 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 received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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

NICE National Institute for Health and Care Excellence

About you

Table 1: About you

Your name	XXXXXXXXXXXXXX
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Servier Laboratories
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**N/A**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**N/A**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2: Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Reporting of the indirect treatment comparison was not sufficiently transparent (see sections 3.3 and 3.4)	No	The company appreciates that the EAG requested more information on the indirect treatment comparison at the clarification question stage. This has allowed the company to provide clearer information on the data and methods informing the indirect comparison, and how the hazard ratio applied in the cost-effectiveness analysis was derived.
Uncertainty in the extrapolation of overall survival for ivosidenib (see section 4.2.6)	No	The company acknowledges that the EAG notes there is little to choose between several parametric curves in terms of statistical fit; however, the company maintain that the log-normal curve is the most suitable for informing OS in the ivosidenib arm of the model. The EAG note a tendency towards favouring the generalized gamma curve, based on visual fit to the observed data and the middle ground estimate of extrapolated survival landmarks. However, the log-normal curve provides both a good visual fit to the observed data, and has the lowest AIC, second lowest BIC, and lowest combined AIC/BIC of all the of the 6 included parametric survival models, indicating it does provide the best statistical fit to the observed data. Furthermore, although one expert consulting during the company submission noted it was difficult to comment on the long-term plausibility of the extrapolations, and one acknowledged that none of the curves appeared completely implausible, a third expert expressed a slight preference for the log-logistic over the log-normal curve. Despite this, as the log-normal provides a more conservative estimate of survival in

		the long-term compared with the log-logistic curve, the log-normal was selected in the company base case. In NICE TA722, the log-logistic curve was used for decision making which estimated 5-year OS in the pemigatinib arm of 11%. Although it is acknowledged that TA722 considered a different molecular population within CCA; a more conservative approach was taken in the company submission here, as the log-logistic curve provided the most optimistic long-term estimate of OS for ivosidenib and was therefore ruled out. In conclusion, the company appreciates that it is challenging to fully resolve this issue in the absence of longer-term follow up data. However, the company believes that the most robust approach is to base the curve selection on the statistical goodness of fit (given maturity of the data from the ClarIDHy study, comparability in the visual fit, and plausibility of the long-term estimates), and prefer the use the log-normal curve for ivosidenib OS.
Whether to allow for ivosidenib treatment beyond progression (see section 4.2.6)	Yes	The company maintains that it is appropriate to assume that patients do not receive treatment after progression in the cost-effectiveness analysis, to provide the most accurate estimate of ivosidenib costs in NHS England practice. In interviews conducted independently with three clinical experts (as reported in the company submission), all clinicians indicated that treatment with ivosidenib would be stopped upon progression in practice. New evidence provided in this response includes an updated summary of product characteristics (SmPC) for ivosidenib and prescribing information following GB marketing authorisation on 5th july 2023 The wording contained within the SmPC, which was updated on 05/07/2023, states treatment should be continued until disease progression or until treatment is no longer tolerated by the patient. The approach taken in the company base case is therefore consistent with the marketing authorisation for ivosidenib. As it is not possible to adjust the survival estimate for the proportion of patients who received treatment beyond progression within the ClarIDHy study, and it would be inappropriate to simply exclude these patients from the analysis (without breaking

		randomization), the company believe that the capping of the ToT curve at PFS provides a suitable, pragmatic approach to accurately capturing treatment costs.
Whether to include treatment wastage for ivosidenib (see section 4.2.8)	Yes	The base case in the company submission did not include wastage for oral treatments (instead, a per 7-day model cycle cost was estimated for ivosidenib, effectively assuming packs could be split). However, the EAG-preferred base case includes wastage for oral therapies by assuming a new pack of ivosidenib would be dispensed to patients at the beginning of model cycles in which less than a week's supply of tablets remains. Further clinical opinion sought by the company at the technical engagement stage has indicated that ivosidenib pack splitting would not occur in NHS England practice. Therefore, the company has revised its post technical engagement base case (Table 4), to account for ivosidenib wastage (using approach in the EAG preferred base case). The company considers this key issue to be resolved, following alignment of the EAG and revised company base case.
Modelling of time on treatment for mFOLFOX, and its acquisition and administration costs (see section 4.2.8)	No	The company acknowledges that the EAG's clinical expert advised that patients receiving mFOLFOX may only return to hospital for PICC removal following completion (discontinuation) of their treatment course. However, the company maintain that the administration costs used in the company submission are suitable for informing the analysis. • Firstly, the cost incurred for patients returning to hospital to have their infusion line removed by a nurse (NHS National Cost Collection 2020/21 - Non-consultant led, non-admitted face-to-face attendance, follow-up, medical oncology, WF01A) is consistent with the approach used for decision making in the prior appraisal in CCA (TA722) and prior appraisals involving 46-hour 5-FU (TA476). • Secondly, although patients may not have the PICC line removed each cycle, it is necessary to remove the pump, which may be conducted in a hospital setting or by a district nurse at home – assuming that the pump removal is solely conducted by a district nurse may underestimate the true administration cost of mFOLFOX. • Thirdly, there is a risk associated with PICC devices, which may require replacement of the line during a chemotherapy course (due to factors such as

		inflection and clotting). This risk of replacement is not captured when assuming patients only return to hospital at the end of their treatment course. • Finally, PICC national guidelines state that the line needs to be flushed and dressed every week, which will have an associated tariff cost due to required nurse time Therefore, the company believes that assuming patients would receive a non-consultant led, follow-up medical oncology appointment provides a reasonable assumption for representing the administration costs associated with mFOLFOX. Furthermore, the company believes that the EAG's preferred base case assumption of fitting an exponential curve to the median number of treatment cycles to estimate the mFOLFOX ToT curve may underestimate the true cost of administering mFOLFOX in practice. The company highlights that, when extrapolating beyond the trial period for treatments without a cap on the number of cycles, estimating an exponential curve to predict ToT may be a suitable approach. However, it is reasonable to assume that patients are more likely to complete a course of treatment with a fixed maximum duration (such as mFOLFOX which is administered for a up to 12 cycles), compared with treatment administered in a longer-term setting. Therefore, assuming patients discontinue at a constant rate based on the median number of cycles may underestimate the 'true' ToT curve. In conclusion, the company believe that, in the absence of a reported mFOLFOX ToT curve, assuming ToT is equivalent to PFS is the most suitable approach for informing the cost-effectiveness model.
Whether and how to include subsequent treatment costs (see section 4.2.8)	No	The company maintains that, in the base case analysis, the exclusion of subsequent treatment costs is an appropriate assumption. This is consistent with the approach in the only prior NICE appraisal in CCA (TA722), whereby subsequent treatment costs were not considered (despite OS landmarks in TA722 being higher than those modelled in the *IDH1* population considered within this appraisal). Although a proportion of patients received subsequent treatments in the ClarIDHy study, many of these were other investigational therapies, as there are no active treatments recommended by NICE for patients with advanced/metastatic CCA in a 3L+ setting.

		Furthermore, it is often the case that patients enrolled in a clinical trial are fitter than those seen in clinical practice. As such, due to the poor prognosis of patients with previously treated advanced/metastatic CCA, it may be more reasonable to assume that most patients would go on to receive BSC in a community palliative setting following disease progression. In conclusion, the company believes that excluding subsequent treatment costs (an assumption which is applied consistently across all treatment arms), is the most suitable modelling approach.

Abbreviations: AIC, Akaike Information Criteria; BIC, Bayesian information criterion; BSC, best supportive care; CCA, cholangiocarcinoma; EAG, External Assessment Group; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; PICC, peripherally inserted central catheter; TA, technology appraisal; ToT, time on treatment.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3: Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Include a clinical examination and blood test every month for ivosidenib for the first three months of treatment	See sections 1.7 and 4.28	No	The EAG-preferred base case assumes that clinical examinations and blood tests would be conducted every month for the first three months of treatment, in the ivosidenib arm only. However, the company maintains that modelling clinical examinations and blood tests every 3 months is the most suitable approach. • Firstly, the company preferred approach aligns with the healthcare resource use estimates used for decision making in the only prior NICE appraisal in advanced/metastatic CCA (TA722). • Secondly, ESMO guidance for biliary tract cancer recommends that, during systemic and locoregional therapy for advanced disease, follow-up should be conducted at a frequency of 8-12 weeks. • Thirdly, the company's approach assumes that monitoring (with regards to clinical examinations and blood tests) is based on the health status of a patient, rather than the treatment administered. • Furthermore, the EAG notes that one clinical expert consulted by the company stated that they would see patients/conduct blood tests in the progression-free state once every treatment cycle. The company therefore believes that applying increased monitoring costs for those on

			treatment with ivosidenib, but not those on treatment with mFOLFOX, introduces bias in favour of mFOLFOX. The company also considers that, of the remaining 2 experts consulted by the company, one noted the estimates from TA722 were aligned with expectation, and the other indicated that (despite the possibility of more frequent monitoring in general [not specific to ivosidenib]) the estimates could be plausible for the economic model. • Finally, one of the clinical experts consulted by the company noted that they would not consider there to be any differences in the monitoring between treatment arms. The other initially noted they would not expect differences between treatment arms but went on to consider that mFOLFOX patients could be monitored more frequently, as it is administered in hospital every two weeks and due to side effects. Therefore, on balance, the company consider that aligning healthcare resource estimates with the values used in TA722, and assuming monitoring is determined by health state rather than treatment arm, is the most appropriate modelling approach, and is possibly conservative owing to additional resource use that may be required for mFOLFOX patients treated in practice.
Additional issue 2: Apply weighted healthcare resource group costs inclusive of non-elective long and short stays to adverse events	See sections 1.7 and 4.28	Yes	The EAG raised concerns that using non-elective short stay costs (sourced from NHS reference costs) per the original company base case may underestimate the cost of managing adverse events. Therefore, the company has revised its post technical engagement base case (Table 4) to align with the preferences of the EAG, by assuming adverse event management costs are represented by a weighted average of non-elective long-term and non-elective short-term stays. The company considers this additional issue to be resolved, following alignment of the EAG and revised company base case.
Additional issue 3: Health state utility dependent	See sections 1.7 and 4.27	Yes	The EAG-preferred base case uses the utility model with covariates for progression status and treatment status; based on concerns raised by the

<table>
<tr>
<td>on progression and treatment status from ClarIDHy</td>
<td></td>
<td></td>
<td>
EAG that progression status is assumed to have no independent effect on utility.

