Medicinrådet

Bilag til Medicinrådets anbefaling vedr. ivosidenib til behandling af cholangiocarcinom med IDH1 (R132)-mutation efter mindst én tidligere systemisk behandling

Nationalt dansk appendix til fælles nordisk rapport

Vers. 1.0

Bilagsoversigt

1. JNHB rapport vedr. ivosidenib til behandling af cholangiocarcinom med IDH1 (R132)-mutation
2. Ansøgers notat til Rådet vedr. ivosidenib til behandling af cholangiocarcinom med IDH1 (R132)-mutation
3. Forhandlingsnotat fra Amgros vedr. ivosidenib til behandling af cholangiocarcinom med IDH1 (R132)-mutation
4. Ansøgers endelige ansøgning vedr. ivosidenib til behandling af cholangiocarcinom med IDH1 (R132)-mutation

JNHB
Joint Nordic HTA-Bodies

Joint Nordic HTA-Bodies
Health Technology assessment report

Tibsovo (ivosidenib)

Film-coated tablet

Assessed indication
Tibsovo 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.

Date for publication of report: 2024-XX-XX

Case number DMC: EMS-2024-00029
Case number Fimea: FIMEA/2024/002022
Case number Landspitali: IS240403
Case number NOMA: ID2022_129
Case number TLV: 885/2024

Joint Nordic HTA-Bodies

Joint Nordic HTA-Bodies (JNHB) formerly known as FINOSE started as a bottom-up initiative by the HTA authorities in Finland, Norway and Sweden and was launched in Stockholm in 2018. The collaboration extended to comprise Denmark in 2023 and Iceland in 2024. In June 2024 FINOSE changed its name and became Joint Nordic HTA-Bodies (JNHB).

JNHB offers efficient and transparent joint health technology assessments of medicinal products in the five Nordic countries. The assessments include both relative effectiveness and health economics. Decisions on price and reimbursement as well as recommendations for use, are made at the national level in each country. By working together and sharing knowledge, JNHB aim to produce high-quality assessment reports that provide solid support for national decisions.

The basis for the collaboration is outlined in a Memorandum of Understanding, signed in April 2024 by the collaborating HTA bodies;

- Danish Medicines Council (DMC),
- Finnish Medicines Agency (Fimea),
- Landspitali- The National University Hospital of Iceland,
- Norwegian Medical Products Agency (NOMA) and
- Dental and Pharmaceutical Benefits Agency (TLV) in Sweden.

In this assessment of Tibsovo, NOMA was assessor, TLV co-assessor and DMC and Landspitali reviewers. Tibsovo is an out-patient drug in Finland, which means that the product is not within Fimea's remit. Therefore, Fimea were observers during the assessment.

Assessors: Ida Jonson (clinical assessor, NOMA), Ania Urbaniak (statistical assessor, NOMA), Hannah Almqvist (health economist, TLV).

Reviewers: Ehm Astrid Andersson Galijatovic (DMC), Anna Kollerup Iversen (DMC), Filippa Nyboe Norsker (DMC), Sif Sumarliðadóttir (Landspitali), Eva Ágústsdóttir (Landspitali).

Clinical experts: Margareta Heby (överläkare, Skånes onkologiska klinik), Are Korsnes Kristensen (St. Olavs Hospital), Inger Marie Løes (Haukeland universitetssykehus), Olav Dajani (Oslo universitetssykehus) and fagudvalget vedr. leverkræft (DMC) Leverkræft (medicinraadet.dk). The clinical experts have been consulted on current clinical practice and in interpretation of the clinical material. The JNHB group is not bound to the statements of the experts, interpretations and opinions on which the cost-effectiveness analysis should be based on.

Company: Servier

Address DMC:
Dampfærgevej 21-23, 3. sal.
2100 København Ø

Address Fimea:
PL 55, 00034 FIMEA

Address Landspitali:
Skaftahlíð 24
105 Reykjavik

Address NoMA:
PO Box 240 Skøyen
0213 Oslo

Address TLV:
Box 225 20, 104 22 Stockholm

Summary

- JNHB has made a joint health economic assessment of Tibsovo (ivosidenib) for the treatment of IDH1-mutated cholangiocarcinoma (CCA).
- Cholangiocarcinoma (CCA) is a tumor of the bile duct epithelium, and depending on their anatomical site of origin, CCAs are classified into intrahepatic (iCCA), perihilar (pCCA) or distal (dCCA). CCA is a rare form of cancer and IDH1 is mutated in 10-20 % of iCCAs and >1 % of pCCA/dCCA. CCAs tend to present at an advanced stage and have a poor prognosis with a five-year relative survival rate in the range of 2 - 15% for iCCA.
- Tibsovo 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.
- The active substance in Tibsovo, ivosidenib, works by inhibiting the mutant IDH1 enzyme. Gain-of-function mutations in IDH genes lead to the accumulation of the oncometabolite 2-hydroxyglutarate (2-HG), and inhibition can restore the normal cellular differentiation by decreasing 2-HG levels in tumor cells.
- JNHB agrees with Servier that FOLFOX and BSC are relevant comparators. JNHB clinical experts state that FOLFOX is the more relevant of the two, but that efficacy of FOLFOX is limited in comparison to BSC for the relevant patient population.
- Results from the ClarIDHy trial showed that patients who received Tibsovo were progression free for median 1.3 months longer and lived a median of 5.2 months longer than patients receiving placebo after adjusting for crossover (OS: HR 0.49, 95% CI: 0.34 – 0.70). The study design, a placebo-controlled study allowing crossover, introduces uncertainty in the estimate of OS benefit as this is not generalizable to clinical practice where patients do not receive targeted therapy after progression in second line. An analysis that corrects for crossover introduces additional assumptions and uncertainties in the results.
- Tibsovo is compared to FOLFOX through an indirect treatment comparison (ITC) between the ClarIDHy and the ABC-06 trials. The results from the indirect comparison are highly uncertain due to differences in the study populations and study design as well as low patient numbers. The results of the indirect comparisons are inconclusive (HR for OS 0.62 (95 % CI: 0.33 – 1.18)).
- Tibsovo is generally well tolerated and clinical experts consider the safety profile as favorable compared to FOLFOX (or similar chemotherapy regimens).
- The cost of treatment with Tibsovo is approximately 173,000 SEK per 30 days.
- Servier has submitted a cost-effectiveness analysis using a partitioned survival model, in which patients who have been treated with Tibsovo are compared with patients who have received best supportive care (BSC) or FOLFOX.
- When Tibsovo is compared to BSC, the cost per QALY in the JNHB base case is approximately 3.5 million SEK. QALYs gained are 0.40.
- When Tibsovo is compared to BSC, JNHB sensitivity analyses illustrate that changes in extrapolation of OS and modelling of time on treatment have an impact on the cost-effectiveness results and the cost per QALY, in all JNHB's sensitivity analyses, falls within a relatively narrow range (approximately 3.2 to 3.7 million SEK). Uncertainties related to the crossover adjustment in the ClarIDHy trial could not be explored in sensitivity analyses.
- When Tibsovo is compared to FOLFOX, the cost per QALY in the JNHB base case is approximately 4.3 million SEK. QALYs gained are 0.29.
- When Tibsovo is compared to FOLFOX, JNHB sensitivity analyses illustrate that changes in the constant HR used in extrapolation of OS has the greatest impact on the cost-effectiveness results. In the comparison of Tibsovo versus FOLFOX, the cost per QALY in JNHB's sensitivity analyses falls within a wide range (approximately 2.4 mil-

lion SEK to Tibsovo being dominated). The robustness of the indirect treatment comparison results is uncertain, as the method of using a constant HR to model relative effect for OS could not be explored in sensitivity analyses.

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1 Scope

This JNHB report is the result of a joint Nordic assessment of ivosidenib (Tibsovo) for the treatment of 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.

The assessment is primarily based on the documentation presented by Servier.

The aim of the JNHB report is to support national decisions on price and reimbursement as well as recommendations for use, in Denmark, Iceland, Norway and Sweden regarding Tibsovo. The primary focus of this report is the assessment of relative effectiveness, safety and cost effectiveness of Tibsovo. The JNHB report may be complemented with national appendices with additional local information and conclusions.

P (population)	Adult patients with locally advanced or metastatic IDH1-mutated CCA previously treated by at least one prior line of systemic therapy
I (intervention)	Tibsovo
C (comparison, comparators)	Best supportive care (BSC) and FOLFOX
O (outcomes)	• Overall survival (OS) • Progression free survival (PFS) • Adverse events • Health-related quality of life •
HE (health economy)	• QALYs • Costs • Incremental cost-effectiveness ratio (ICER)

2 Medical background

2.1 Cholangiocarcinoma

Cholangiocarcinoma (CCA) is a rare form of cancer that arises from the bile duct epithelium. Depending on their anatomical site of origin, CCAs are classified into intrahepatic (iCCA), perihilar (pCCA), and distal CCA (dCCA). Each subtype has a unique presentation and distinct clinical features, but all tend to present at an advanced stage and have a poor prognosis (1). Five-year relative survival rates range from 2% to 15% for iCCA and from 2% to 30% for pCCA/dCCA (2). In the European Union (EU), the incidence varies across countries from 0.5/100,000 (in Spain) to 3.36/100,000 (in Italy). The mean prevalence for biliary tract cancer is considered to be approximately 1.3/10,000 in the EU (3).

Surgery is the primary curative treatment option for early-stage biliary tract cancer. CCAs tend to present at an advanced stage, and only around 20 % of tumors are considered resectable. For unresectable CCA, therapeutic options are very limited and the prognosis for CCA has not significantly improved in recent years (1). However, many molecular alterations have recently been described in CCAs, some of which represent potential therapeutic targets. IDH1 and IDH2 mutations are examples of such targets and are mutated in about 10-20 % of iCCAs.

IDH1 mutations lead to the production and build-up of 2-HG, an oncometabolite that promotes tumorigenesis. 2-HG has been implicated in disrupting metabolic homeostasis, causing

epigenetic alterations, impairing cellular differentiation and most recently in regulation of the tumor microenvironment. IDH1 mutation seems to be a prognostic marker of favorable outcomes in glioma (4), but the prognostic value of this mutation in CCA is currently uncertain (5).

2.2 Tibsovo

2.2.1 Therapeutic indication

Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a mutation in the IDH1-gene (IDH1 R132) who were previously treated by at least one prior line of systemic therapy (6).

2.2.2 Mechanism of action

The active substance in Tibsovo, ivosidenib, is an inhibitor of the mutant IDH1 enzyme. Mutant IDH1 converts alpha- ketoglutarate (αKG) to 2-hydroxyglutarate (2-HG) which blocks cellular differentiation and promotes tumorigenesis in both hematologic and non-hematologic malignancies. The mechanism of action of ivosidenib beyond its ability to reduce 2-HG levels and restore cellular differentiation is not fully understood (6).

2.2.3 Posology and method of administration

The recommended dose is 500 mg ivosidenib (2 x 250 mg tablets) taken orally once daily. Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient (6).

2.3 Current treatment options

2.3.1 Current treatment in the Nordic countries

Patients should both be in relatively good general condition (ECOG 0-2) and have satisfactory liver and kidney function to be able to tolerate systemic oncological treatment.
Gemcitabine combination chemotherapy is the first choice for locally advanced disease, metastatic disease or inoperable local relapse. The most common gemcitabine combination is gemcitabine-cisplatin (Gem-Cis), and alternative combinations are Gem-Ox (oxaliplatin) and Gem-Cap (capecitabine). The PD-(L)1 inhibitors durvalumab and pembrolizumab were recently granted marketing authorization in combination with Gem-Cis in first line treatment of biliary tract cancers. Checkpoint inhibition is now a part of the standard first line treatment of this patient population in the JNHB countries.

There is no established second line treatment, and European guidelines (7) for the treatment of biliary tract cancers state that CCAs are enriched for actionable targets and recommend molecular analysis in patients with advanced disease suitable for systemic treatment. Such targets include, FGFR2, HER2, BRAF, and microsatellite instability (MSI) in addition to IDH1 mutations. The implementation of next-generation sequencing to test for such targets differs between the JNHB countries. In Denmark and Norway testing is largely implemented, but in Sweden no treatment options for the different targets are currently reimbursed and testing is only done in a few patients.
Aside from targeted treatments, patients who are treatment-motivated and in good general condition can receive folinic acid and fluorouracil (5-FU) in combination with either oxaliplatin (FOLFOX/FLOX) or irinotecan (FOLFIRI/FLIRI) based on what has been administered previously.