The company acknowledges the EAG's concerns and presented utility models with covariates for progression status only and progression and treatment status in scenario analysis; but maintains that the best-fitting model (with covariates for treatment status and Grade 3+ TRAEs) was selected in the base case.

A stepwise procedure was followed to determine the independent variables to be included in the model. Additional information presented within this response includes the AIC values for the additional utility models including progression status as covariates that were presented in scenario analysis (compared with the base case model):
<table>
<tr><th>Utility model</th><th>AIC</th></tr>
<tr><td>Treatment status and Grade 3+ TRAEs</td><td>-130.048</td></tr>
<tr><td>Progression status</td><td>-126.747</td></tr>
<tr><td>Progression status and treatment status</td><td>-127.907</td></tr>
</table>

It is noted that progression-based values represent a typical approach taken to inform utilities for cost-effectiveness models. However, given the availability of patient-level data from ClarIDHy providing EQ-5D data, the company was able to optimise the specification of the regression model, which in this case favoured an alternative approach. The company highlights that alternative approaches to capturing utility other than by progression status alone have been considered in previous appraisals conducted by NICE, including (in addition to treatment status) time-to-death approaches (examples include TA590, TA691, and TA638) and response-based approaches (examples include TA653).

In conclusion, the company maintains that using the best-fitting utility model is appropriate for the cost-effectiveness analysis base case. Scenario
</td>
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</table>

			analysis testing the alternative utility models around the company revised post technical engagement base case are presented in Table 5.
Additional issue 4: The additional cost of IDH1 testing to identify the eligible population in the Ivosidenib arm	See sections 1.7 and 4.2.8	No	At an advisory board held by the company in May 2022, it was thought that routine testing was not yet available in all areas for IDH1. However, 6-12 months later, when the company conducted clinical insight meetings, all clinicians stated routine testing was now included in the national genomic test directory, and is now beingreported in parts of the country. Therefore, Servier believes that the cost of IDH1 testing should not be incorporated into the model base case.

Abbreviations: AIC, Akaike Information Criteria; CCA, cholangiocarcinoma; EAG, External Assessment Group; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; NICE, National Institute for Health and Care Excellence; TA, technology appraisal; TRAE, treatment-related adverse event.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4: Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER (individual impact of each change)
Original company base case			• Versus BSC, [redacted] • Versus mFOLFOX, [redacted]
N/A	The formula to cap the time on treatment with mFOLFOX at 24 weeks, equating to a maximum of 12 treatment cycles, allows up to 25 weeks of treatment and captures the cost of 13 treatment cycles.	Correct minor error in model code to cap mFOLFOX treatment cycles at a maximum of 12 (per the EAG preferred base case).	• Versus BSC[redacted] • Versus mFOLFOX,[redacted]
Key issue 4: Inclusion of treatment wastage for ivosidenib	No wastage was assumed for oral therapies (with costs applied as a per 7-day model cycle average). Effectively assuming packs could be split, and patients finish their existing pack before a new pack is administered.	Account for ivosidenib wastage (using approach in the EAG preferred base case).	• Versus BSC, [redacted] • Versus mFOLFOX, [redacted]
Additional issue 2: Apply weighted healthcare	NHS reference costs (non-elective short stay) were selected to	NHS reference costs (weighted average non-	• Versus BSC, [redacted] • Versus mFOLFOX, [redacted]

resource group costs inclusive of non-elective long and short stays to adverse events	represent adverse event management costs.	elective long stay and non-elective short stay) were selected to represent adverse event management costs (per the EAG preferred base case).	
Company's revised base case following technical engagement (change from company submission base case)			• Versus BSC, [redacted] • Versus mFOLFOX, [redacted]

Abbreviations: BSC, best supportive care; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin.

Sensitivity analyses around revised base case

Tornado diagrams showing the results of the one-way sensitivity analysis around the revised base case are presented in Figure 1, for the comparison with BSC (left) and mFOLFOX (right), the key model drivers were consistent with those identified in the original company submission.

Figure 2 presents incremental cost-effectiveness planes from 5,000 probabilistic iterations for the comparison with BSC (left) and mFOLFOX (right). Figure 3 presents the cost-effectiveness acceptability curve. Probabilistic results were comparable with the revised deterministic base case presented in Table 4.

Scenarios from the original company submission were re-run around the revised company base case, with results presented in Table 5.

Figure 1: Tornado diagram (revised company base case), INMB versus BSC (left) and mFOLFOX (right)

Abbreviations: BSC, best supportive care; CT, computerised tomography; ECG, electrocardiogram; HCRU, health-care resource use; HR, hazard ratio; INMB, incremental net-monetary benefit; IV, intravenous; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; ToT, time on treatment; WTP, willingness to pay.

Note: INMB calculated using a WTP threshold of £30,000 per QALY gained. Incremental QALYs account for a x1.7 severity modifier. Correlated inputs with joint uncertainty (such as parametric survival model coefficients and utility regression model coefficients) are not included in the OWSA.

Figure 2: Incremental cost-effectiveness plane, versus BSC (left) and mFOLFOX (right)

Abbreviations: BSC, best supportive care; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; PSA, probabilistic sensitivity analysis; WTP, willingness-to-pay; QALYs, quality-adjusted life years.

Figure 3: Cost-effectiveness acceptability curve

Abbreviations: BSC, best supportive care; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; WTP, willingness-to-pay.

Table 5: Scenario analyses around revised company base case

Scenario #	Incremental versus BSC			Incremental versus mFOLFOX		
	Costs (£)	QALYs (x1.7 modifier)	ICER (£/QALY) (x1.7 modifier)	Costs (£)	QALYs (x1.7 modifier)	ICER (£/QALY) (x1.7 modifier)
Revised company base case	[redacted]					
Time horizon, 10 years						
Time horizon, 25 years						
Discount rates, 1.50%						
Discount rates, 6.00%						
Ivosidenib OS, log-logistic						
Ivosidenib OS, generalised gamma						
Ivosidenib OS, exponential						
BSC OS, Gompertz						
BSC OS, exponential						
Ivosidenib PFS, generalised gamma						
Ivosidenib PFS, log-logistic						
BSC PFS, log-logistic						
Ivosidenib ToT, exponential						
Ivosidenib OS, PFS and ToT, log-logistic						
Ivosidenib OS, PFS and ToT, generalised gamma						
Ivosidenib OS, PFS and ToT, exponential						
BSC OS and PFS, Gompertz						
PFS assessment, investigator assessed						
mFOLFOX PFS curve, generalised gamma						
mFOLFOX PFS approach, naïve HR versus ivosidenib						
mFOLFOX PFS approach, exploratory RMST analysis						
mFOLFOX ToT approach, exponential through median						
Ivosidenib, dose interruptions approach						

Allow treatment beyond progression	[redacted]
Include IDH1 testing costs	
Source of utility values, TA474	
Source of utility values, ClarIDHy, progression	
Source of utility values, ClarIDHy, progression & treatment status	
Exclude intravenous administration disutility	
Exclude adverse event disutility values	

Abbreviations: BSC, best supportive care; HR, hazard ratio; NICE, National Institute of Health and Care Excellence; OS, overall survival; PFS, progression-free survival; PSMs, parametric survival models; RDI, relative dose intensity; RMST, restricted-mean survival time; TA, technology appraisal; ToT, time on treatment.

ID6164 - Technical engagement - Appendix

As requested, company revised base case results following technical engagement are presented in fully incremental probabilistic analysis in Table 1 (equivalent to Table 53 in the company submission), and fully incremental deterministic analysis in Table 2 (equivalent to Table 54 in the company submission).

Table 1: Revised company base-case results following technical engagement (probabilistic), equivalent to Table 53 in the CS

Technologies	Total			Incremental (versus BSC)			ICER versus BSC (£/QALY) (x1.7 modifier)	ICER incremental (£/QALY) (x1.7 modifier)
	Costs	LYG	QALYs	Costs	LYG	QALYs (x1.7 modifier)		
BSC	[redacted]	[redacted]	[redacted]					
mFOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

Table 2: Revised company base-case results following technical engagement (deterministic), equivalent to Table 54 in the CS

Technologies	Total			Incremental (versus BSC)			ICER versus BSC (£/QALY) (x1.7 modifier)	ICER incremental (£/QALY) (x1.7 modifier)
	Costs	LYG	QALYs	Costs	LYG	QALYs (x1.7 modifier)		
BSC	[redacted]	[redacted]	[redacted]					
mFOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

Thank you for highlighting the minor discrepancy in the QALY shortfall estimate reported in the company submission for the comparison with mFOLFOX. The parameters used to produce the QALY shortfall calculations in the original company submission are provided in Table 3, alongside the corrected proportional QALY shortfall estimate. Within the context of this appraisal, the criteria for applying x1.7 severity modifier/QALY weight are met.

Table 3: QALY shortfall (mFOLFOX comparison)

Parameter	**Value**
Starting age (years)	[redacted]*
Sex distribution (% female)	63.24%*
QALYs with disease (mFOLFOX arm)	[redacted]
Proportional shortfall (corrected)	95.89%
QALY weight	x1.7

Note: *Sex distribution and starting age rounded to 0 decimal places per the requirements of the published QALY shortfall tool
Abbreviations: QALY, quality-adjusted life year.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ivosidenib for treating advanced cholangiocarcinoma with an *IDH1* mutation after at least 1 therapy [ID6164]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (see section 1.1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please 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.