2.3.2 Comparator

Servier states that, based on treatment guidelines and given the lack of an established standard of care specifically for the treatment of IDH1 mutated patients with CCA in the JNHB countries, the main comparator is best supportive care (BSC). BSC (placebo) is also the comparator in the pivotal clinical trial for Tibsovo, the ClarIDHy trial.
Servier further states that based on advice given at a pre-meeting, in order to add an active treatment comparator, FOLFOX was chosen as the second comparator based on available data for relative efficacy.

JNHB discussion
JNHB clinical experts stated that most patients eligible for Tibsovo treatment will receive chemotherapy (FOLFOX or equivalent) in current clinical practice. BSC will only be relevant for a small proportion of patients, such as patients with no effect or poor tolerance for first line chemotherapy. The clinical experts did, however, state that in their experience chemotherapy has limited efficacy over BSC.

JNHB conclusion: JNHB agrees with Servier that FOLFOX and BSC are relevant comparators. JNHB clinical experts state that FOLFOX is the more relevant of the two, but that efficacy of FOLFOX is limited in comparison to BSC for the relevant patient population.

3 Clinical efficacy and safety

The assessment of clinical efficacy and safety is mainly based on the evidence included in the submission dossier prepared by Servier.

3.1 Clinical trials

3.1.1 Design and methods of the clinical trials

Table 1 Summary of relevant trials

Study	Study design	Treated study population	Intervention	Efficacy endpoints
ClarIDHy (8, 9) NCT02989857	- phase 3 - randomised (2:1) - double-blind - placebo-controlled - multicentre, international	Previously treated patients with advanced IDH1 mutated CCA N = 126	Ivosidenib, 500 mg daily (oral) (N = 126) Placebo once daily in continuous 28-day cycles (N = 61)	Primary: - PFS Key secondary: - OS - AEs - HRQoL
ABC-06 (10) NCT01926236	- phase 3 - randomised - open-label - multicentre, UK	Previously treated patients with advanced biliary tract cancer (including CCA, gallbladder and ampullary carcinoma) N = 162	FOLFOX*, every 2 weeks for a maximum of 12 cycles. (N = 81) Active symptom control (ASC) (N = 81)	Primary: - OS Key Secondary: - PFS (FOLFOX-arm only) - ORR (FOLFOX-arm only) - AEs - HRQoL

*FOLFOX regimen: oxaliplatin 85 mg/m2, L-folinic acid 175 mg [or folinic acid 350 mg], fluorouracil 400 mg/m2 [bolus], and fluorouracil 2400 mg/m2 as a 46-h continuous intravenous infusion.

ClarIDHy

The ClarIDHy trial was a double-blind, placebo-controlled phase 3 trial that enrolled patients from 49 different hospitals across six countries. Adult patients with previously treated nonresectable or metastatic IDH1 mutated cholangiocarcinoma were randomized 2:1 to receive either Tibsovo or placebo (BSC). Randomization was stratified by number of prior therapies (1 vs. 2). Over the span of two years, 187 patients were randomly assigned to either Tibsovo (n=126) or placebo (n=61).
Crossover was allowed for patients in the placebo-arm who experienced radiographic disease progression (as assessed by the investigator). The primary endpoint was progression free survival (PFS, as assessed by the independent radiology center, IRC).

Included patients had 1 or 2 previous lines of therapy and an ECOG PS score of 0-1. A summary of baseline characteristics for the patients in ClarIDHy is presented in Table 2.

Table 2 Baseline characteristics, ClarIDHy

Parameter	Ivosidenib (n=126)*	Placebo (n=61)	Parameter	Ivosidenib (n=124)**	Placebo (n=61)
Median age, years (range)	61 (33 to 80)	63 (40 to 83)	Race, n (%)		
Sex, n (%)			American Indian or Alaska Native	1 (1)	0
Male	44 (35)	24 (39)	Asian	15 (12)	8 (13)
Female	82 (65)	37 (61)	Black or African American	1 (1)	1 (2)
ECOG at baseline, n (%)			Native Hawaiian or Other Pacific Islander	1 (1)	0
0	50 (40)	19 (31)	White	70 (57)	35 (57)
1	75 (60)	41 (67)	Other	1 (1)	0
2	0	1 (2)	Not reported	1 (1)	0
3	1 (1)	0	Missing	34 (27)	17 (28)
IDH1 mutation, n (%)			T (tumor) stage at initial diagnosis, n (%)		
R132C	86 (68)	45 (74)	T0	0	1 (2)
R132L	21 (17)	7 (11)	T1	13 (11)	9 (15)
R132G	17 (14)	6 (10)	T2	54 (44)	25 (41)
R132S	2 (2)	1 (2)	T3	13 (11)	11 (18)
R132H	0	2 (3)	T4	13 (11)	5 (8)
Cholangiocarcinoma subtype, n (%)			Tx	25 (20)	8 (13)
Intrahepatic	113 (90)	58 (95)	Missing	6 (5)	2 (3)
Extrahepatic/perihilar	5 (4)	1 (2)	N (lymph node) stage at initial diagnosis, n (%)		
Unknown	8 (6)	2 (3)	N0	40 (32)	23 (38)
Extent of disease at screening, n (%)			N1	45 (36)	19 (31)
Local/regional	9 (7)	5 (8)	N2	1 (1)	1 (2)
Metastatic	117 (93)	56 (92)	Nx	31 (25)	16 (26)
Previous lines of therapy, n (%)			Missing	7 (6)	2 (3)
1 prior line	66 (53)	33 (54)	M (metastasis) stage at initial diagnosis, n (%)		
2 prior lines	58 (47)	28 (46)	M0	47 (38)	33 (54)
Regions, n (%)			M1	63 (51)	23 (38)
Asia	7 (6)	5 (8)	Mx	9 (7)	4 (7)
Europe	33 (27)	16 (26)	Missing	5 (4)	1 (2)
North America	84 (68)	40 (66)			

* May 31, 2020 data cutoff (8), ** January 31, 2019 data cutoff (9)

Crossover adjustment

Patients on placebo were allowed to cross over to the active treatment arm and receive Tibsovo after radiographic documented disease progression (as assessed by the Investigator and after consultation with the Sponsor Medical Monitor). Overall, 43/61 placebo patients received Tibsovo (secondary analysis, May 31, 2020 data cut-off). The primary OS analysis was based on the ITT set and included all OS data, including data after crossover. However, to adjust for the crossover effect from placebo to Tibsovo on OS, an advanced modelling method such as rank

preserving structural failure time (RPSFT) method, was pre-specified. RPSFT assumes that Tibsovo after the switch is acting by multiplying survival time by a given factor (acceleration factor) relative to placebo and assumes the treatment effect is the same for all subjects regardless of when treatment is received (common treatment effect). The methodology is described further in Appendix 1 – Crossover-adjustment methodology.

ABC-06

The ABC-06 clinical trial was an open-label, randomised phase 3 trial done in 20 sites in the UK. Adult patients with locally advanced or metastatic biliary tract cancer (including cholangiocarcinoma, gallbladder or ampullary carcinoma) with documented radiological disease progression to first-line Gem-Cis chemotherapy were randomly assigned (1:1) to active symptom control (ASC) and FOLFOX or ASC alone. Randomization was stratified by platinum sensitivity, serum albumin concentration, and disease stage (locally advanced vs metastatic).
The primary endpoint was overall survival.

The study is completed, and the final results are reported (10).

Included patients had a maximum of 1 previous line of therapy and an ECOG PS score of 0–1. A summary of baseline characteristics for patients included in ABC-06 is presented in Table 3.

Table 3 Baseline characteristics, ABC-06

	ASC alone group (n=81)	ASC plus FOLFOX group (n=81)
Sex		
Female	44 (54%)	38 (47%)
Male	37 (46%)	43 (53%)
Age, years		
Median	65 (59–72)	65 (59–72)
Range	26–81	26–84
Platinum sensitivity*		
Resistant or refractory†	47 (58%)	54 (67%)
Sensitive	34 (42%)	27 (33%)
Albumin*		
<35 g/L	21 (26%)	19 (23%)
≥35 g/L	60 (74%)	62 (77%)
Disease stage*		
Locally advanced	15 (19%)	14 (17%)
Metastatic	66 (81%)	67 (83%)
Tumour site		
Intrahepatic	38 (47%)	34 (42%)
Extrahepatic	19 (23%)	26 (32%)
Gallbladder	17 (21%)	17 (21%)
Ampulla	7 (9%)	4 (5%)
Histology		
Adenocarcinoma	74 (91%)	73 (90%)
Other‡	7 (9%)	8 (10%)
Grade of differentiation		
Well	5 (6%)	9 (11%)
Moderately	41 (51%)	37 (46%)
Poorly	11 (14%)	9 (11%)
Not specified	23 (28%)	26 (32%)
Missing	1 (1%)	0
ECOG performance status		
0	28 (35%)	25 (31%)
1	52 (64%)	55 (68%)
Missing	1 (1%)	1 (1%)
Had previous surgery	38 (47%)	34 (42%)
Previous cisplatin and gemcitabine		
Duration, months	4·8 (2·9–5·3)	4·9 (2·8–5·5)
≥6 months	6 (7%)	13 (16%)§
Baseline CA19.9 (U/mL)¶	443 (46–5714)	162 (25–1903)
Baseline carcinoembryonic antigen (U/mL)¶	6 (3–16)	6 (3–24)
Baseline CA125 (U/mL)¶	42 (20–168)	52 (21–159)

JNHB assessment of design and methods of clinical trials

The treatment arms in ClarIDHy seem well balanced and JNHB clinical experts confirm that the patient population is representative of the relevant patient population in the JNHB countries. The median age of CCA in the JNHB countries is higher than the median age in ClarIDHy. However, the JNHB clinical experts describe that the relevant patient population, patients that can tolerate second line systemic treatment, might be younger than the CCA patient population as a whole. It is uncertain what the exact median age of the relevant patient population is.

In ClarIDHy, 70.5% of patients in the placebo group crossed over to Tibsovo upon radiographic disease progression as determined by Investigator. Given that in clinical practice patients who

discontinue BSC/FOLFOX would not currently receive a targeted therapy upon progression, the use of an ITT analysis, where crossover is ignored, would likely underestimate the effect of Tibsovo with respect to the current treatment algorithm. JNHB agrees that a crossover-adjusted analysis for OS is appropriate.

The RPSFT method was used to reconstruct the survival curve for patients receiving placebo, as if crossover had never occurred. There are several methods to adjust for crossover (11), but RPSFT is a suitable technique to correct for crossover in small trials, with relatively little information on covariates, and for trials where a large proportion of patients crossover. The analysis was also prespecified in the statistical analysis plan which is a strength as it minimizes data-driven analysis. Advantages of the RPSFT model include using the complete data set of patients in the trial and that ranking of the observed time-to- event data is preserved after adjustment. It is a limitation that the method does not use information on patient covariates, which may affect the probability of crossover.

The main assumption behind the validity of the RPSFM is the common treatment effect assumption, i.e. that the size of the treatment effect of Tibsovo is the same at randomization, and at the point of treatment switch from placebo to Tibsovo. Servier considers this assumption to hold as the median survival times of switchers (9.1 months) is similar to patients originally assigned to Tibsovo (10.3 months). JNHB also notes that ClarIDHy was stratified by previous lines of therapy and that the OS subgroup analysis shows a consistent treatment effect. Overall, although the assumption will never truly hold, JNHB agrees that it is likely to be approximately true.

Re-censoring was applied only to patients in the control group. As the re-censoring involves data being re-censored at an earlier time point, the longer-term survival information is lost. This is seen in Figure 3 through a shorter KM curve and a lower number of patients at risk in the crossover-adjusted vs ITT placebo group. While re-censoring is important to ensure that the new survival times in the placebo group are interpretable after crossover-adjustment, a good practice is to provide results with and without re-censoring to assess the robustness of the findings to the different censoring methodology. Such analyses have not been provided.
The "treatment group" (or "ever treated") RPSFTM approach, where the treatment effect is applied from randomization until death, regardless of discontinuation, was applied in Servier's base case. This approach is more similar to a standard ITT analysis of randomized groups. An alternative would be an "on-treatment" (or "as treated") approach of RPSFTM method where the treatment effect is only received while a patient is "on" treatment, and it disappears as soon as treatment is discontinued (12). JNHB acknowledges that the "treatment group" approach is more intuitive. Specifically, if OS ITT analysis (a gold standard) does not correct for treatment discontinuation, is it reasonable to expect RPSFTM to not account for that either. On the other hand, the assumption of continuous treatment effect beyond treatment discontinuation has not been justified and the robustness of the results to this assumption has not been demonstrated by Servier. According to Latimer (13), the two analyses are likely to result in similar estimates of counterfactual survival times (i.e. survival time in the placebo group as if there were no switchers) because the "as treated" analysis attributes a larger treatment effect to a shorter time period, and the "ever treated" analysis attributes a smaller treatment effect to a longer timer period. Consequently, JNHB has not requested the "on-treatment" analysis.