Do not include medical information about yourself or another person that could identify you or the other person.

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.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **16th August 2023.** 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 received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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

NICE National Institute for Health and Care Excellence

Part 1: Treating cholangiocarcinoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	CHIARA BRACONI
2. Name of organisation	UNIVERSITY OF GLASGOW / NHS SCOTLAND
3. Job title or position	PROFESSOR, CHAIR IN HEPATOBILIARY ONCOLOGY, CONSULTANT MEDICAL ONCOLOGIST
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with cholangiocarcinoma? ☐ A specialist in the clinical evidence base for cholangiocarcinoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NONE
8. What is the main aim of treatment for cholangiocarcinoma?	This approval concerns the use of Ivosidenib (IDH1 inhibitor) in chemo-refractory advanced cholangiocarcinoma patients.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	In this setting the main aims will be to improve symptomatology (assessed by QoL), to delay tumour progression (measured by progression free survival), and to extend life expectancy (measured by overall survival).
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A clinically significant treatment response in this setting includes: -prolongation of Progression Free Survival (PFS) as time from the starting of a second line treatment to date of tumour progression (date of Progressive Disease). PFS rate at 12 months with current standard of therapy is 0%. -extension of overall survival (OS), as time from the first dose of second line treatment to the date of death. A median OS greater than 6 months is expected for a new treatment to be better than the current standard of care. -symptoms control. Pain is the main symptom reported by patients with iCCA.
10. In your view, is there an unmet need for patients and healthcare professionals in cholangiocarcinoma?	Cholangiocarcinoma is a rare tumour with incidence < 5/100,000 in UK. Cholangiocarcinoma is anatomically divided into subtypes: intrahepatic (if originates from bile ducts within the liver), perihilar (if originates from bile ducts at the confluence between left and right bile ducts), distal (if originates in the common bile duct), gallbladder cancer (if originates in the gallbladder). Despite this classification can affect the surgical treatment recommended for early stage resectable cholangiocarcinoma, treatment of advanced cholangiocarcinoma patients does not differ across the subtypes. However, recent genomic profiling has shown that enrichment of different molecular alterations can occur within the subtypes, with enrichment of IDH1 mutations being prevalent in intrahepatic cholangiocarcinoma. Cholangiocarcinoma treatment represents an unmet need. Median overall survival (from starting first line to death) ranges between 6 and 12 months with the current standard of care, which includes a first line chemotherapy with Cisplatin-Gemcitabine (or gemcitabine monotherapy) and a second line chemotherapy with mFolfox in UK. Specifically, chemo-refractory cholangiocarcinoma patients (those who have progressed after first line chemotherapy) have a poor prognosis with paucity of effective treatment options. Expected median overall survival of advanced chemo-refractory cholangiocarcinoma patients is 6 months.

	To date the only recommended therapy is chemotherapy with mFolfox, which however gives marginal benefit with RR 5%, PFS rate at 12 months of 8.6% at 12 months, median OS of 6 months and grade 3/4 toxicity in 60% of patients.
11. How is cholangiocarcinoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	ESMO guidelines are international European guidelines that guide treatment of biliary tract cancer (including cholangiocarcinoma), which suggests the use in second line of mFolfox and that of targeted therapies (including IDH-1 inhibitors) according to the molecular alterations of each tumour. (Vogel Ann Oncol 22). In UK, chemo-refractory cholangiocarcinoma patients who have progressed to first line chemotherapy do currently receive the following treatment: -Active Symptomatic Control (ASC) and mFOLFOX chemotherapy (combination of oxaliplatin and fluorouracil) which comprises of intravenous administration of chemotherapy and requires a central venous access (PICC line or PORT-a-CATH) to enable 46-hrs infusion of fluorouracil without need for overnight stay. The chemotherapy is given in hospital every 2 weeks and requires bloods taken every two weeks before each administration of chemotherapy. This treatment has been approved on the bases of the ABC-06 trial (Lamarca, JCO 2019 Vol37;15abstr4003), which has shown clinical benefit over ASC alone in patients with biliary cancers (including cholangiocarcinoma). RR was 5%, PFS rate at 12Months of 8%. Median Overall Survival for ASC+mFolfox was 6.2 months vs 5.3 months for ASC alone. At 1 year 26% were still alive in the ASC+mFolfox while only 11% were alive in the ASC arm. Expected median OS: 6.2 months -Active Sympotmatic Control (ASC) if patient's fitness is not satisfactory for second line chemotherapy with mFolfox. In this case the median OS is expected to be < 5.3 months, with <9% being alive at 1 year.

	Expected median OS: <5.3 months Please note that currently only 40% undergo mFolfox as second line with majority receiving best supportive care. Molecular profiling is currently recommended within the NHS for cholangiocarcinoma and treatment for FGFR2 inhibitor is recommended in tumours harbouring FGFR2 fusions. The current pathway of care is well defined across UK. After failure to first line chemotherapy, patients are offered second line treatment with ASC+mFolfox providing their fitness is appropriate. The judgement of fitness is subjected to medical assessment and scored according to the Eastern Cooperative Oncology Group (ECOG). Patient with performance status ECOG 0-2 are offered ASC+mFolfox. In case of ECOF 3-5 patients are supported with ASC. The same pathway of care is applied across UK, independently on regional areas. I currently work in Scotland, where this approach is taken. I have been working in England from 2014 to 2019 and the same pathway of care was followed. Ivosidenib would change the treatment of IDH1 mutant cholangiocarcinoma after failure to first line therapy. Ivosidenib would impact on: - quality of life by --improving symptom control ((as shown in the QoL assessment where Ivosidenib offered better control). --delaying tumour progression (PFS rate at 12 months was 22% with ivosidenib, 0% with plavebo, and is expected to be 8% with mFolfox))

	-- reducing neutropenia incidence, that can lead to need for hospital admissions. - life expectancy (as median OS of 10.9 months compares very favourably with the historical 6 months) - reducing costs related to infusional therapy -- reducing need for hospital visits (as Pemigatinib is an oral treatment) -- no need for central venous accesses (as Pemigatinib is an oral treatment)
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Currently there is no access to IDH1 inhibitors in UK. Therefore, even if a patient is identified with a IDH1 mutant tumour, he/she is not offered the best available treatment. Ivosidenib would be used in the secondary setting, in specialist clinics under the supervision of medical oncologists. No investment are needed, as this is an oral treatment and requires no additional infrastructures to the existing ones Current standard of care includes mFolfox which requires intravenous administration of oxaliplatin (over 2 hours) and fluorouracil (in bolus and over 48 hours). This requires: 7-10 days before starting treatment: central venous access (PICC line or PORT-a-CATH) to be inserted by vascular /radiology department. Risk associated with these devices include infection (2%) and clotting (20%), which may require replacement of the line during the course of chemotherapy. Day 0 of each cycle: outpatient oncology appointment for pre-chemotherapy assessment and prescription.

	Day 1 of each cycle: administration of i.v. mFolfox in hospital in Medical Day Care Units with dedicated trained nurses. Day 3 of each cycle: removal of pump (hospital or district nurse at home). Cycles will be repeated every 14 days Treatment with Ivosidenib will be given as oral administration requiring: Day 1 of each cycle: outpatient oncology appointment for pre-treatment assessment and prescription. Assessment every 4 weeks.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I expect Ivosidenib to provide a clinically meaningful benefit compared with current standard of care as shown in the phase III randomized trial compared to best supportive care. Even in comparison to mFolfox which is the current SOC for 40% of patients, Ivosidenib compares favourably for IDH1 mutant tumours from cross-trial comparisons in terms of PFS, and OS.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Ivosidenib would be restricted to all patients with IDH1 mutation without any further biomarkers.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	It is an oral treatment, please see notes above.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No, genomic testing is currently performed
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes, as demonstrated In the Claridhy trial patients have reported a benefit in QOL with improvement of their symptoms and social life,
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	I believe the use of Ivosidenib in chemo refractory cholangiocarcinoma would make a significant impact on health-related benefits for these patients by improving their quality of life, extending their life expectancy (as discussed above). Cholangiocarcinoma patients lack effective therapeutic options. Ivosidenib fills this gap by confirming a remarkable value for a subpopulation of patients.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Ivosidenib is well tolerated. Physician report to have been unable to distinguish placebo and treatment arm In the trial. The grade 3 AE reported in the trial (Ascitis) was more likely to be associated with progressive disease.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	Yes

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA722]?	No
23. How do data on real-world experience compare with the trial data?	Real life data for Ivosidenib are not available yet.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. 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. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality nolegislation	no

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. 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.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Reporting of the indirect treatment comparison was not sufficiently transparent (see sections 3.3 and 3.4 of EAR)	The ClarIDHy trial is a phase 3 randomized trial which compares Ivosidenib and Best Supportive Care. However, an indirect comparison has been performed with the ABC-06 trial as 40% of patients undergo Folfox as second line. Foflox includes a heterogenous group of patients, which include iCCA (44%). However, IDH1 mutation rate in ABC-06 is not known, so it is not possible to perform a matched comparison. Another difference between ClarIDHy and ABC-06 relates to the number of lines patients received after first line. Nonetheless, even when matched to patient from the Claridhy, who had only one previous line (as per ABC06 eligibility criteria), ivosidenib resulted advantageous.
Uncertainty in the extrapolation of overall survival for ivosidenib (see section 4.2.6)	I would expect OS 5 years for iCCA patients undergoing Ivosidenib being around 5-6% We are lacking prospective data. However, real life data from the ENSCCA international registry (including overall more than 2500 patients with cholangiocarcinoma), sets a 5yr OS for iCCA at 3.1 %.

Which, if any, of the distributions in Table 18 of the EAR have clinically plausible landmark overall survival estimate for ivosidenib?	However, this reflects an OS for the whole population starting first line SACT. We do know that some iCCA are more aggressive than others and that OS may be affected by comorbidities. Therefore, I would expect 5yr OS to be higher for patients undergoing Ivosidenib, because 1) the Ivo sidenib population would be better selected with less comorbidities and better prognosis, 2) there was less second line SACT prescribed in ENSCCA registry as patients were treated before ABC-06, 3) ivosidenib is providing an advantage on survival.
Whether to allow for ivosidenib treatment beyond progression (see section 4.2.6) Would ivosidenib continue to be offered after progression in NHS clinical practice?	I would not recommend ivosidenib after progression.
Whether to include treatment wastage for ivosidenib (see section 4.2.8) How would ivosidenib be dispensed if used in NHS clinical practice (i.e how frequently and in what quantity) and would	It will be dispensed every 4 weeks, but I will ask patients to be medically assessed after 2 weeks for the first month to assess tolerability and every 4 weeks afterwards.

there be monthly wastage?	
Modelling of time on treatment for mFOLFOX, and its acquisition and administration costs (see section 4.2.8) How often is a peripherally inserted central catheter removed during treatment with mFOLFOX and when?	See above. Patients are asked to have a central venous access system at beginning and then flushed and dressed every two weeks.
Whether and how to include subsequent treatment costs (see section 4.2.8) What are the expected subsequent treatments for patients receiving mFOLFOX, best supportive care	If patient is still fit at progression to Ivosidenib, I would offer subsequent treatment (first choice clinical trial and if not other SACT such as Folfox)

and ivosidenib (were it recommended)?	
Other issue 1: **Include a clinical examination and blood test every month for ivosidenib in the first three months of treatment (see section 4.28, p47)** Is this an appropriate assumption to model?	I would repeat blood tests and at least do a phone assessment every 4 weeks before dispensing the new batch of ivosidenib. CT scan and physical examination will be every three months.
Other issue 2: **Apply weighted healthcare resource group costs inclusive of non-elective long and short stays to adverse events (see section 4.28, p47-48)**	Majority of Grade 3 AE will require a 2-3 days admission. The only ones which may require an extended stay is pneumonia and acute kidney injuries.
Other issue 3: **Health state utility dependent on progression and treatment status**	I cannot comment

from ClarIDHy (see section 4.27, p42-44)	
Are there any important issues that have been missed in EAR?	No

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Ivosidenib provides clinically relevant benefit (symptom control, tumour growth control and advantage in survival) over best supportive care as per the Claridhy trial (randomized phase III trial)
Ivosidenib provide clinically relevant benefit (symptom control, tumour growth control and advantage in survival) over mFOlfox through indirect comparison (as 12 months PFS rate is 22% vs 8% and median OS is 10.6 vs 6.2 months)
Ivosidenib is very well tolerated
I would recommend Ivosidenib after failure to first line for cholangiocarcinoma patients with IDH1 mutation, and I would monitor the patient with blood tests every 4 weeks and radiological assessment every 3 months

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ivosidenib for treating advanced cholangiocarcinoma with an *IDH1* mutation after at least 1 therapy [ID6164]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (see section 1.1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please 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.

Do not include medical information about yourself or another person that could identify you or the other person.

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.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **16th August 2023.** 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 received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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

Part 1: Treating cholangiocarcinoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	John Bridgewater
2. Name of organisation	UCL
3. Job title or position	Prof
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with cholangiocarcinoma? ☒ A specialist in the clinical evidence base for cholangiocarcinoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for cholangiocarcinoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Cholangiocarcinoma is operable with curative intent in a minority of patients. The majority of those who go to surgery relapse with advanced disease therefore the majority of cholangiocarcinoma patients receiving treatment do so on a palliative

	basis. The intention therefore would be to improve survival while maintaining quality of life.
9. 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)	Currently the median overall survival for all patients treated with standard of care chemotherapy (cisplatin gemcitabine) in the UK is 11.7 months. A clinically significant benefit is an improvement in median progression free your overall survival of 1 to 2 months or an improvement in the 1 and 2-year survival would be very meaningful for this poor outcome malignancy. Second-line standard of care chemotherapy is FOLFOX however the benefit from this is modest, providing a survival benefit of approximately 1 month. This is offered to patients but in the context of the balance conversation about quality of life and best supportive care.
10. In your view, is there an unmet need for patients and healthcare professionals in cholangiocarcinoma?	Yes, there is a very significant unmet need.
11. How is cholangiocarcinoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	The British Society of gastroenterology (BSG) guidelines are currently in press. They closely resemble the European Society of medical oncology (ESMO) guidelines. [1] The pathway of care is described but real world evidence published by the user organisation AMMF suggests that this is uncommonly adhered to. [2] Critically for this application it is uncertain how many patients currently are profiled for IDH1 mutation as permitted by the NHS England national directory (NHS England » National genomic test directory). IDH1 mutated patients would represent a maximum of between 5 to 10% of all cholangiocarcinomas diagnosed in the UK every year. In the context of uncertain demographics this is likely to be between 150-300 patients per annum in total. It is likely that currently only a minority of these patients receive testing. Furthermore it would be uncertain as to the time scale of optimal adherence to testing guidance. Some patients will clearly not be suitable for testing because of poor performance status.

	Ivosidenib would be used following first-line and second line standard of care treatment and have a very significant impact on the quality of life and survival of these patients.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This is a novel therapy and will be used in the same context as described in the ClarIDHy clinical study. [3] [4] This is following failure of standard of care therapy and in the UK is likely to be either following first-line cisplatin and gemcitabine or second-line FOLFOX. This is an oral medication with very modest toxicity and would be given in the outpatient clinic setting.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The ClarIDHy study demonstrated an improved progression free survival and potentially an improved overall survival. The treatment is without significant toxicity and therefore should provide improved survival without an impact on quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The ClarIDHy study did not identify any subgroups who would be more or less likely to benefit. Critically the benefit was present in both second and third line therapy.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	This is an oral medication.

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)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	IDH1 testing is on the National directory.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	My clinical impression is that quality of life is maintained whilst on ivosidenib.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Ivosidenib will be potentially a second targeted therapy for cholangiocarcinoma, the first being pemigatinib for FGFR 2 fusion positive cholangiocarcinomas. Targeted therapies for this cancer of high unmet need unlikely her to have significant benefits with modest toxicities. As such it is a step change in the treatment of these malignancies.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects on ivosidenib are modest.

20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The ClarIDHy study was running in the UK and the study population resembles that found in the UK. He progression free and overall survival benefit is the outcome of greatest importance. There was crossover in the study making the overall survival outcome difficult to interpret however further analysis using a protocol planned RPSFT adjustment was positive. Subsequent to the ClarIDHy there has been an expanded use programme and a phase 3B study run in the UK. I am not aware of any further toxicities that have emerged.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA722]?	No
23. How do data on real-world experience compare with the trial data?	Further experience as described in the response to question 20 has suggested that the study outcome is compatible with real world experience.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. 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	N/A

partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. 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.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Reporting of the indirect treatment comparison was not sufficiently transparent (see sections 3.3 and 3.4 of EAR)	The plan to use RPSFT was not given in the original protocol.
Uncertainty in the extrapolation of overall survival for ivosidenib (see section 4.2.6) Which, if any, of the distributions in Table 18 of the EAR have	As above

clinically plausible landmark overall survival estimate for ivosidenib?	
Whether to allow for ivosidenib treatment beyond progression (see section 4.2.6) Would ivosidenib continue to be offered after progression in NHS clinical practice?	In clinical practice this would be unlikely. If the patient were sufficiently fit, they would be offered FOLFOX. If unfit, best supportive care.
Whether to include treatment wastage for ivosidenib (see section 4.2.8) How would ivosidenib be dispensed if used in NHS clinical practice (i.e how frequently and in what quantity) and would there be monthly wastage?	Wastage would occur and should be included.
Modelling of time on treatment for mFOLFOX, and its	CVC would be inserted once.

acquisition and administration costs (see section 4.2.8) How often is a peripherally inserted central catheter removed during treatment with mFOLFOX and when?	
Whether and how to include subsequent treatment costs (see section 4.2.8) What are the expected subsequent treatments for patients receiving mFOLFOX, best supportive care and ivosidenib (were it recommended)?	Patients progressing on either FOLFOX or ivosidenib ae likely to be offered the alternative treatment if sufficiently fit. If unfit, they would be offered BSC. Patients on BSC are unlikely to proceed to either treatment.
Other issue 1: **Include a clinical examination and blood test every month for ivosidenib**	Yes

in the first three months of treatment (see section 4.28, p47) Is this an appropriate assumption to model?	
Other issue 2: **Apply weighted healthcare resource group costs inclusive of non-elective long and short stays to adverse events (see section 4.28, p47-48)**	Agreed but these are unlikely to be greater on ivosidenib versus BSC
Other issue 3: **Health state utility dependent on progression and treatment status from ClarIDHy (see section 4.27, p42-44)**	N/A
Are there any important issues that have been missed in EAR?	Not that I know of.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Cholangiocarcinoma is a cancer of unmet need
Between 150-300 patients a year in the UK would be eligible for IDH1 targeting (available on National Directory)
IDH1 targeting with ivosidenib provides >30% PFS rate at 6 months compared to <5% for BSC
IDH1 targeting with ivosidenib provides a median PFS from 1.4m to 2.7m
Ivosidenib is an oral therapy with very modest toxicities

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

1. Vogel A, Bridgewater J, Edeline J, et al. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology 2023;34(2):127-140. DOI: 10.1016/j.annonc.2022.10.506.
2. 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):3825-3842. (In eng). DOI: 10.3748/wjg.v29.i24.3825.
3. Abou-Alfa GK, Macarulla T, Javle MM, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. The Lancet Oncology 2020;21(6):796-807. DOI: 10.1016/S1470-2045(20)30157-1.

4. Zhu AX, Macarulla T, Javle MM, et al. Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With IDH1 Mutation: The Phase 3 Randomized Clinical ClarIDHy Trial. JAMA Oncology 2021;7(11):1669-1677. DOI: 10.1001/jamaoncol.2021.3836.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ivosidenib for treating advanced cholangiocarcinoma with an *IDH1* mutation after at least 1 therapy [ID6164]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with cholangiocarcinoma or caring for a patient with cholangiocarcinoma. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (see section 1.1 and Table 1).