JNHB conclusion:
The patient population is representative of the relevant Nordic patient population. JNHB agrees that a crossover-adjusted OS analysis is appropriate as it reflects the clinical treatment algorithm. The used RPSFTM is appropriate for high crossover rates and the assumption behind the approach seems to approximately hold. The approach was prespecified in the protocol. The base case analysis with a "treatment group" approach and re-censoring is acceptable. However, Servier has not provided results from sensitivity analyses so the robustness of the main results could not be assessed.

3.2 Results for clinical efficacy and safety for the ClarIDHy trial Tibsovo vs. BSC

Primary endpoint; Progression free survival (PFS, by IRC assessment)
PFS is defined as the time from date of randomization to date of first documented disease progression, or date of death due to any cause. Progression was assessed by the independent radiology center (IRC) per response evaluation criteria in solid tumours (RECIST) v1.1.
PFS was analysed at the time of primary analysis (January 31, 2019 data cut off), at which time 61.3% (76/124) of the patients in the Tibsovo-arm had progressed compared to 82.0% (50/61) of the patients in the placebo-arm.

The median PFS was 2.7 months for patients in the Tibsovo-arm compared to 1.4 months for patients in the placebo-arm (HR, 0.37, 95% CI: 0.25 - 0.54, p < 0.0001).

For the patients who crossed over from placebo to Tibsovo following progression (N= 43), the median PFS after crossover (by investigator assessment) was 1.6 months (95% CI: 1.4 – 3.8) (3). The 6-months PFS rate was 32% and the 12-months PFS rate was 22% for the Tibsovo-arm. In comparison PFS rates in the placebo group were not estimable (NE) and as of the primary analysis data cut, no patients in the placebo group were free from progression for ≥ 6 months. The Kaplan-Meier (KM) analysis of PFS for the Tibsovo and placebo arms in ClarIDHy is presented in Figure 1.

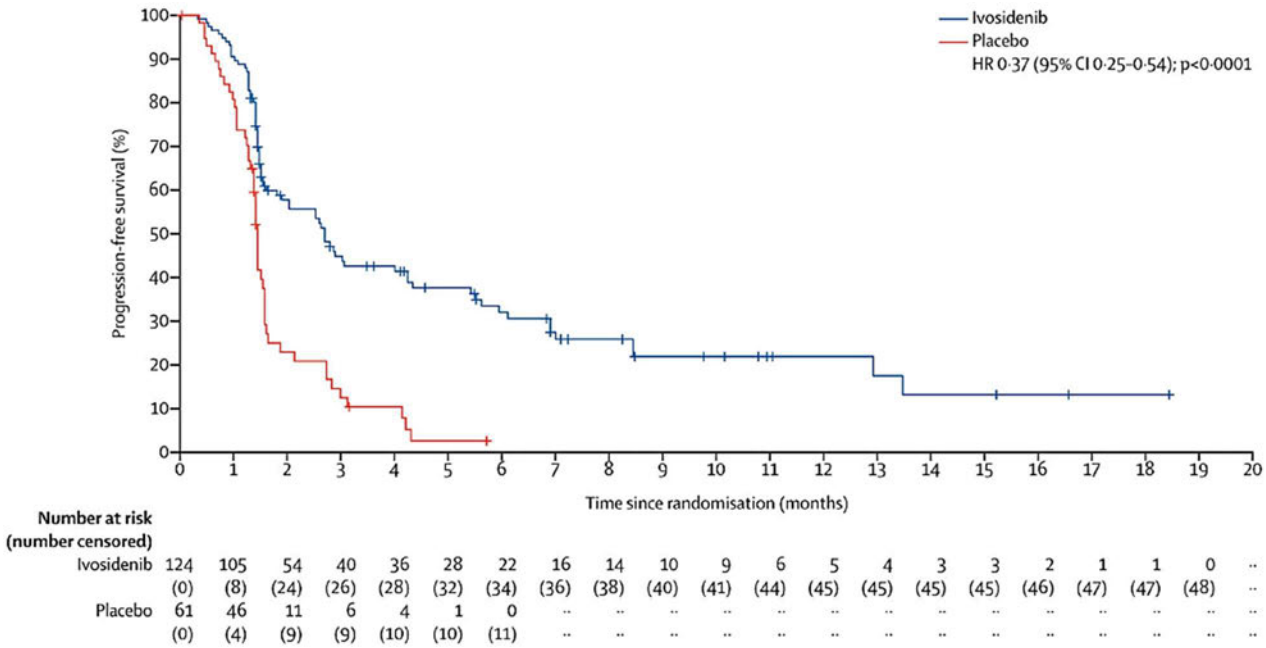


Figure 1 PFS KM curve for ClarIDHy, January 31, 2019 data cut off (9).

The results of the subgroup analysis demonstrated a consistent treatment effect across the pre-defined subgroups (Figure 2).

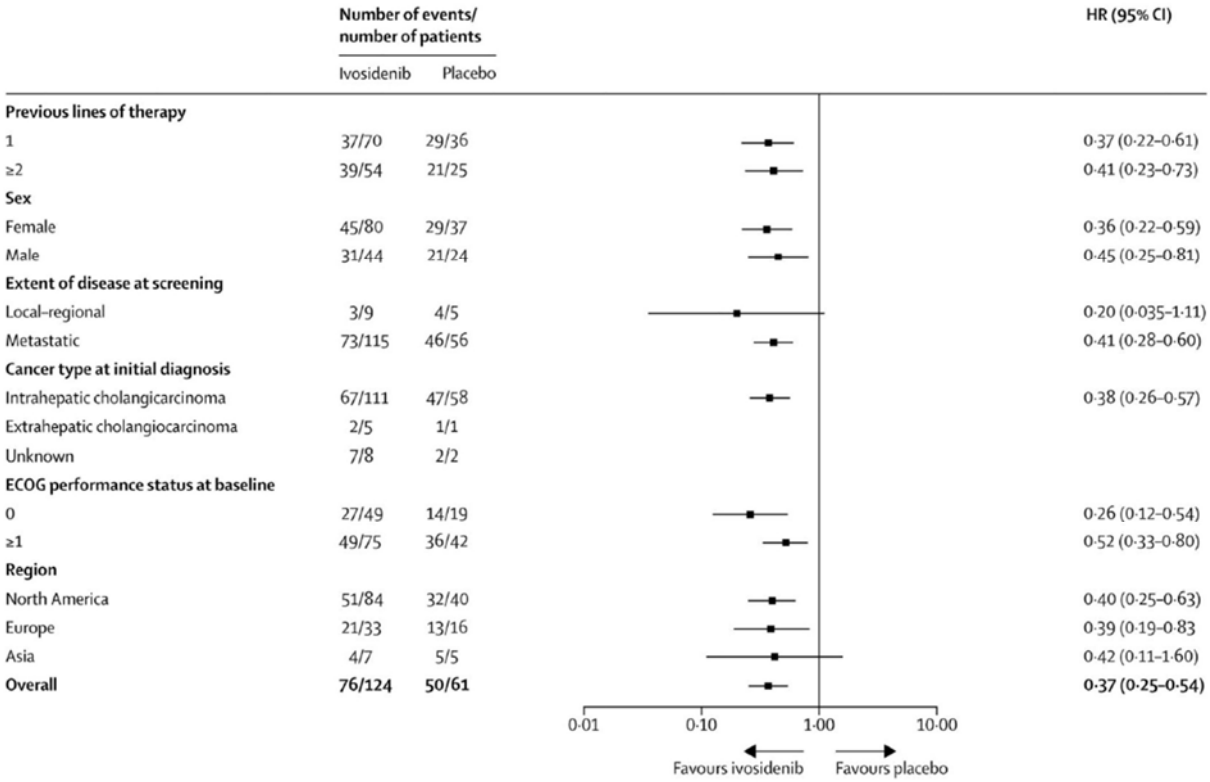


Figure 2 Forest plot of PFS HRs for key subgroups from ClarIDHy, January 31, 2019 data cut off (9).

Secondary endpoints

Overall survival (OS)

Based on the secondary analysis (31st May 2020 data cut-off), before adjusting for crossover, the median OS was 10.3 months (95% CI: 7.8 – 12.4) in the Tibsovo-arm compared with 7.5 months (95% CI: 4.8 – 11.1) in the placebo-arm (HR 0.79, 95% CI: 0.56 – 1.12, p = 0.093). The 12-month OS rate for Tibsovo was 43% (95% CI: 34% - 51 %), compared with 36% (95% CI: 24% - 48%) for placebo.

In the placebo-arm, 43 of the 61 patients (70.5 %) crossed over to receive open-label Tibsovo. After adjusting for crossover using the RPSFT method, the median OS in the placebo-arm was 5.1 months (95% CI: 3.8 – 7.6) compared with 10.3 months in the Tibsovo-arm (HR 0.49, 95% CI: 0.34 – 0.70, p < 0.0001). The Kaplan-Meier (KM) analysis of OS for the Tibsovo and placebo arms before and after adjusting for crossover is presented in Figure 3.

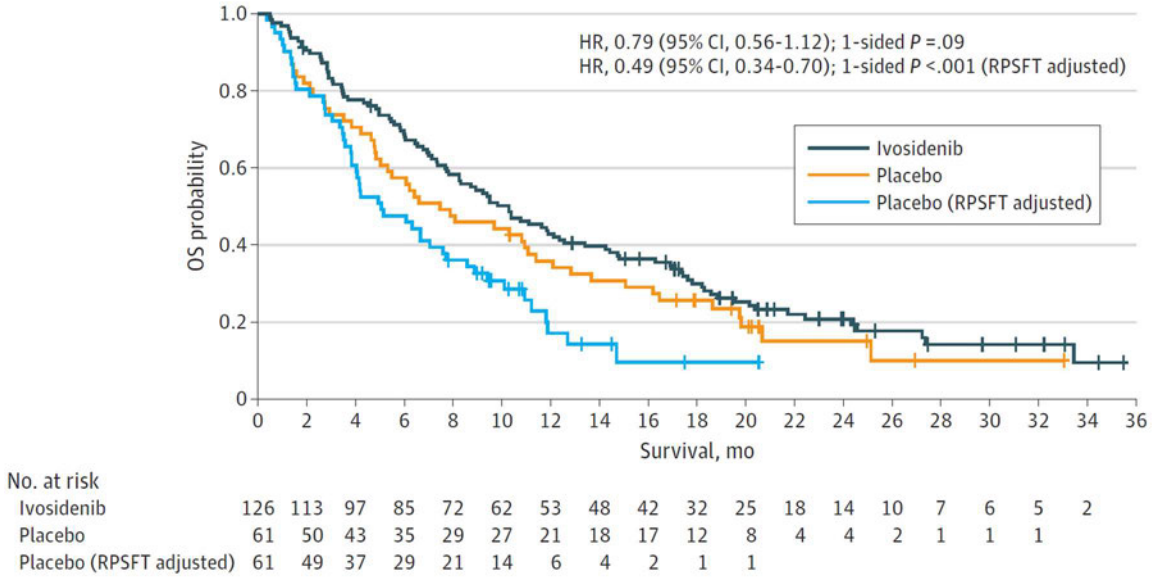


Figure 3 OS KM curve for ClarIDHy, May 31, 2020 data cut off (8).

Response rate (ORR) and duration of response (DOR)

Based on the primary analysis (31st January 2019 data cut-off) the response rate for Tibsovo was 2,4 % (3 patients with partial responses (PR)) compared with 0 % in the placebo-arm. The duration of response (DOR) in the 3 patients with PR was 2.79, 2.73 and 11.07 months, respectively (14).

A best response of stable disease (SD) was achieved in 51 % of patients (63 of 124) in the Tibsovo-arm compared to 28 % of patients (17 of 61) in the placebo-arm before crossover. The median duration of SD was 6.5 months in the Tibsovo-arm, 6.4 months in patients after crossover to Tibsovo, and 3.0 months in the placebo-arm before crossover (3).

Results for safety for Tibsovo

The most common adverse reactions were fatigue (43%), nausea (42%), abdominal pain (35%), diarrhea (35%), decreased appetite (24%), ascites (23%), vomiting (23%), anemia (19%) and rash (15%) (6).

In ClarIDHy, the incidence of treatment emergent adverse events (TEAEs) was quite similar in both arms (97.6% vs 96.0%). The incidence of Grade ≥3 TEAEs, however, was higher in the Tibsovo-arm (51.2% vs 37.3%). The most common TEAEs of grade ≥ 3 (in all patients who received Tibsovo vs. placebo) were ascites (9.0% vs. 6.8%), anemia (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%)

Serious TEAEs were reported for 35.0% of patients receiving Tibsovo, compared to 23.7% of patients receiving placebo. The serious TEAEs were considered associated with treatment for 2% of patients in the Tibsovo-arm and 0 % in the placebo-arm.

Electrocardiogram QT prolonged, identified as an AE of special interest (AESI), is characterized by EMA as an important risk associated with Tibsovo treatment which can lead to life-threatening ventricular arrhythmias, and result in sudden cardiac death. The incidence of QT prolongation (any grade) was higher in the Tibsovo-arm in ClarIDHy compared with the placebo arm (9.8% vs 3.4%) with 2 (1.6%) patients with grade >3 TEAE in the Tibsovo-arm.
EMA concludes that, taking into account the recommendations implemented to minimize the risk of QT prolongation, the safety profile of Tibsovo is considered acceptable and manageable (3).

JNHB discussion Tibsovo vs. BSC

Efficacy

The ClarIDHy trial demonstrates that Tibsovo increases both median progression free- and overall survival in previously treated patients with IDH1-mutated advanced CCA. Treatment with Tibsovo led to an increase in median PFS of 1.3 months in the Tibsovo arm compared to the placebo arm (2.7 months for Tibsovo vs. 1.4 months for BSC). Tibsovo treatment led to a gain of 5.2 months (10.3 months for Tibsovo vs. 5.1 months for BSC) in median OS after adjusting for crossover using the RPSFT method.

The results from ClarIDHy are encumbered with some uncertainty, mainly related to study design and endpoints. Scientific advice given by EMA suggested that a control arm consisting of investigator's choice would be more clinically relevant and that such a study design would remove the need for crossover, making OS a possible primary endpoint. Clinical experts consulted by JNHB indeed stated that the majority of patients eligible for Tibsovo treatment would currently be given chemotherapy.

However, the clinical experts consulted by JNHB uniformly agree that the results from ClarIDHy are clinically relevant and highlight both the demonstrated gain in median PFS, and the increased proportion of patients with stable disease in the Tibsovo arm compared with BSC, as these patients generally progress very quickly in clinical practice. In ClarIDHy, the proportion of patients with stable disease was 51 % in the Tibsovo arm compared to 28 % in the placebo arm. The median duration of stable disease was doubled for the Tibsovo treated patients compared to placebo (6,5 months vs. 3 months).

The JNHB clinical experts also describe that an extended period with stabilized disease will give a pause from chemotherapy that in turn may make the patients eligible for another round of chemotherapy.

Safety

Tibsovo is generally well tolerated and the JNHB clinical experts stated that many of the most common adverse events reported in ClarIDHy, could likely also be symptoms of the disease rather than side effects of the treatment. However, ECG QT prolongation has been identified as an important risk of Tibsovo, and restrictive recommendations have been implemented in the SPC (6).

JNHB conclusion:
The results from the ClarIDHy trial show efficacy in terms of increased median PFS and OS in previously treated patients with IDH1-mutated advanced CCA. Patients who received Tibsovo in ClarIDHy were progression free for median 1,3 months longer and lived a median of 5,2 months longer than patients receiving placebo. Study design and choice of primary endpoint hamper the translation into current clinical practice, but results are considered clinically relevant. Further, Tibsovo is well tolerated, but is associated with higher rate of grade≥3 adverse events compared to BSC and an important risk of QT prolongation that requires continuous monitoring.

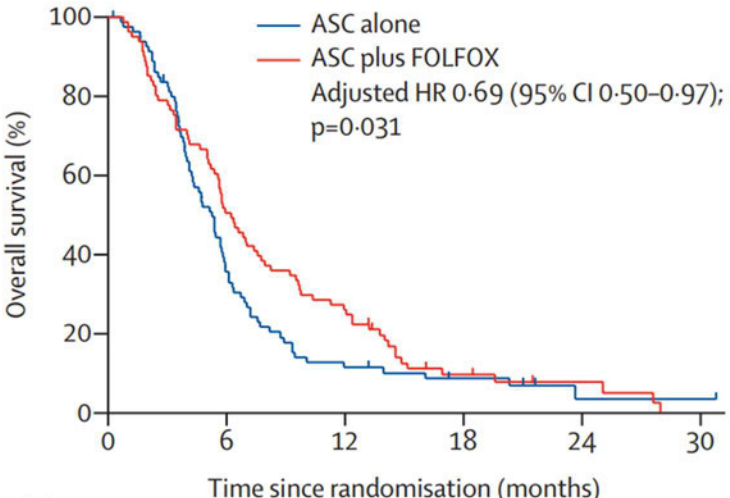
3.3 Indirect comparisons of Tibsovo vs. FOLFOX

There are no head-to-head trials for Tibsovo vs FOLFOX. Consequently, Servier conducted an indirect treatment comparison (ITC). A systematic literature review (SLR) was conducted to identify relevant trials for evidence synthesis (Appendix 2 – Indirect treatment comparison (from Servier's submission and responses)). The ABC-06 study was identified as the source of FOLFOX PFS and OS data whereas ClarIDHy was used for Tibsovo. The ABC-06 study investigated modified FOLFOX regimen as 2L chemotherapy vs. active symptom control (ASC) for advanced BTC. ClarIDHy included almost exclusively iCCA patients (9), while ABC-06 included all BTC patients, of which, less than half were diagnosed with iCCA (44%) (10). To align ClarIDHy patient population to ABC-06, patients with 1 prior line of treatment and an ECOG performance status of 0-1 were selected (N=97 from 187 in the ITT population). The following methods for ITC have been used:

- An anchored matching-adjusted indirect comparison (MAIC) for OS due to availability of a common placebo/ASC arm (i.e. an anchor) in ABC-06 and ClarIDHy
- An unanchored MAIC for PFS due to lack of published PFS-data for the ASC arm (i.e. lack of an anchor) in ABC-06
- A Bucher approach for OS

Servier chose to use MAIC derived estimates in the cost-effectiveness model (CEM). The results from Bucher analysis are used as a scenario analysis. Crossover-adjusted OS curves are used for the ITC. Further details on the ITC methodology are presented in Appendix 2 – Indirect treatment comparison (from Servier's submission and responses).

<u>Results for clinical efficacy and safety for the ABC-06 trial FOLFOX vs. ASC (10)</u>
The results of the ABC-06 trial showed a modest effect of adding FOLFOX to ASC. Median overall survival increased by 0.9 months with the addition of FOLFOX, from 5.3 months in the ASC-arm to 6.2 months in the FOLFOX-arm (HR 0·69, 95% CI: 0·50 – 0·97, p=0·031). The Kaplan-Meier (KM) analysis of OS for the FOLFOX and ASC arms in ABC-06 is presented in Figure 4.



Number at risk (number censored*)						
ASC alone	81 (0)	28 (2)	9 (2)	5 (4)	1 (6)	1 (6)
ASC plus FOLFOX	81 (0)	41 (0)	21 (0)	6 (3)	3 (5)	0 (5)

Figure 4 OS KM curve from the ABC-06 trial (10).

The overall survival rate increased with the addition of FOLFOX from 35·5 % (95 % CI: 25·2 – 46·0) at 6 months and 11·4 % (95 % CI: 5·6 – 19·5) at 12 months in the ASC-arm to 50·6 % (95

% CI: 39·3 – 60·9) at 6 months and 25·9 % (95 % CI: 17·0 – 35·8) at 12 months in the FOLFOX-arm.

Grade 3–5 adverse events were reported in 52% of patients in the ASC-arm compared to 69% patients in the FOLFOX-arm, including three chemotherapy-related deaths (one each due to infection, acute kidney injury, and febrile neutropenia).

Results for clinical efficacy of ivosidenib vs. FOLFOX from the ITC

The key ITC results are presented in Table 4. The effective sample size (ESS) for the OS analysis was 29 for placebo and 56 for Tibsovo which was a small decrease from the N=97 in the selected subset of ClarIDHy but a considerable reduction from 61 for placebo and 126 for Tibsovo in the ITT analysis. The ESS for the PFS analysis was 54 for Tibsovo. Both Tibsovo and FOLFOX had a significant effect vs placebo/ASC on OS in an unadjusted analysis. An ITC via Bucher approach resulted in a hazard ratio (HR) of 0.58 (95 % CI: 0.31 – 1.09) for Tibsovo vs FOLFOX. After adjusting for age, sex, extent of disease at baseline, and ECOG status, the HR increased to 0.62 (95 % CI: 0.33 – 1.18). The HR for PFS was 0.97 (95 % CI: 0.57 – 1.66) after adjusting for the same factors.

Table 4 ITC results before (Bucher method) and after MAIC adjustment. A subgroup of patients with 1 prior line of treatment and an ECOG performance status of 0-1 was selected from ClarIDHy. Crossover-adjusted placebo curves were used for ClarIDHy.

Analysis	Comparison	HR	95%CI
OS Anchored MAIC ClarIDHy vs ABC-06	Unadjusted		
	Ivo vs placebo	0.40	(0.23, 0.69)
	FOLFOX vs ASC	0.69	(0.50, 0.97)
	Ivo vs FOLFOX (Bucher method)	0.58	(0.31, 1.09)
	MAIC-adjusted (base case analysis)		
	Ivo vs placebo	0.43	(0.25, 0.74)
	FOLFOX vs ASC	0.69	(0.50, 0.97)
	Ivo vs FOLFOX	0.62	(0.33, 1.18)
PFS Unanchored MAIC ClarIDHy vs ABC-06	Unadjusted		
	Ivo vs placebo	Not estimated or used due to unanchored framework	
	FOLFOX vs ASC		
	Ivo vs FOLFOX (Bucher method)	0.92	(0.61, 1.39)
	MAIC-adjusted (base case analysis)		
	Ivo vs placebo	Not estimated or used due to unanchored framework	
	FOLFOX vs ASC		
	Ivo vs FOLFOX	0.97	(0.57, 1.66)

JNHB assessment

Studies included in the MAIC were identified through a Systematic Literature Review (SLR) conducted by Servier on January 30, 2024, according to the PRISMA guidelines.

Due to the lack of a randomized control trial between Tibsovo and FOLFOX, Servier has conducted an ITC via MAIC (base case analysis) or Bucher method (a scenario analysis for OS only). An anchored MAIC based on relative effects was conducted for OS due to availability of a common control arm, whereas an unanchored MAIC based on absolute effects from the Tibsovo arm and the FOLFOX arm was conducted for PFS due to the lack of a common anchor. In theory, an anchored MAIC will produce an unbiased estimate only if effect modifying factors were collected in individual studies and are used in the analysis. Prognostic factors should be cancelled out by using a relative treatment effect vs a common comparator in each individual

study. Therefore, prognostic factors should be excluded from an anchored MAIC. Inclusion of prognostic factors may lead to overfitting, and unnecessary decrease the effective sample size (ESS). An unanchored MAIC, on the other hand, requires the inclusion of all prognostic factors and effect modifiers. MAIC does not adjust for differences in study design or follow-up time.

Comparison of included studies
ClarIDHy was used as a source of data for Tibsovo whereas ABC-06 was used as a source of data for FOLFOX.

ClarIDHy was a multicenter, international, randomized, double-blind, placebo-controlled phase 3 study to evaluate Tibsovo in patients with unresectable, locally advanced or metastatic CCA and an IDH1 mutation previously treated with a gemcitabine or 5-fluorouracil (5-FU) containing regimen. PFS per independent radiology center (IRC) was used for the primary endpoint supported by OS (key secondary endpoint). PFS was censored due to the start of subsequent anticancer therapy, due to a gap since the previous disease assessment, crossover or after local PD at the time of last adequate IRC assessment. Radiographic assessments (CT or MRI) were conducted at screening, every 6 weeks for the first 8 assessments (i.e. through week 48), and every 8 weeks thereafter (±5 days). A central review of collected images and response assessment per RECIST v1.1 was conducted by the IRC. Patients in the placebo group were allowed to cross upon radiological progression. Median follow-up duration was 8.6 months (95% CI: 7.4 – 10.6) for the Tibsovo arm and 9.1 months (95% CI: 5.2 – 11.4) for the placebo arm at the 2020 data cut-off. The study ran between 2017 and 2021.