A patient perspective could help either:

Patient expert statement

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 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).

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.

Patient expert statement

Ivosidenib for treating advanced cholangiocarcinoma with an *IDH1* mutation after at least 1 therapy [ID6164]

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **16th August 2023.** 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 received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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

Part 1: Living with this condition or caring for a patient with cholangiocarcinoma

Table 1 About you, cholangiocarcinoma, current treatments and equality

1. Your name	Helen Morement
2. Are you (please tick all that apply)	☐ A patient with cholangiocarcinoma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with cholangiocarcinoma? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	**Cholangiocarcinoma-UK and Imperial College (Prof Shahid Khan)**
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 ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I draw my experience from my work with AMMF – The Cholangiocarcinoma Charity.

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with cholangiocarcinoma? **If you are a carer (for someone with cholangiocarcinoma) please share your experience of caring for them**	I am CEO of the charity AMMF. We support patients with cholangiocarcinoma (CCA) and their caregivers, providing them with information on treatments and clinical trials. We communicate with patients and their loved ones on a one to one basis by email and telephone, and face to face at our annual conference and with roundtable discussion groups, and the many patients using AMMF's private discussion groups on social media. www.ammf.org.uk
7a. What do you think of the current treatments and care available for cholangiocarcinoma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	While the incidence of CCA is increasing year on year, with parallel mortality, there remains limited treatments available under the NHS for those with this cancer. Currently a resection is the only potentially curative treatment there is for CCA, so inoperable patients are left with very limited options. The standard first line treatment for those with inoperable CCA is the chemotherapy combination, Gemcitabine and Cisplatin – and this treatment has not been improved on for over a decade. Comparison with advances in the treatments and care of those with many other cancers in this country, and for those with CCA in other countries, is unfavourable. From my experience, both CCA patients and their loved ones find understanding a diagnosis of CCA and its implications extremely difficult. Many of those who are inoperable struggle to comprehend that there really is no effective, curative treatment, and ask AMMF for advice on, 'treatments not available under the NHS'.

8. If there are disadvantages for patients of current NHS treatments for cholangiocarcinoma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The standard first line treatment for those with inoperable CCA is the chemotherapy combination, Gemcitabine and Cisplatin – and this treatment has not been improved on for over a decade. It is given intravenously, which means repeated visits to hospital, which is disruptive to life in general, and to family life. Also, patients starting this chemotherapy will not know if this will be effective for them or not. If it is effective for them, it may only be to the point of extending their life for a few months. Patients may endure a number of side effects with this chemotherapy, including repeated infections requiring hospitalisation which takes them away from their families – a very difficult situation when their life expectancy is so short.
9a. If there are advantages of ivosidenib 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?** **9c. Does ivosidenib help to overcome or address any of the listed disadvantages of current treatment that**	For those with CCA, treatment in the second line is standard chemotherapies – which may or may not be helpful - and/or best supportive care. Ivosidenib is a treatment offered in a second line setting to those CCA patients with a certain molecular mutation – IDH1. Because this is a 'targeted therapy', those with the IDH1 mutation and eligible for ivosidenib will know from the outset that this treatment 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.

you have described in question 8? If so, please describe these	Plus, as an oral therapy, this has certain quality of life advantages over an intravenous therapy, including spending less time in hospital receiving treatment.
10. If there are disadvantages of ivosidenib over current treatments on the NHS please describe these. For example, are there any risks with ivosidenib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Patients and carers do not see disadvantages in the treatment, but they see disadvantage in that it is not currently available to those who might otherwise be eligible to receive it.
11. Are there any groups of patients who might benefit more from ivosidenib 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	All those patients with CCA, who have an IDH1 mutation, and who fit the eligibility criteria should benefit from ivosidenib.
12. Are there any potential equality issues that should be taken into account when considering cholangiocarcinoma and ivosidenib? 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	None 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?	CCA patients and carers see that this therapy has been approved in other countries, and those in this country who would be eligible to receive it find it very difficult to understand why it is not available to them under the NHS.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Reporting of the indirect treatment comparison was not sufficiently transparent (see sections 3.3 and 3.4)	
Uncertainty in the extrapolation of overall survival for ivosidenib (see section 4.2.6)	

Whether to allow for ivosidenib treatment beyond progression (see section 4.2.6) We consider patient perspectives may particularly help to address this issue In your experience, do people continue with treatment on ivosidenib (or other treatments for cholangiocarcinoma) after progression?	
Whether to include treatment wastage for ivosidenib (see section 4.2.8) We consider patient perspectives may particularly help to address this issue If you have any experience with orally	

administered treatments did you find that there was any monthly wastage?	
Modelling of time on treatment for mFOLFOX, and its acquisition and administration costs (see section 4.2.8) We consider patient perspectives may particularly help to address this issue Is a peripherally inserted central catheter (PICC) removed after each treatment, or at discontinuation of mFOLFOX treatment?	
Whether and how to include subsequent treatment costs (see section 4.2.8)	

We consider patient perspectives may particularly help to address this issue Would there be any treatments subsequent to best-supportive care for people with cholangiocarcinoma?	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The incidence CCA is increasing year on year, with parallel mortality
- There are very limited treatments currently available under the NHS to those with an inoperable CCA, in either the first or second line setting.
- Patients undergoing standard chemotherapies for CCA will not know if the treatment will work for them or not, until they have undergone several cycles of treatment – and if treatment does work, the survival benefit may be very limited.
- In the second line setting, ivosidenib, a targeted therapy, offers those with the IDH1 mutation the hope of extended survival over the more standard chemotherapies and/or best supportive care.
- As an oral therapy, this has certain quality of life advantages over an intravenous therapy, including spending less time in hospital receiving treatment.

Thank you for your time.

Your privacy

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Ivosidenib for treating advanced cholangiocarcinoma with an *IDH1* mutation after at least 1 therapy [ID6164]

ERG critique of the company's response to technical engagement

Produced by Aberdeen HTA Group

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Contains [redacted]

In their response to technical engagement, the company addressed the issues raised in the ERG report and provided some revised economic analyses. This addendum to the ERG report provides a brief critique of the company response to the issues identified. It should be read in conjunction with the company's technical engagement response document.

Key issues

The key issues raised in the EAG report are outlined in Table 1. A summary of each issue can be found in the Executive summary of the main ERG report. A point-by-point critique of the company's response to each issue is provided below.

Table 1 Summary of key issues

ID6164	Summary of issue	Report sections
1	Reporting of the indirect treatment comparison was not sufficiently transparent.	3.3, 3.4
2	Uncertainty in the extrapolation of overall survival for ivosidenib	4.2.6
3	Whether to allow for ivosidenib treatment beyond progression	4.2.6
4	Whether to include treatment wastage for ivosidenib	4.2.8
5	Modelling of time on treatment for mFOLFOX, and its acquisition and administration costs	4.2.8
6	Whether and how to include subsequent treatment costs	4.2.8

Issue 1. Reporting of the indirect treatment comparison was not sufficiently transparent

The EAG raised a concern that the company's indirect treatment comparison with mFOLFOX, using the Bucher method, had not been transparently reported. In particular, the company relied on a subgroup of ClarIDHy trial participants to derive the survival hazard ratio used in the Bucher ITC. This was not clearly described or justified by the company in their report or in response to a clarification question. The EAG suggested that additional detail be provided by the company, as the ITC provides a key input to the economic model.

It is unfortunate that the company has provided no further details or justification for their ITC approach. As a result, this remains an area of uncertainty which has a large influence on the ICER. The criticisms outlined in the EAG report have not been addressed, and include:

- *Lack of justification and clarity over selection of the ClarIDHy trial subgroup used in the ITC – including the need to exclude patients with more than one prior line of therapy, when subgroup analysis did not find a difference in the effect of ivosidenib by prior lines of therapy.*
- *Lack of clarity over the data cut used for the ITC, since the numbers reported for the ITC subgroup do not appear to match with numbers available in the final OS data cut for the ClarIDHy trial.*[1]
- *Lack of transparency in reporting of the analysis used to obtain the crossover adjusted survival HR for ivosidenib feeding into the ITC – including the baseline characteristics by treatment arm in the selected subgroup, presentation of the Kaplan Meir curves before and after crossover adjustment, and details of the crossover adjustment in the selected subgroup.*

Without the above details, the EAG finds it difficult to comment on the robustness of the HR derived from the company's ITC with mFOLFOX.

Issue 2. Uncertainty in the extrapolation of overall survival for ivosidenib

The company disagrees with the EAGs selection of the generalized gamma curve. They have reiterated their arguments underpinning their selection of the log-normal – maintaining their belief that it provides the best justified selection. They also note that a more optimistic log-logistic curve was used for decision making in NICE TA722,[2] which estimated 5-year OS of 11% in the pemigatinib arm, albeit in different molecular population of CCA.

The EAG acknowledge the company's arguments and accept there is no clearly preferred single option with respect to extrapolation of OS. However, on balance of the AIC, BIC, and visual fit to the observed KM data, the EAG still believes the generalised gamma curve provides a plausible option for the reasons outlined in its report. It provides a middle ground in terms of extrapolated survival landmarks compared with the lowest AIC, log-normal, and the lowest BIC, exponential, curve (Figure 1). This remains an important issue that warrants consideration by the committee. Accepting that this uncertainty cannot be fully resolved, the EAG presents an alternative EAG base case analysis using the log-normal in place of the generalised gamma curve for extrapolation of ivosidenib OS (see Appendix).