The ABC-06 clinical trial was a phase 3, open-label, randomized trial done in 20 sites with expertise in managing biliary tract cancer across the UK. Included patients had documented radiological disease progression to first-line cisplatin and gemcitabine chemotherapy and an ECOG status of 0–1. The primary endpoint was overall survival, assessed in the intention-to-treat population. Patients in the ASC plus FOLFOX group underwent radiological tumor evaluation by CT (and optional MRI if clinically indicated) 12 weeks after the start of chemotherapy, at the end of chemotherapy, and every 3 months thereafter until documentation of disease progression. All radiological evaluations were investigator assessed, with no central review. Upon disease progression patients on ASC were allowed treatment with experimental therapies in the context of phase 1 clinical trials. The study ran between 2014 and 2019. The median follow-up was 21·7 months (IQR 17·2–30·8).

The limitation of the ABC-06 study is that it was conducted in one country, whereas ClarIDHy is an international study and hence the placebo/ASC arm might be more generalizable. In addition, the ABC-06 study is older and routine molecular profiling was not available for participating patients hence the IDH1 mutation status is unknown. Lastly, the open-label design of ABC-06 might have introduced performance, attrition, or assessment bias. The authors write that they cannot exclude that ASC in the chemotherapy group was more meticulous than in the ASC alone group. Furthermore, radiological tumor evaluation was much more frequent in ClarIDHy. In addition, the PFS censoring rules in ClarIDHy are quite conservative and have not been published in the ABC-06 protocol precluding the proper comparison. Lastly, there was a major difference in follow-up time but given the maturity of KM data this is unlikely to bias the results.

Overall, there are major differences in ClarIDHy and ABC-06 study designs, especially in terms of PFS definition (investigator assessment vs central review, likely different censoring rules), frequency of radiographic assessments and the open-label assessment in ABC-06.

Selection of variables for weighting
Comparisons to ABC-06 were conducted on the subset of the ClarIDHy patient population with an ECOG of 0 or 1, and 1 previous line of treatment (sample size =97), to better match the eligibility criteria of ABC-06.

Individual patients in ClarIDHy were weighted (i.e. their impact on the group was upgraded or downgraded) in order to match aggregated ABC-06 patient characteristics in terms of the four variables, 1) age, 2) gender, 3) ECOG and 4) disease stage. The same variables were selected for anchored (OS) and unanchored (PFS) analyses. Servier selected variables for weighting based on availability of patient characteristics across both studies, their statistical significance when used in a regression model, as well as factors included in the MAIC in a previous assessment of pemigatinib to NICE (15). CCA subtype was included in a scenario analysis but led to a large decrease in a sample size.

The clinical experts contacted by JNHB agree that ECOG status, previous treatment and disease status are the most important prognostic factors, but age and gender might have a smaller prognostic value. However, the list is not exhaustive as other factors such as underlying predisposing causes (such as primary sclerosing cholangitis, or any type of liver cirrhosis) and comorbidities, CA19.9 levels, cholestasis, and response to previous therapy were also mentioned as being prognostic. There is limited and conflicting data on whether IDH1 mutational status has prognostic value, the same is true for CCA subtypes.

Overall, the four variables (age, gender, ECOG and disease stage) can be agreed to have a prognostic value and should be included in the unanchored MAIC. However, no justification has been provided for whether these can also be considered effect modifiers and therefore included in an anchored MAIC. A subgroup analysis of OS shows that albumin levels could be an effect modifier for FOLFOX (10) whereas ECOG could be an effect modifier for Tibsovo (16).

Comparison of patient characteristics between ClarIDHy (subset intended for the ITC) and ABC-06
Prior to MAIC adjustment, the largest difference was in CCA subtypes, i.e. 90% in ClarIDHy had iCCA compared to 44% in ABC-06, and 3% vs 28%, respectively, had eCCA. There was no data on IDH1 mutation in the ABC-06 trial but a large difference between the trials can be expected since the ClarIDHy study population is selected based on IDH1 mutation. In addition, the subset of the ClarIDHy patient population intended for the ITC for OS differed slightly compared to ABC-06 in terms of age (8% difference in % of those of ≥65), gender (15 % difference in % male), ECOG (6 % difference in % with status 0) or extent of disease (10% difference in % metastatic). These differences consistently disadvantaged the ABC-06 population compared to ClarIDHy in terms of prognosis.

After weighting, patient characteristics were balanced in terms of age, gender, ECOG and extend of disease. An additional analysis that included CCA subtype as a variable for weighting drastically decreased the effective sample size and was thus disregarded in this assessment. The differences in CCA subtypes therefore remained. Similar differences were present between the Tibsovo arm (from the ClarIDHy subset intended for the ITC for PFS) and FOLFOX arm.

In terms of age, gender, ECOG and extend of disease the MAIC adjustment removed some bias that favored Tibsovo. On the other hand, there remained a large difference in the proportions of CCA subtype and IDH1 mutation. However, the prognostic/effect modifying properties of these variable are unclear. Collection of patient characteristics in ClarIDHy seems limited compared to ABC-06. Therefore, it is unclear how adjusting for 4 characteristics affected the unmeasured characteristics.

Proportional hazard assumption
The resulting HR of 0.62 between Tibsovo and FOLFOX for OS is based on the anchored MAIC comparison of the relative effect of Tibsovo vs placebo (HR = 0.43) and the relative effect of FOLFOX vs ASC (HR=0.69). As the OS KM curve for FOLFOX is extrapolated through the application of a constant treatment effect relative to Tibsovo, the HR is assumed constant over time and independent on the follow-up time. Therefore, the validity of the HR relies on a proportional hazard (PH) assumption. The PH assumption for Tibsovo vs placebo (for OS) was examined via a log cumulative hazard plot that showed a constant treatment effect over time.

The PH assumption was further supported by a Schoenfeld residual plot that showed a horizontal pattern and the PH test with p = 0.43. Similar diagnostic tests were not presented for FOLFOX vs ASC despite the request. JNHB have digitalized OS KM data from ABC-06 publication and examined the PH assumption using Stata 18.0. As shown in Figure 5, the log cumulative hazard curves cross 3 times demonstrating that the PH assumption for FOLFOX+ASC vs. ASC is questionable. However, Schoenfeld residuals do not show a clear pattern and the PH test p-value of 0.202 indicates that the assumption cannot be rejected. Overall, the diagnostic tests show an inconsistent picture; the uncertainty around the hazard proportionality could question the validity of the application of a constant treatment effect between FOLFOX and Tibsovo when extrapolating KM data. It may also explain the poor fit of modelled OS to the FOLFOX KM data (see Figure 10). Alternative approaches such as piecewise constant HR or time-varying HRs to model the effect more accurately over different time intervals have not been explored by Servier.

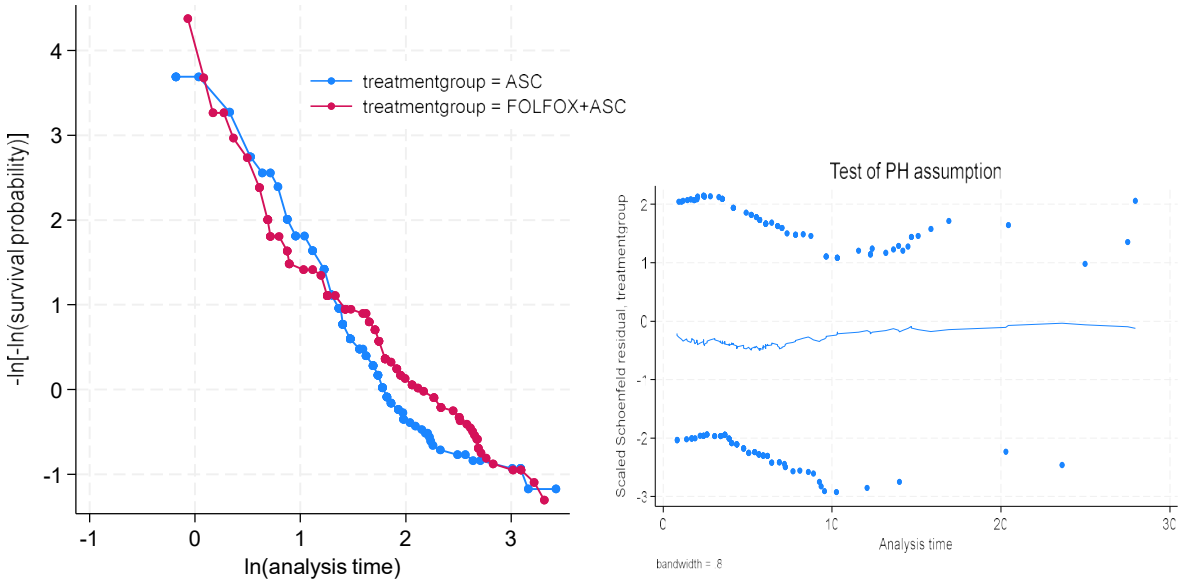


Figure 5 Log cumulative hazard plot (left) and Shoenfeld residual plot (right) for FOLFOX + ASC vs ASC (based on ABC-06 published OS KM curves (10)). Analysis performed by JNHB using Stata 18.0.

The PH assumption also does not hold for PFS. However, as PFS KM curves are extrapolated directly (i.e. not through the application of a constant treatment effect, a HR), the lack of proportionality is not a methodological obstacle for PFS (see chapter 4.2.1).

Results

The ITC results indicate that Tibsovo may have a positive effect on OS vs. FOLFOX, however, the results are not statistically significant, and the uncertainty of the results is high as demonstrated by broad confidence intervals. The ITC results are consistent between the MAIC and Bucher approaches with the MAIC method producing a slightly higher HR of 0.62 (0.33,1.18) compared to 0.58 (0.31, 1.09).

There was no indication of a difference between Tibsovo and FOLFOX in terms of PFS (HR=0.97, 95%CI 0.57, 1.66) in an unanchored MAIC. Note that a HR is not an appropriate estimator in this case due to lack of the hazard proportionality. The lack of effect could be directly concluded from the overlapping log-cumulative hazard plots and survival curves. The difference in effect on PFS compared to OS for Tibsovo relative to FOLFOX could reflect the difference in the mechanism of action of the two treatments. FOLFOX is a cytotoxic drug that kills tumor cells, preventing progression, but most CCA patients develop resistance to the drug, leaving the cancer to grow with undiminished aggressivity, shortening life expectancy. Tibsovo

on the other hand works by reducing 2-HG, an oncometabolite that has a strong effect on tumor progression through numerous pathways and the effect of Tibsovo seems to be primarily driven by its ability to stabilize the disease, which affects both PFS and OS. It could also be a result of methodological differences between ClarIDHy and ABC-06 that potentially favor FOLFOX (i.e. open-label design, less frequent PFS evaluations).

Lastly, the relative effect is measured in a subset of ClarIDHy patients who had 1 prior line of treatment and an ECOG performance status of 0-1. This restriction excluded 50% of the ITT population threatening the generalizability of the results. However, as patient characteristics are similar between the ITT population and the subset population pre- and post-MAIC adjustment, the relative effect is considered representative to the ITT population. There were only a few patients excluded due to having ECOG status 2, and the number of previous treatment lines does not seem to be an effect modifier (as concluded form a subgroup analysis for OS).

Safety
The most important safety events with FOLFOX are infections, anaemia, bleeding, nausea, vomiting, diarrhoea and sensory disturbances. Studies on second-line FOLFOX chemotherapy for patients with advanced BTC show that the most common severe (grade 3+) adverse events are neutropenia and fatigue (10, 17, 18). The treatment extends over 3 days, and one cycle extends over 14 days. This means that treatment is given every 2 weeks. At day 1 in each cycle the patient is in the hospital, where the treatment is administered through a port under the skin for 3 hours. After 3 hours, a pump with fluorouracil is mounted and the patient is carrying the pump for the next 46 hours. The port and the pump are of discomfort for the patient both when the port is placed and during the 46 hours the patient must wear the pump and sleep with it. JNHB clinical experts believe that Tibsovo will be equally or better tolerated than the chemotherapy regimens that are currently administered to patients.

JNHB conclusion:
The relative effect of Tibsovo vs. FOLFOX is highly uncertain. The lack of a head-to-head study between Tibsovo and FOLFOX is a major limitation. Overall, the results of the indirect treatment comparison are very uncertain and although favouring Tibsovo the results are not statistically significant. The indirect comparison is based on the ClarIDHy and ABC-06 studies that differ in design that may bias the results. Some of the differences could not be adjusted for in the analysis. As the collection of patient characteristics was limited in ClarIDHy, bias resulting from not including the remaining variables in the adjustment could not be assessed. Lastly, the PH assumption may not hold for the OS comparison. Consequently, the presented HR for OS is highly uncertain. Clinical experts consider the safety profile of Tibsovo favorable compared to currently administered chemotherapy regimens

4 Cost-effectiveness methods

The following chapter is based on the dossier submitted by Servier. All assumptions described are based on the application if not otherwise stated. The conclusion boxes after each section give a short assessment of the choices related to key parameter inputs, methods used, simplifications and scientific judgements made by Servier. The results of the JNHB analyses are presented in section 5.2.