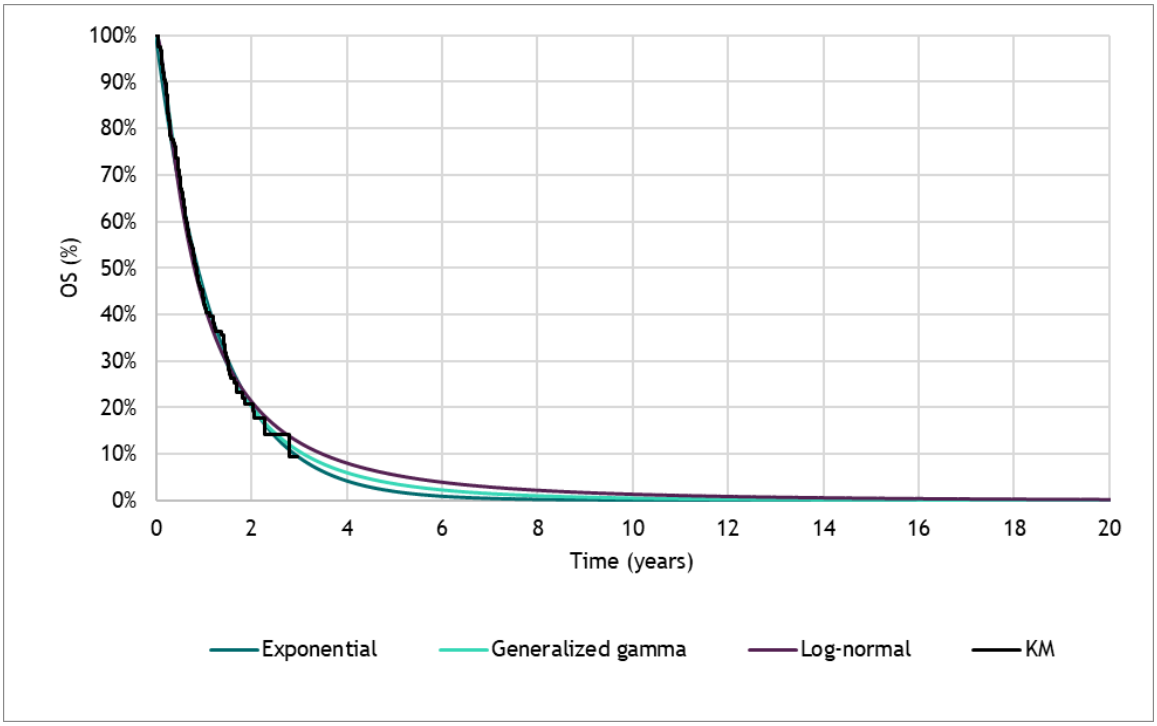

Figure 1 Alternative extrapolations of ivosidenib OS

Issue 3. Whether to allow for ivosidenib treatment beyond progression

The company assume that treatment with ivosidenib is discontinued upon disease progression. The company note new wording to their SmPC, in line with the GB marketing authorisation, which does state that "treatment should be continued until disease progression or until treatment is no longer tolerated by the patient". They further reiterate expert opinion suggesting ivosidenib would be stopped on progression in practice.

The EAG has remaining concerns that the company's approach artificially reduces expected time on treatment with ivosidenib compared to what was observed in the ClarIDHy trial, and what might be expected in routine practice. There are two related concerns here:

1. *The company stated that in ClarIDHy, "treatment with ivosidenib beyond progression was permitted where the investigator deemed that there was clinical benefit" (Company submission, document B, section B.3.2.3.1). Thus, we expect that this treatment beyond progression may have had a positive effect of OS. The company's approach results in the treatment costs being potentially misaligned with the efficacy data used in the model.*
2. *The observed ivosidenib KM data for PFS and ToT look to be closely related, particularly in the tails of the observed distributions (see Figure 4 of EAG report).*

The chosen extrapolation for PFS, however, falls below both the observed PFS and ToT data. Even if treatment is to be stopped upon progression, the poorly fitting PFS curve may artificially reduce extrapolated ToT compared to what would be expected in practice. The more mature ToT data may in fact provide a reasonable guide for extrapolation of longer term PFS.

The EAG believe this issue remains unresolved and needs to be discussed by the committee.

Issue 4. Whether to include treatment wastage for ivosidenib

The EAG questioned the validity of the company's assumptions around splitting of packs and zero wastage of prescribed ivosidenib. Following further consultation with clinical experts, the company has received feedback that pack splitting would not occur in routine practice in the NHS in England, and so has revised its base case to include wastage as per the EAGs preferred approach; i.e. full packs of 30 are dispensed one at a time, and a new pack of ivosidenib is dispensed to patients at the beginning of model cycles in which less than a week's supply of tablets remains.

The EAG believes this is more realistic and should adequately account for wastage so long as patients are dispensed one pack of ivosidenib at a time. If dispensing follows a three-monthly supply, in line with the follow-up schedule, this approach could still underestimate the cost of treatment.

Issue 5. Modelling of time on treatment for mFOLFOX, and its acquisition and administration costs

The EAG criticised the company's approach of assuming that ToT for mFOLFOX follows progression free survival, up to maximum of 12 cycles. This is because it fails to account for discontinuation due to other reasons and overestimates the number of cycles that patients receive in the model compared to what was observed in the ABC-06 trial,[3] the source of efficacy data for mFOLFOX. Therefore, the EAG preferred to use an exponential curve for ToT fitted to the median number of cycles observed in the ABC-06 trial. This is used to extrapolate the proportion of patients remaining on treatment up to 12 cycles.

In their response to technical engagement, the company argue that this approach, when applied to a fixed duration treatment protocol, may underestimate the proportion that

complete the full course (12 cycles). They argue that it is reasonable to assume that patients are more likely to complete a full course of treatment when it is of fixed duration (12 cycles), and so assuming a constant rate based on the median may underestimate the true ToT curve.

The EAG has checked the impact in the model of applying the constant rate of discontinuation based on the median number of mFOLFOX cycles observed in the ABC-06 trial. This results in an [redacted] *cycles and* [redacted] *of the cohort completing (incurring the cost of) 12 cycles of mFOLFOX. This compares to a reported IQR of 2 to 6 cycles and 16% reported to have completed all 12 cycles in the ABC-06 trial.*[3] *Thus, the EAGs preferred approach appears to provide a reasonable fit to the observed treatment data from ABC-06.*

For this reason, and for consistency with the efficacy data informing the model, the EAG continues to prefer the approach of allowing time on mFOLFOX treatment to follow an exponential distribution informed by the median number of cycles from ABC-06. The EAG considers that this issue remains unresolved, and that it has a moderate impact on the ICER.

The Company also argue against the EAG's revised administration assumptions for mFOLFOX. Based on its clinical expert advice, the EAG suggested that the company had overestimated the cost of administering mFOLFOX by assuming patients return to hospital (Non-consultant led OP appointment) to have their PICC removed after each mFOLFOX treatment cycle, rather than once at completion/discontinuation of treatment. Based on its clinical advice, the EAG assumed that patients would require a district nurse visit to remove their chemotherapy pump during each treatment cycle, and would only trigger a further outpatient appointment to have their PICC removed following completion (discontinuation) of their treatment course. In their response to technical engagement, the company argue that their approach, of applying a Non-consultant led OP appointment for each treatment cycle, is still appropriate because 1) it is consistent with the assumptions of prior appraisals in this area; 2) some patients may return for a non-consultant led OP appointment to have their pump removed after each cycle, even if not their PICC; 3) there are risks associated with PICCs, such as infection, which may require line replacement prior to completion of the treatment course; and 4) national guidelines suggest a line be flushed and dressed every week, which will have an associated tariff cost due to required nurse time. They, therefore, believe their approach is more suitable.

The EAG acknowledges the company's point that practice may vary across patients and trusts, and that pump removal and care may trigger non-consultant led OP appointments for some patients. Reflecting on these points, and further uncertainty related to the availability of up-to-date costs for district nurse home visits, the EAG has chosen to realign its mFOLFOX administration costing assumptions with those of the company. Whilst the true cost of pump removal and PICC care between chemotherapy cycles remains uncertain, the impact on the ICER is relatively small, and the EAG acknowledges that its prior estimates may underestimate the true administration costs.

Issue 6. Whether and how to include subsequent treatment costs

At the clarification stage, the company confirmed that a proportion of patients in the ClarIDHy trial subsequently went on to receive further treatment (most frequently chemotherapy) following progression on ivosidenib. This subsequent treatment may have influenced the overall survival observed in the trial. The EAGs clinical expert also advised that subsequent treatment with mFOLFOX is consistent with what might be expected in routine practice if ivosidenib is introduced. The EAG, therefore, believe that costs of subsequent mFOLFOX treatment following progression on ivosidenib should be included in the model. Whilst a proportion of patients who received BSC in the ClarIDHy trial also received subsequent treatment following crossover to ivosidenib, this is not consistent with clinical practice. The EAG believe, however, that any potential benefit of this will have been adjusted out by the company's RPSFT analysis used to inform OS on BSC in the model.

In their response, the company have argued that exclusion of subsequent treatment costs is an appropriate assumption, citing consistency with the only prior NICE appraisal in CCA (TA722).[2] They further note the investigational nature of subsequent therapies received by patients in ClarIDHy and suggest that patients in clinical trials are often fitter than those treated in routine practice, suggesting it is more reasonable to assume that patients will move to BSC following progression on ivosidenib in routine practice.

The EAG maintains that it is more appropriate to account for the cost of subsequent therapy in the ivosidenib arm of the model, as this is consistent with the efficacy data informing the model and *expected clinical practice should ivosidenib be approved for routine use. The EAG consider this issue to be unresolved and requiring discussion by the committee.*

Additional Issues

Frequency of clinical monitoring with ivosidenib

The company argue against an EAG base case assumption of applying monthly clinical examination and blood testing costs for patients on ivosidenib during the first three months of treatment. The EAG assumed this based on its clinical expert advice, suggesting that more frequent follow-up may be expected when commencing a new oral therapy such as ivosidenib.

The EAG, however, acknowledges the company's arguments relating to recommended frequency of follow-up for advanced biliary tract cancer in ESMO guidance, and the lack of clarity on whether more frequent testing may also occur for mFOLFOX. Thus, the EAG has aligned its analysis with the company's on this point. It has a relatively minor impact on the ICERs.

Apply weighted healthcare resource group costs inclusive of non-elective long and short stays to adverse events

The company note that that they have aligned their revised base case with the EAGs preferred approach to costing adverse events, which applies weighted average healthcare resource group costs inclusive of non-elective long and short stays to adverse events.

The EAG agrees with the company's approach and considers this issue resolved.

Health state utility dependent on progression and treatment status from ClarIDHy

The company argues that health state utility should be incorporated only by treatment status in their model, rather than health state. They present evidence to suggest that this provided the best fit based on the AIC of several models tested.

The EAG maintain that whilst this approach may provide a good fit to the utility data observed in ClarIDHy, it is unsuitable for application in the model because it lacks face validity and inherently biases against mFOLFOX and BSC, where the on-treatment period is of fixed duration or non-existent. The EAG further note that the company present only the

AIC figures for their considered models, and that differences are small. The EAG continues to prefer utility values linked to progression status or progression status and treatment status.

The additional cost of IDH1 testing to identify the eligible population in the Ivosidenib arm

The company reiterated their arguments that that they believe IDH1 testing costs should not be included in the model, on the basis that "*it is now in the national genomic test directory and is now being reported in parts of the country*."

The EAG acknowledge that IDH1 testing is in the test directory but understands that this does not mean it will necessarily be requested or reported. Since ivosidenib, if it is recommended, will be the only IDH1 targeted treatment available for CCA the requirement for IDH1 testing in the patient population seems to be linked to its recommendation. Thus, the EAG believe that the marginal cost of IDH testing should be applied in the base case model. The EAG believe this issue remains unresolved.

EAG revised modelling assumption

The EAG has maintained its preferred modelling assumptions as outlined in section 6 of the main EAG report, except for ivosidenib monitoring costs and mFOLFOX administration costs which have now been aligned with the company's preferred assumptions.

The EAG prefers to apply an exponential function fitted to the median number of mFOLFOX cycles received by patients in the ABC-O6 study. Since the first version of this critique was submitted, an error was subsequently identified in the model implementation of this approach, resulting from the median number of treatment cycles (n=5) being equated a median time on treatment of 10 weeks. With the first treatment cycle being administered at time zero, this resulted in a median of 6 treatment cycles being modelled (starting at 0, 2, 4, 6, 8 and 10 weeks) rather than 5. To correct this, the EAG has reset the median time on treatment to equate with 50% of the cohort receiving 5 treatment cycles. This generates an IQR of [redacted] receiving the maximum 12 cycles, compared to the reported IQR of 2 to 6 cycles and 16% receiving the maximum 12 cycles in ABC-06.

For consistency with the intended approach, the EAG has updated its post technical engagement analysis with the above correction. The results are found in the following tables and figures, which can replace those provided in the first version of this critique.
Table 1 shows the cumulative impact of the EAGs base case modelling assumptions compared to company's revised base case. Table 2 and 3 present the full incremental analysis of the EAGs deterministic and probabilistic base case results respectively. Figures 2-4 present the graphical output of the PSA for the EAG revised base case, and Table 4 presents the results of deterministic scenario analysis on the EAGs revised base case.

As indicated above, the EAG have also provided an alternative set of base case results in which the log-normal distribution (as per the company's preference) is used in place for the generalised gamma for ivosidenib OS. These results are provided in the Appendix at the end of this document.

Table 1 EAG's preferred base case model assumptions – cumulative impact of changes on the company's revised ICER

Preferred assumption	Incremental versus BSC				Incremental versus mFOLFOX			
	Cost (£)	QALY (x1.7 modifier)	ICER (x1.7 modifier)	Change	Cost (£)	QALY (x1.7 modifier)	ICER (x1.7 modifier)	Change
Company revised base case	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	
1. OS extrapolation (ivosidenib): generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. Allow for ivosidenib treatment beyond progression (ivosidenib arm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. ToT extrapolation (ivosidenib): generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. ToT mFOLFOX: Exponential curve fitted to median number of treatment cycles in ABC-06	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Include subsequent treatment with mFOLFOX following progression on ivosidenib only*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. Recycle the discounted cost stream of mFOLFOX as an index treatment, to model its cost as a subsequent treatment (ivosidenib arm only)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. Apply the expected cost of subsequent FOLFOX treatment to all transitions out of the PFS state, to avoid over adjusting for the proportion who progress from the PF state (ivosidenib arm only).	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8. Include IDH testing for the ivosidenib arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9. Health state utility: By progression and Tx status (EAG base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

*Scenarios that use the company's estimate of expected subsequent FOLFOX treatments costs are corrected to reference the median number of treatment cycles (n=5) from the ABC-06 trial, rather than median number of treatment weeks (n=10), to calculate expected cost of subsequent mFOLFOX treatment

Table 2 EAG deterministic base case (full incremental analysis)

Technologies	Total			Incremental (versus BSC)			ICER versus BSC (£/QALY) (x1.7 modifier)	ICER incremental (£/QALY) (x1.7 modifier)
	Costs	LYG	QALYs	Costs	LYG	QALYs (x1.7 modifier)		
BSC	[redacted]	[redacted]	[redacted]					
mFOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

Table 3 EAG probabilistic base case (full incremental analysis)

Technologies	Total			Incremental (versus BSC)			ICER versus BSC (£/QALY) (x1.7 modifier)	ICER incremental (£/QALY) (x1.7 modifier)
	Costs	LYG	QALYs	Costs	LYG	QALYs (x1.7 modifier)		
BSC	[redacted]	[redacted]	[redacted]					
mFOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

Figure 2 Incremental cost-effectiveness scatter plot (EAG base case - Ivosidenib versus BSC)

Figure 3 Incremental cost-effectiveness scatter plot (EAG base case - Ivosidenib versus mFOLFOX)

Figure 4 Cost-effectiveness acceptability curves (EAG base case)

Table 4 Selected scenario analysis around the EAG base case (deterministic)

Parameter/ assumption	EAG base case	Scenario	Incremental versus BSC				Incremental versus mFOLFOX			
			Cost (£)	QALY (x1.7 modifier)	ICER (x1.7 modifier)	Change	Cost (£)	QALY (x1.7 modifier)	ICER (x1.7 modifier)	Change
EAG base case			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS extrapolation (ivosidenib)	Generalised gamma	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility source	ClarIDHy (Progression and Tx status	ClarIDHy (progression status)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ClarIDHy (Treatment status)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		NICE TA208 (mGC) by progression status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib ToT	Allow beyond progression	Cap and PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib wastage	Included	No wastage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment	Included following progression on ivosidenib	Excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

References

1. Zhu AX, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with IDH1 mutation: the phase 3 randomized clinical ClarIDHy trial. JAMA Oncol. 2021;7(11):1669-77.
2. National Institute for Health and Care Excellence. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [TA722]. 2021. Available from: https://www.nice.org.uk/guidance/ta722 (Accessed 29 August 2023).
3. Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol. 2021;22(5):690-701

Appendix: Alternative EAG base case using the lognormal distribution for extrapolation of ivosidenib overall survival

Table A1 EAG alternative deterministic base case (full incremental analysis) – log-normal for ivosidenib OS

Technologies	Total			Incremental (versus BSC)			ICER versus BSC (£/QALY) (x1.7 modifier)	ICER incremental (£/QALY) (x1.7 modifier)
	Costs	LYG	QALYs	Costs	LYG	QALYs (x1.7 modifier)		
BSC	[redacted]	[redacted]	[redacted]					
mFOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

Table A2 EAG alternative probabilistic base case (full incremental analysis) – log-normal for ivosidenib OS

Technologies	Total			Incremental (versus BSC)			ICER versus BSC (£/QALY) (x1.7 modifier)	ICER incremental (£/QALY) (x1.7 modifier)
	Costs	LYG	QALYs	Costs	LYG	QALYs (x1.7 modifier)		
BSC	[redacted]	[redacted]	[redacted]					
mFOLFOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ivosidenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

Figure A1 Incremental cost-effectiveness scatter plot (EAG alternative base case - Ivosidenib versus BSC) – log-normal for ivosidenib OS

Figure A2 Incremental cost-effectiveness scatter plot (EAG alternative base case - Ivosidenib versus mFOLFOX) – log-normal for ivosidenib OS

Figure A3 Cost-effectiveness acceptability curves (EAG base case) – log-normal for ivosidenib OS

Ivosidenib for treating advanced cholangiocarcinoma with an *IDH1* mutation after at least 1 therapy [ID6164]

Addendum: Further analysis and figures for the 1st committee meeting

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Figure 1 below shows selected OS curves for ivosidenib, the agreed Weibull curve for BSC, and the derived OS curve for mFOLFOX; the mFOLFOX curve (red) is derived by applying the hazard ratio from the Bucher ITC (based on the crossover adjusted ClarIDHy subgroup) to the EAGs preferred generalised gamma curve for ivosidenib. The company differ in that they prefer the lognormal curve for ivosidenib OS, and apply the HR for mFOLFOX to this instead. Also shown on the graph is the mFOLFOX curve when using the using the crossover adjusted ITT population rather than the subgroup from ClarIDHy to inform the ITC. Under this scenario, the hazard ratio is more conservative, and there is a smaller difference in OS between mFOLFOX and ivosidenib. It may be noted, however, that this infers a larger OS benefit for mFOLFOX versus BSC which appears inconsistent with the magnitude of benefit observed for mFOLFOX in the ABC-06 trial.