4.1 Company model description

Servier has submitted a cost-effectiveness analysis using a partitioned survival model, in which patients who have been treated with Tibsovo are compared with patients who have received best supportive care (BSC) or FOLFOX. The model has five health states: progression-free on-treatment (PFS-ON), progression-free off-treatment (PFS-OFF), progressed disease on-treatment (PD-ON), progressed disease off-treatment (PD-OFF) and death.

All patients start in the PFS-ON health state where they receive either Tibsovo or a comparator treatment. Over time, patients can either remain progression-free (and on-treatment), or transition into the PFS-OFF state or the PD-ON state.[1] From these two states, patients can transition into the PD-OFF state. Patients can transition to the absorbing death state from any of the other four states. All patients, whether 'on' or 'off' treatment, receive active symptom control throughout the time horizon.

Baseline characteristics of the patient group entering the model are aligned with the population of ClarIDHy. Patients are assumed to be 61 years old at model entry. Costs and effects are discounted at an annual rate of three percent, which is the rate used in the Swedish base case. The time horizon of the model is a lifetime horizon, represented as a maximum of 40 years given the baseline age of the population. The model uses a cycle length of one week. Half-cycle corrections were not conducted.

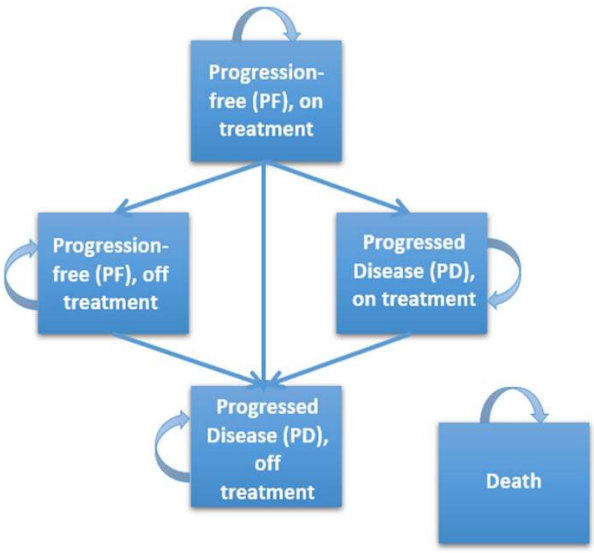


Figure 6 Servier's health economic model

JNHB conclusion: JNHB concludes that the model structure is suitable to evaluate the decision problem. According to some of JNHB's consulted clinical experts, patients eligible for treatment with Tibsovo could be somewhat older than 61 years. Adjusting the mean age at

[1] The PD-ON state only exists in the Tibsovo versus BSC comparison. When Tibsovo is compared with FOLFOX, all patients are assumed to discontinue treatment upon progression (see section 4.3.2).

model entry has a small impact on the cost-effectiveness results. This is illustrated in a sensitivity analysis.

4.2 Effectiveness outcomes

For the comparison of Tibsovo versus BSC, the survival curves informing the model states were based on time-to-event data, expressed in Kaplan-Meier (KM) curves, as derived from ClarIDHy (May 2020 data cut for OS and January 2019 data cut for PFS).

For the comparison of Tibsovo versus FOLFOX, there is no head-to-head clinical trial to inform the efficacy and clinical data between the two treatments. Therefore, Servier has conducted a matching adjusted indirect comparison (MAIC) between ClarIDHy and ABC-06 (data cut April 2020). An anchored MAIC was performed for OS and an unanchored MAIC was performed for PFS (see section 3.2).

4.2.1 Clinical effectiveness

In order to evaluate the clinical outcomes over a longer time horizon than that observed in the trials, parametric model fittings to data for OS and PFS were conducted. Six parametric distributions were considered: exponential, Weibull, Gompertz, log-normal, log-logistic and generalized gamma.

Tibsovo versus BSC

The survival analysis was conducted using KM curves for Tibsovo and RPSFT-adjusted BSC from ClarIDHy (see section 3.1). To assess the suitability of each model fit, the AIC and BIC of the parametric models as well as cumulative log-hazard plots in ClarIDHy were examined (see Appendix 3 – parametric fits, AIC/BIC and log-cumulative hazard plots). Based on these, a jointly fitted log-normal curve was chosen as Servier's base case parametric fitting for the OS and PFS comparison between Tibsovo and BSC.

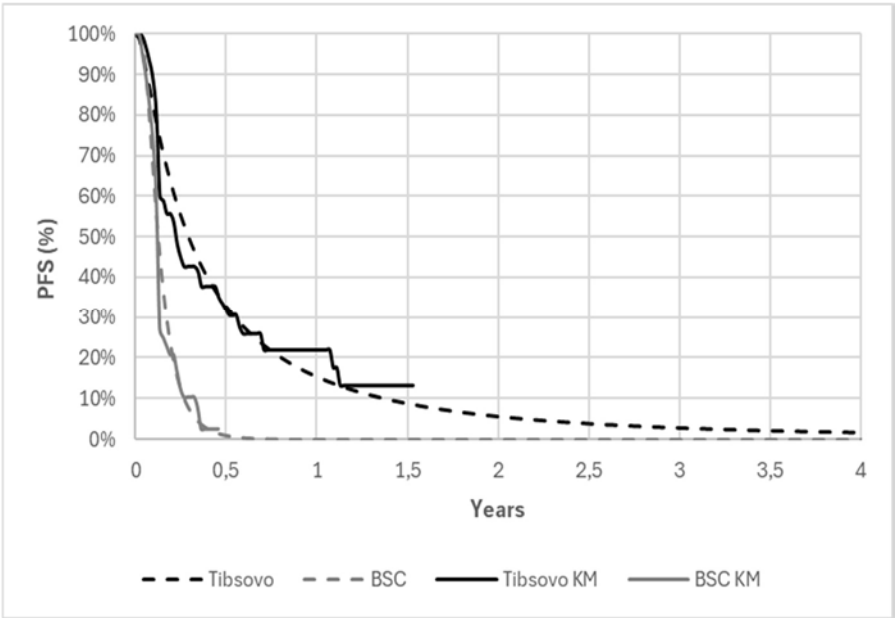


Figure 7 KM estimates from ClarIDHy and extrapolation of PFS in Servier's base case (versus BSC); jointly fitted log-normal curves

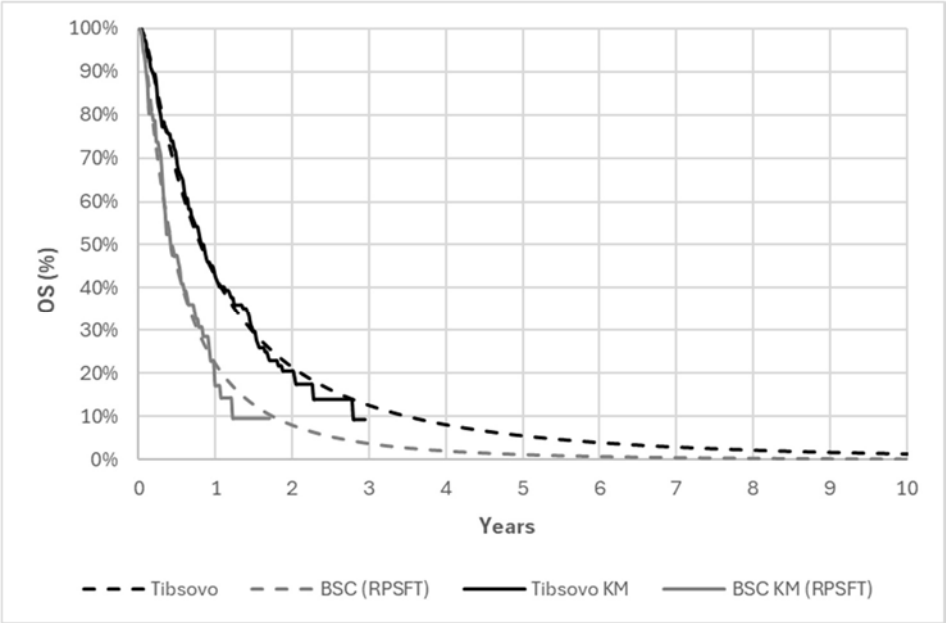


Figure 8 KM estimates from ClarIDHy and extrapolation of OS in Servier's base case (versus BSC); jointly fitted log-normal curves

Tibsovo versus FOLFOX
Progression-free survival
Data from ClarIDHy regarding PFS were weighted to produce a KM curve for Tibsovo. For FOLFOX, the digitized KM curve for ASC+FOLFOX from ABC-06 was used. Parametric fittings were assessed based on goodness of fit using the AIC, BIC, visual inspection and the clinical plausibility of the extrapolations (see Appendix 3 – parametric fits, AIC/BIC and log-cumulative hazard plots). The independent log-normal distribution was chosen as Servier's base case parametric fitting for the PFS comparison between Tibsovo and FOLFOX.

Overall survival
Data from ClarIDHy regarding OS were also weighted to produce a KM curve for Tibsovo. Based on visual inspection, a jointly fitted Weibull curve was chosen as Servier's base case parametric fitting. For OS, Servier concluded that the proportional hazards assumption was satisfied and therefore the relative treatment effect of Tibsovo compared to FOLFOX was presented in the form of a constant hazard ratio (HR). The HR utilizes both the HR of Tibsovo versus RPSFT-adjusted BSC and the published HR comparing FOLFOX + ASC versus ASC (see section 0). The constant HR for Tibsovo vs FOLFOX is equal to 0.62 (95% CI: 0.327 – 1.183).

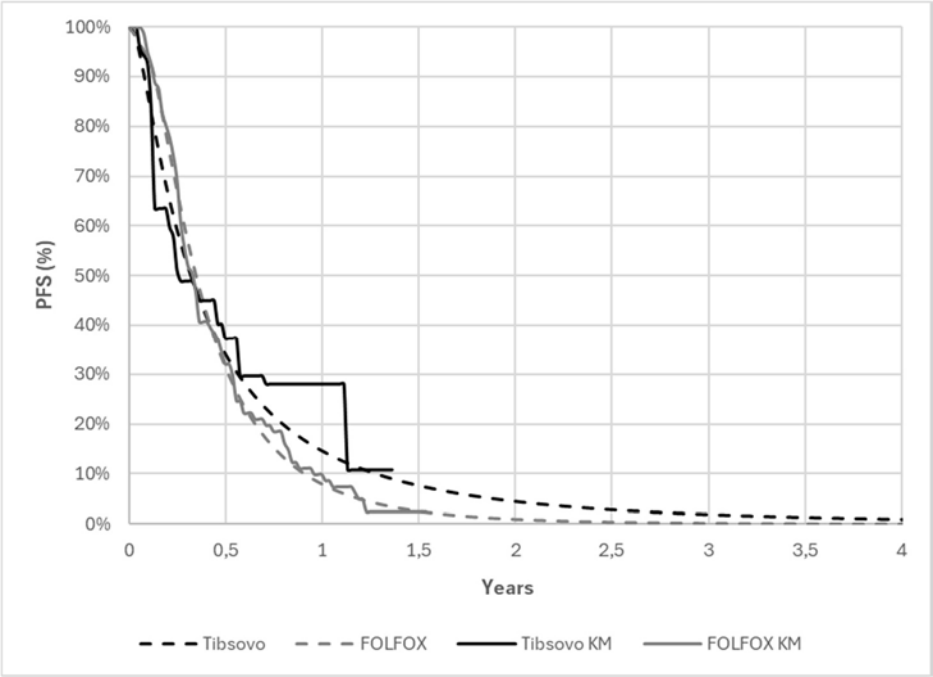


Figure 9 KM estimates from ClarIDHy and ABC-06 and extrapolation of PFS in Servier's case (versus FOLFOX); independently fitted log-normal curves

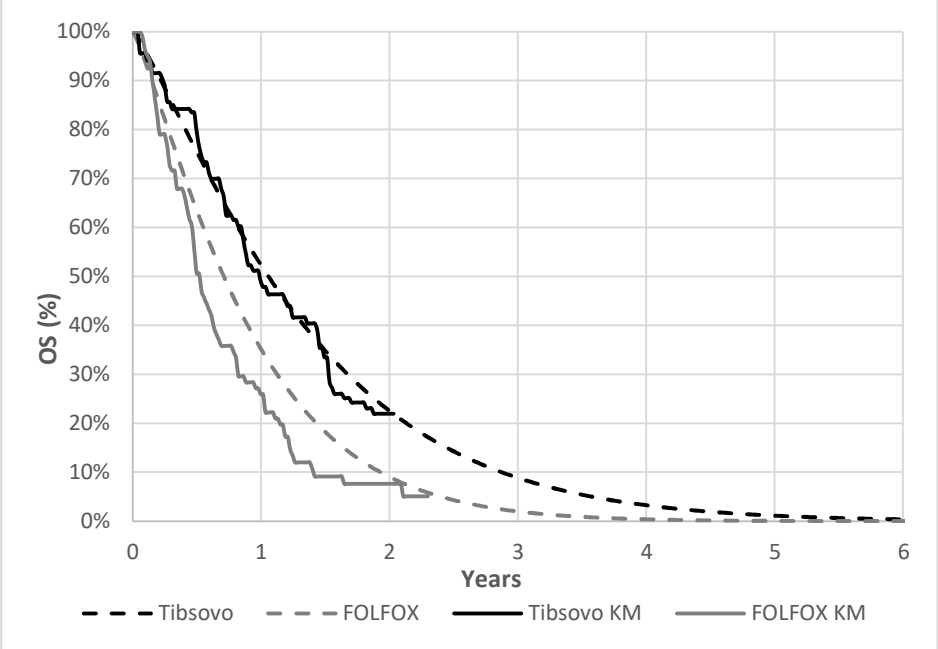


Figure 10 KM estimates from ClarIDHy and ABC-06 and extrapolation of OS in Servier's base case (versus FOLFOX); jointly fitted Weibull curves

JNHB discussion

Overall survival

Servier's extrapolation of OS for patients treated with BSC and FOLFOX, respectively, is supported by a majority of JNHB's consulted clinical experts.

As previously described, the results from Servier's indirect comparison between Tibsovo and FOLFOX are uncertain. A constant treatment effect (HR=0.62) is assumed but may not hold. In addition, the estimate was not statistically significant (95 % CI: 0.327 – 1.183). Varying the HR by its confidence interval has a large impact on the cost-effectiveness results, while the choice of parametric distribution is of less importance as survival data from ClarIDHy and

ABC-06 are mature. Moreover, Servier's modelling technique (proportional hazard assumption) results in a poor fit of the extrapolation to the KM data from ABC-06. However, this assumption could be considered conservative, as extrapolation with a better fit to the KM data would result in a larger number of gained life years for Tibsovo versus FOLFOX.

In the comparison of Tibsovo versus FOLFOX, Servier assumes a four-year survival rate of three percent for Tibsovo. Meanwhile, in the comparison of Tibsovo versus BSC, Servier assumes a four-year survival rate of eight percent. After seven years, some patients are still expected to be alive. The JNHB clinical experts estimate that a small share of patients treated with Tibsovo could still be alive four years after starting second line treatment. It is, however, difficult to predict whether the survival rate would be as high as eight percent.

There is a difference in undiscounted life years for the Tibsovo arm, depending on the comparator (1.57 versus 1.36 for BSC and FOLFOX, respectively). This can partly be explained by the difference in populations for Tibsovo: ITT versus MAIC-weighted. However, it is also due to Servier's choice of parametric distributions. The log-normal distribution, used to model OS for Tibsovo versus BSC, generates a decreasing hazard rate over time which creates a flatter survival curve with a longer tail. The Weibull distribution used to model OS for Tibsovo versus FOLFOX, generates an increasing hazard rate over time which creates a steeper survival curve with a shorter tail.

Based on available study data from ClarIDHy as well as statements from JNHB's clinical experts, JNHB considers Servier's estimation of long-term OS in patients receiving Tibsovo, compared to BSC, to be uncertain and possibly overestimated. For the comparison of Tibsovo versus BSC, JNHB finds it more appropriate to use a Weibull distribution. The four-year survival rate for Tibsovo is three percent, which corresponds to the survival rate in the Tibsovo arm when compared to FOLFOX (see Figure 11 and Table 5 below).

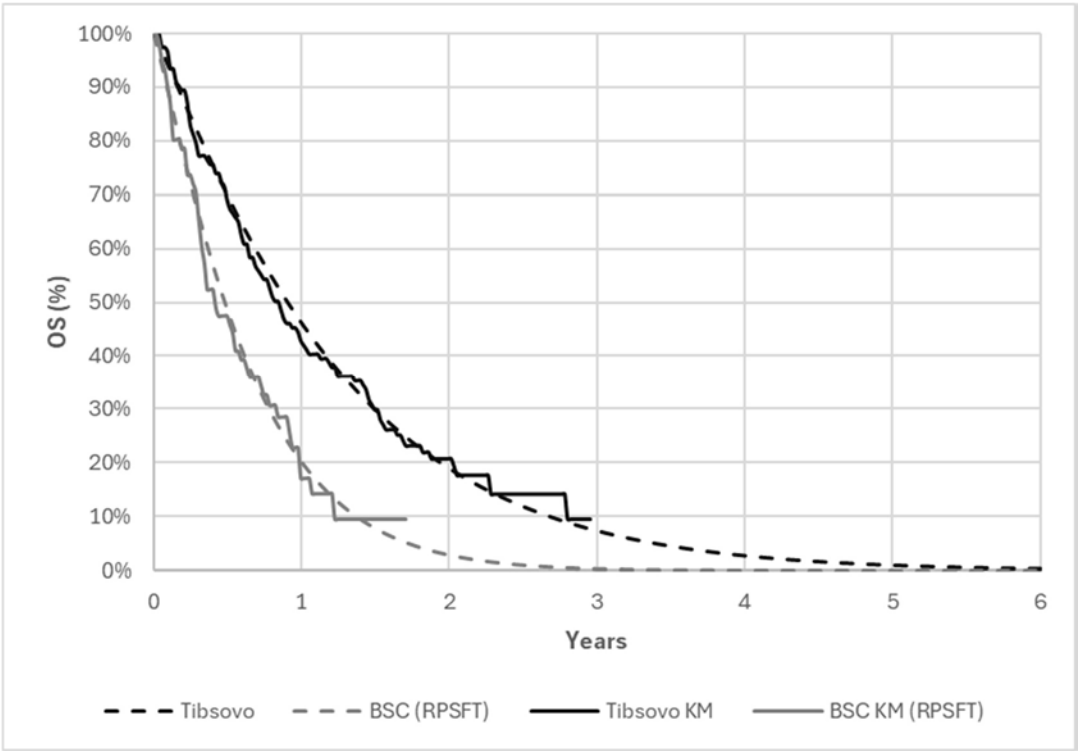


Figure 11 KM estimates from ClarIDHy and extrapolation of OS in JNHB base case (versus BSC); jointly fitted Weibull curves

Table 5 1–5-year survival rates for Tibsovo in JNHB base case

Comparator	(%) patients alive year 1	(%) patients alive year 2	(%) patients alive year 3	(%) patients alive year 4	(%) patients alive year 5
BSC	46%	19%	7%	3%	1%
FOLFOX	52%	22%	9%	3%	1%

Progression-free survival
Servier's modelling of PFS for Tibsovo versus FOLFOX is uncertain. The matching indirect comparison results in an HR close to 1 (HR: 0.97; 95 % CI: 0.57 – 1.66).

When Tibsovo is compared with BSC and FOLFOX, it is assumed that approximately five percent of the patients in the Tibsovo arm will be progression-free after two years. In the JNHB base case a Weibull distribution, which generates an increasing hazard rate over time, is used to model OS. Since the risk of dying is assumed to increase over time, the JNHB also finds it reasonable to assume that the risk of progressing increases over time. However, when applying a Weibull distribution for PFS, all patients are assumed to have progressed within three years. For this reason, JNHB uses the same parametric distribution as Servier to extrapolate PFS for both comparisons (log-normal distribution).

Survival data from ClarIDHy and ABC-06 are mature. In the comparison of Tibsovo versus BSC, the choice of parametric distribution has a small impact on the cost-effectiveness results. In the comparison of Tibsovo versus FOLFOX, the modelled treatment duration corresponds to the PFS curve (see section 4.1 and 4.3.2). This means that the choice of parametric distribution has a somewhat larger impact on the cost-effectiveness results, which is illustrated in sensitivity analyses.

JNHB conclusion: In the base case, JNHB uses the same parametric distribution as Servier to extrapolate PFS for both comparisons (log-normal distribution). More conservative parametric distributions are explored in a sensitivity analysis.

Servier's modelling of OS for Tibsovo is uncertain. The extrapolations result in a difference in undiscounted life years for the Tibsovo arm, depending on the comparator. Based on available study data from ClarIDHy as well as statements from JNHB's clinical experts, JNHB considers Servier's estimation of long-term OS in patients receiving Tibsovo, compared to BSC, to be uncertain and possibly overestimated. For the comparison of Tibsovo versus BSC, JNHB applies a Weibull distribution for OS. Other parametric distributions are explored in a sensitivity analysis.

For the comparison of Tibsovo versus FOLFOX, JNHB uses the same parametric distribution as Servier to extrapolate OS (Weibull distribution). Different parametric distributions are explored in a sensitivity analysis.

The hazard ratio obtained in the indirect comparison is highly uncertain. Varying the hazard ratio by 95% CI is explored in a sensitivity analysis. The PH assumption is uncertain, which also affects the extrapolations, but cannot be explored in a sensitivity analysis.

4.2.2 Health related quality of life

Health-related quality of life data was obtained from ClarIDHy (May 2020 data cut) in the form of EQ-5D-5L responses. Quality of life was measured three times over the follow-up (four times for patients in the BSC arm who crossed over to Tibsovo). Servier has not submitted response proportions and reasons for non-completeness so the bias could not be assessed.

Servier has compared different mixed model repeated measures (MMRMs) specifications (with four, three or two variables) and selected a model with two variables (treatment status and TRAE grade ≥ 3). Upon request Servier submitted model diagnostics which showed that the underlying assumptions of homoscedasticity, normality of residuals and linearity of predictor-outcome association hold.

Mapping using the algorithm by Hernández-Alava, and statistical analyses were conducted to obtain the EQ-5D-3L utility values using the UK value set, which is the preferred values for the Swedish base case (19, 20)

In Servier's base case, progression-free patients off treatment have a lower quality of life than progressed patients who remain on treatment. According to Servier, results from the statistical analysis indicate that treatment discontinuation is a better predictor of utility values than progression status.[2] In addition, Servier claims that the assumptions are in line with previous NICE appraisals for pemigatinib, sorafenib and regorafenib (15, 21, 22).

Table 6 Utility values used by Servier in the health economic model

Health state	Utility value	Standard deviation	Number of patients in MMRM	Number of assessments in MMRM
Progression-free on treatment	0.725	0.017	46	50
Progression-free off treatment	0.656	0.035	2	2
Progressed on treatment	0.725	0.017	29	32
Progressed off treatment	0.656	0.035	94	114

A single disutility (-0,093) was applied to all adverse events.[3] The model also considers general population age utility adjustment, using the Swedish population values (23). Disutility due to adverse events and age adjustment both have a minor impact on the cost-effectiveness results.

JNHB discussion

HRQoL is measured in the same study as the study for relative effect (ClarIDHy) and is thus estimated directly from a relevant patient population. However, the validity of the values for progression-free patients "off treatment", as well as progressed patients "on treatment" are highly limited by the low number of observations informing the estimation of utility values.

Further, the JNHB clinical experts find it unlikely that progressed patients on treatment would have a higher quality of life than progression-free and progressed patients who have discontinued treatment. Patients who have experienced significant radiographic disease progression are likely to have a lower quality of life than progression-free patients, regardless of treatment status. JNHB therefore adjusts the utility weights so that all progression-free patients have a utility of 0.725, while progressed patients have a utility of 0.656.

JNHB conclusion: Servier's estimation of utility values is associated with uncertainties due to the small number of observations for some health states. In addition, bias could not be assessed as Servier has not submitted response proportions and reasons for non-completeness. JNHB adjusts the utility weights so that all progression-free patients have a utility of 0.725. All progressed patients are assumed to have a utility of 0.656. The utility weights are also varied by the standard deviations in a sensitivity analysis.

[2] Servier has not included this analysis in the submission.
[3] Ascites, Anaemia, Biliary event, Blood bilirubin increased, Fatigue, Hyponatremia, Hypophosphatemia, Infection and Neutropenia.

4.3 Costs and resource utilization

The following direct medical costs have been considered in the model: drug acquisition and administration, monitoring, adverse events and terminal care costs.

4.3.1 Dosage/Administration

Tibsovo is administered orally at a daily dose of 500 mg (2 x 250 mg). Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient (6).