Figure 1: OS extrapolation for ivosidenib, BSC and mFOLFOX (referent to EAG preferred generalised gamma curve for ivosidenib)

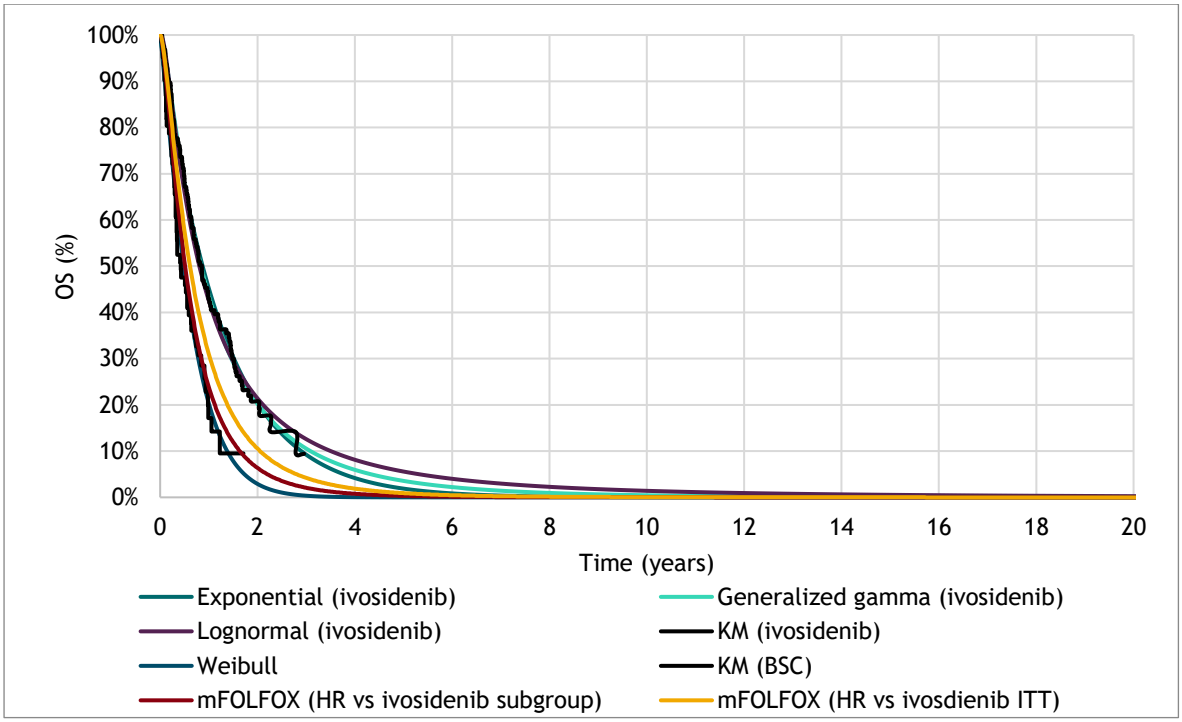


Figure 2 below shows the Kaplan Meier (KM) plots and selected curve fits for ivosidenib PFS and ToT. The KM curves for PFS and ToT are closely related, but the ToT data are more mature. Whilst the PFS generalised gamma (green) had the best statistical fit for PFS, the company discounted it because it produces implausible long-term extrapolations - crossing the OS curve. On this basis the EAG agreed it was not a good option. However, the next best fitting lognormal curve (purple) does not provide a very good visual fit to the observed PFS data, falling below the Kaplan Meier curve in the tail of the distribution. When this is used by the company to cap time on treatment, it leads to underestimation of time on treatment with ivosidenib compared to that observed in ClarIDHy. Thus, the EAG preferred to keep the lognormal PFS curve for ivosidenib but allow ivosidenib ToT to follow the fitted generalized gamma curve for ToT (orange). This may bias slightly against ivosidenib because the selected PFS curve falls below the observed KM data. To test the impact of this, the EAG has provided a further sensitivity analysis (Table 1, below), in which the generalized gamma (green) curve is used for PFS (capped by OS) in the model, whilst retaining the generalized gamma (orange) for ToT. This leads to small reductions in the ICERs compared to the EAG base case.

Figure 2: Ivosidenib PFS and ToT extrapolation

Table 4 Selected scenario analysis around the EAG base case (deterministic)

Parameter/ assumption	EAG base case	Scenario	Incremental versus BSC				Incremental versus mFOLFOX			
			Cost (£)	QALY (x1.7 modifier)	ICER (x1.7 modifier)	Change	Cost (£)	QALY (x1.7 modifier)	ICER (x1.7 modifier)	Change
EAG base case			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR	HR from Bucher ITC (using ClarIDHy subgroup data to align with ABC-06 inclusion criteria)	HR from a Bucher ITC (using the ITT data from ClarIDHy); HR= 0.71 (0.43-1.16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS extrapolation (ivosidenib)	Lognormal	Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; mFOLFOX, modified folinic acid + fluorouracil + oxaliplatin; QALY(s), quality-adjusted life year(s).

Dear Celia

We can clarify the cause of the discrepancy you mention below

Firstly, the IPD from the latest data cut (May 2020) were used in the ITC and we confirm again that the analyses give the same numbers as provided in the tables in the ITC report.

Simply loading the dataset without applying any filters, the IPD contain 126 IVO and 61 placebo patients, all of whom are ITT. Tabulating prior lines of therapy using the "NUMPLT" variable (described as "number of prior lines of therapy") returns the following numbers:

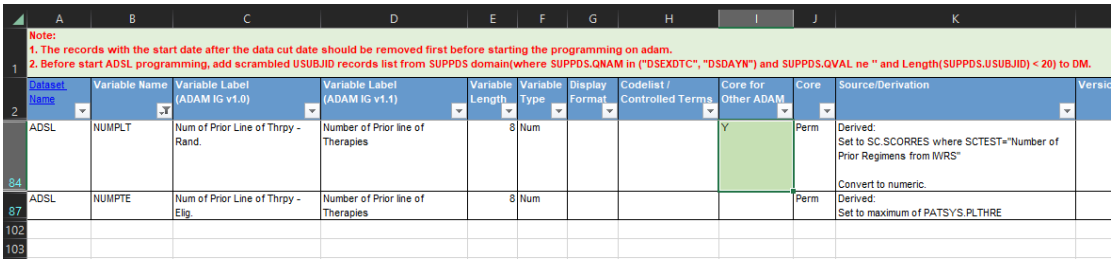
Prior lines of therapy	IVO	Placebo	Total
1	66	33	99
2	60	28	88
Total	126	61	187

The ITCs were performed using this variable. However, there exists another variable named "NUMPTE" with the same description "number of prior lines of therapy", which when used gives the same numbers as the Figure provided in the supplementary file from Zhu et al., as below.

Prior lines of therapy	IVO	Placebo	Total
1	70	36	106
2	56	25	81
	126	61	187

The reason "NUMPLT" was preferred over "NUMPTE" for the ITC is that the former is marked as a "core variable" in the provided data dictionary (see below) and thus presumed to be more relevant. From the variable description it appears that the variable "NUMPLT" includes patient labelled as 'randomised' and the variable "NUMPTE" patients that were eligible for randomization.
Also please note that the figure in Zhu et al from the Supplementary Material of this publication shows different numbers compared to what was used in the ITC. However the Table in the main text of the paper (p. 1673) shows the baseline characteristics, and the prior LoT numbers (66 vs 33 in the IVO arm) are aligned with the approach taken in the ITC (using the NUMPLT variable), see last figured pasted below.

Overall, the supplementary material figure used LoT based on an alternative definition, but in the ITC we remain aligned with the data dictionary provided and the main text of the published paper.



	A	B	C	D	E	F	G	H	I	J	K
1	Note: 1. The records with the start date after the data cut date should be removed first before starting the programming on adam. 2. Before start ADSL programming, add scrambled USUBJID records list from SUPPDS domain(where SUPPDS.QNAM in ("DSEXDTC", "DSDAYN") and SUPPDS.QVAL ne '' and Length(SUPPDS.USUBJID) < 20) to DM.										
2	Dataset Name	Variable Name	Variable Label (ADAM IG v1.0)	Variable Label (ADAM IG v1.1)	Variable Length	Variable Type	Display Format	Codelist / Controlled Terms	Core for Other ADAM	Core	Source/Derivation
84	ADSL	NUMPLT	Num of Prior Line of Thrpy - Rand.	Number of Prior line of Therapies	8	Num			Y	Perm	Derived: Set to SC.SCORRES where SCTEST="Number of Prior Regimens from IWRS" Convert to numeric.
87	ADSL	NUMPTE	Num of Prior Line of Thrpy - Elig.	Number of Prior line of Therapies	8	Num				Perm	Derived: Set to maximum of PATSYS.PLTHRE
102											
103											

Table. Demographic and Baseline Characteristics

Characteristic	Patients, No. (%)	
	Ivosidenib (n = 126)	Placebo (n = 61)
Sex		
Female	82 (65)	37 (61)
Male	44 (35)	24 (39)
Age, median (range), y	61 (33-80)	63 (40-83)
Race		
American Indian or Alaska Native	1 (1)	0
Asian	15 (12)	8 (13)
Black or African American	1 (1)	1 (2)
Native Hawaiian or other Pacific Islander	1 (1)	0
White	71 (56)	35 (57)
Other	1 (1)	0
Not reported	1 (1)	0
Missing	35 (28)	17 (28)
Ethnicity		
Hispanic or Latino	7 (6)	2 (3)
Not Hispanic or Latino	84 (67)	40 (66)
Not reported	0	2 (3)
Missing	35 (28)	17 (28)
Randomization strata, prior line of therapy		
1	66 (52)	33 (54)
2	60 (48)	28 (46)

Updated cost-effectiveness results for committee

Ivosidenib for treating advanced cholangiocarcinoma with an IDH1 mutation after at least 1 therapy [ID6164]

	ICER range [vs BSC]	
	Log-normal OS	Gen gamma OS
Committee preferred ICER range	[redacted]	[redacted]

Analysis of the committee preferred assumptions including the most recent commercial arrangement for ivosidenib

Note: mFOLFOX is extendedly dominated in both scenarios.

Produced By **Aberdeen HTA Group, 30 November, 2023**