FOLFOX is a combination chemotherapy regimen which consists of fluorouracil, oxaliplatin and calcium folinate which are administered by intravenous infusion. In the model, dosing and frequency information were obtained from the ABC-06 trial. Fluorouracil is administered every other week at a dose of 400 mg/m^2 BSA (bolus injection) + 2 400 mg/m^2 continuous infusion over 46 hours. Oxaliplatin is administered every other week at a dose of 0.085 g/m^2 BSA. Calcium folinate is administered every other week at a dose of 0.35 g.

4.3.2 Medicine costs

The cost of treatment with Tibsovo is approximately 173,000 SEK per 30 days.

ClarIDHy provides data regarding the share of patients who experienced dose interruptions. 29.8 percent of patients experienced dose interruptions and the mean duration was 12 days. To account for this, a one-off reduction in costs of 29.8 percent was applied in the first two cycles (14 days) in the PFS state for the Tibsovo arm. The medicine costs in Servier's analysis do not account for wastage which means that no additional costs are included for patients who discontinue treatment in the middle of a 28-day treatment cycle.

Drug acquisition costs for FOLFOX were sourced from Stockholm's Region Procurement Price List (24). When calculating the medicine costs for FOLFOX, Servier has assumed that the patient's BSA is 1.82 m^2.

BSC may include biliary drainage, antibiotics, analgesia, steroids, anti-emetics, palliative radiotherapy and blood transfusions. The costs of these drugs were not explicitly included in the model, as they were expected to apply to both arms equally.

See Table 7 below for details regarding packages, prices and costs.

Table 7 Medicine costs in the health economic model

Treatment regime	Formulation	Drug unit	Pack size	Cost per pack (SEK)
Tibsovo				
Tibsovo	Oral	250 mg	60	173,459
FOLFOX				
Fluorouracil	IV	50 mg/ml, 20 ml	1	35
Oxaliplatin	IV	5 mg/ml, 20 ml	1	56
Calcium folinate	IV	10 mg/ml, 25 ml	1	58

Treatment duration, Tibsovo vs BSC

Treatment duration for patients treated with Tibsovo was modelled using parametric distributions fitted to TTD data from ClarIDHy (May 2020 data cut). The generalized gamma distribution was chosen as the base case parametric fitting. In ClarIDHy, patients could remain on-

treatment after having experienced radiographic disease progression, provided the investigator deemed there was clinical benefit. These patients enter the PD-ON state in the model, meaning the TTD curve is allowed to cross the PFS curve.

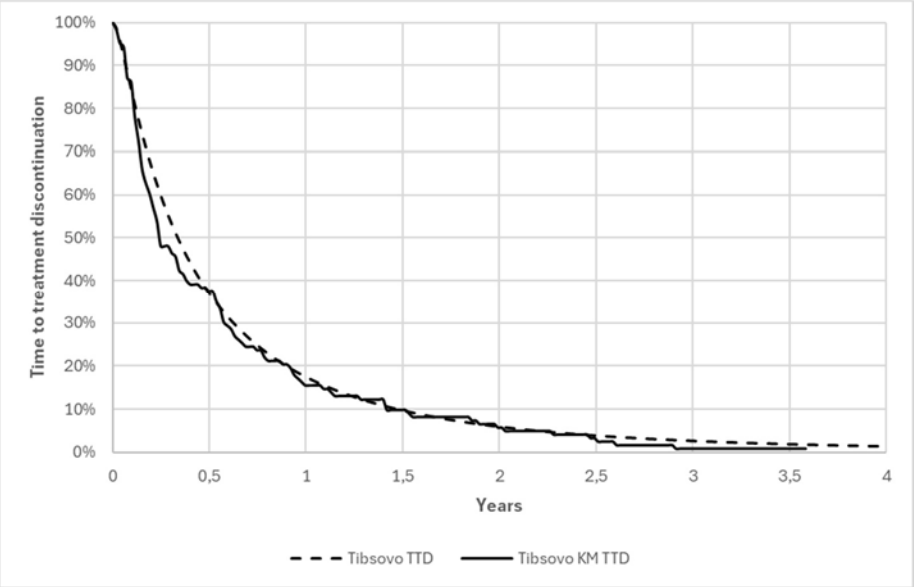


Figure 12 KM from ClarIDHy and extrapolation of TTD for Tibsovo (vs BSC) in Servier's base case

Treatment duration, Tibsovo vs FOLFOX
Servier does not have access to TTD data from ABC-06 and has not provided MAIC-weighted TTD data from ClarIDHy. When Tibsovo is compared with FOLFOX, all patients are assumed to discontinue treatment upon disease progression. Hence, the modelled TTD curve corresponds to the PFS curve (see section 4.2.1).

Maximum treatment duration for patients treated with FOLFOX is 24 weeks. This assumption is based on ABC-06.

JNHB discussion
Tibsovo comes in a pack size of 60 tablets which lasts for 30 days of treatment. It is therefore not reasonable to assume that patients who discontinue treatment in the middle of a 28-day treatment cycle do not incur the whole 28-day treatment cycle cost. In the JNHB base case, the costs for wastage of drugs are included. This means that all patients incur the 28-day treatment cycle costs, even if they discontinue treatment in the middle of the 28-day treatment cycle.

The JNHB clinical experts confirms that it is reasonable to assume a maximum treatment duration of 24 weeks for patients treated with FOLFOX, mainly due to neurotoxicity.

According to the JNHB clinical experts, it is unlikely that patients will continue treatment with Tibsovo post-progression. However, post-progression treatment could have an impact on OS KM estimates from ClarIDHy. When Tibsovo is compared to BSC, it is therefore appropriate to model treatment duration by fitting a parametric distribution to TTD data from ClarIDHy. The generalized gamma distribution used by Servier shows a good statistical fit to the KM estimates.

JNHB conclusion: In the JNHB base case, the costs for wastage of drugs are included. This means that all patients incur the 28-day treatment cycle costs, even if they discontinue treatment in the middle of the 28-day treatment cycle.

In the JNHB base case, treatment duration for patients treated with Tibsovo (versus BSC) is modelled using the generalized gamma distribution fitted to TTD data from ClarIDHy. When

Tibsovo is compared to FOLFOX the PFS curves are used for estimating TTD. Other parametric distributions, as well as a scenario when all patients discontinue treatment at progression, are explored in sensitivity analyses.

4.3.3 Costs for health care and use of resources and other directs costs

Drug administration costs
Tibsovo is administered orally and does not incur any administration costs. For FOLFOX, Servier assumes a chemotherapy administration cost of 8,237 SEK for each intravenous infusion to reflect the prolonged administration of fluorouracil which is administered over a 46-hour time period (25).

Table 8 Drug administration costs in Servier's base case

Item	Unit cost (SEK)	Code
IV administration	6,448	DT016, Läkemedelstillförsel, intravenös (Södra sjukvårdsregionen 2023)
Cytostatic preparation	1,789	H451, Cytostatikaberedning (Södra sjukvårdsregionen 2023)
Total cost per chemotherapy administration	**8,237**	

Monitoring and disease management costs
Unit costs of monitoring and disease management were sourced from Södra sjukvårdsregionen (2023) (25).

The cost categories and the resource use associated with each unit cost were obtained from ClarIDHy and the previous NICE appraisal of pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement (TA722) (15). Patients treated with Tibsovo are assumed to have 12 ECGs per year. This assumption is based on ClarIDHy.

Table 9 Monitoring and disease management costs in Servier's base case, activity per year

Item	Progression-free state	Progressed state	Unit cost
Doctor visit, oncology	4	4	3,560
Electrocardiogram (ECG) monitoring	4 (12 for patients being treated with Tibsovo)	4 (12 for patients being treated with Tibsovo)	1,694
CT scan	4	1	2,568
Blood test	4	4	278

Subsequent treatment costs
All patients, irrespective of treatment arm or health-state, were assumed to continue with ASC after treatment discontinuation. The costs of ASC were not explicitly included in the model, as they were expected to apply to both arms equally (see also section 4.3.2).

Costs for adverse events, genetic testing and terminal care
Unit costs for adverse events were sourced from Södra sjukvårdsregionen (2023) (25). The cost categories were based on previous NICE appraisals in proxy indications (26-28). The costs are low and have a minor impact on the cost-effectiveness results.

Servier's base case does not include the cost of genetic testing for detecting IDH1 mutation, as genetic testing is assumed to occur for all patients prior to treatment.

One-off end of life costs were incurred at the time patients enter the death health state in the model. The costs were assumed as a 10-day cost of 9,910 SEK (total 99,170 SEK), according to the cost for one hospitalization day in palliative care, sourced from Södra sjukvårdsregionen (2023) (25).

4.3.4 Indirect costs

No indirect costs are included in the model.

JNHB discussion

Monitoring and disease management costs

After consulting clinical experts, JNHB concludes that Servier may have underestimated the annual number of oncologist visits and blood tests patients undergo. Given the short survival of patients treated with Tibsovo and the comparators, adjusting the number of healthcare visits has a small impact on the outcome. This is illustrated in a sensitivity analysis. In the JNHB base case, Servier's estimate of monitoring and disease management costs is used.

Subsequent treatment costs

In ClarIDHy, no third line treatment except for ASC was available. According to the JNHB clinical experts, patients previously treated with Tibsovo can receive third line treatment with chemotherapy.

It is uncertain how many patients will receive third line treatment. In addition, the progression rate for third line patients is high, meaning treatment duration is short and the cost of chemotherapy is low. Subsequent treatment costs are likely to have a minor impact on the cost-effectiveness results are therefore not included in the JNHB base case.

Cost for genetic testing

According to Danish and Norwegian clinical experts, genetic testing for detecting IDH1 mutation is part of the routine monitoring and disease management in Denmark and Norway. According to the Swedish clinical expert, genetic testing for detecting IDH1 mutation is not part of the routine monitoring and disease management in Sweden. The unit cost of the genetic testing is 4,228 SEK[4] (29). The incidence of IDH1 mutation has been estimated to be between nine and 18 percent (30). This means that the genetic testing cost assumed in the JNHB base case is 23,489 SEK.[5]

JNHB conclusion: JNHB assumes a chemotherapy administration cost of 8,599 SEK[6] for each intravenous infusion, sourced from Södra sjukvårdsregionen (2024).

Frequencies of monitoring and disease management estimated by Servier are used by JNHB even though they may be somewhat underestimated. Subsequent treatment costs are excluded as suggested by Servier.

In the JNHB base case, a cost for genetic testing is included in the Tibsovo arm. The prevalence of IDH1 is assumed to be 18 percent but is also varied in a sensitivity analysis. JNHB also presents a sensitivity analysis where the cost of genetic testing is not included in the Tibsovo arm.

[4] Code "203 QPCR, IDH1_2"
[5] 4 228 SEK/18%
[6] Code "DT016"

5 Results of the cost-effectiveness analysis

5.1 Servier's base case

5.1.1 Key assumptions in Servier's base case scenario

- Jointly fitted log-normal curves were chosen as the base case parametric fitting for the OS and PFS comparison between Tibsovo and BSC. Independently fitted log-normal curves were chosen as the base case parametric fitting for the PFS comparison between Tibsovo and FOLFOX.
- For the OS comparison between Tibsovo and FOLFOX, a Weibull curve was chosen as the base case parametric fitting for Tibsovo. The relative treatment effect of Tibsovo compared to FOLFOX was presented in the form of a constant hazard ratio (HR) equal to 0.62.
- Utility weights depend on whether the patient is on or off treatment, regardless of progression status.
- For the comparison between Tibsovo and BSC, patients can continue treatment with Tibsovo post progression.
- The medicine costs in Servier's analysis do not account for wastage.
- Costs of subsequent treatments and genetic testing are not included.

5.1.2 Results in Servier's base case scenario

Table 10 Company base case results for Tibsovo vs BSC, SEK

	Tibsovo	BSC	Difference
Drug acquisition costs	1,313,204	0	1,313,204
Administration costs	0	0	0
Other direct costs	159,416	142,911	16,505
Total costs	1,472,620	142,911	1,329,709
Time on treatment (years, undiscounted)	0.64	0.22	0.42
Progression-free life years (undiscounted)	0.61	0.16	0.45
Life years (undiscounted)	1.57	0.80	0.77
Quality-adjusted life years (QALYs)	1.01	0.52	0.49
Cost per QALY gained			**2,737,252**

Table 11 Company base case results for Tibsovo vs FOLFOX, SEK

	Tibsovo	FOLFOX	Difference
Drug acquisition costs	1,188,439	2,721	1,185,718
Administration costs	0	70,967	-70,967
Other direct costs	150,731	145,624	5,107
Total costs	1,339,170	219,312	1,119,858
Time on treatment (years, undiscounted)	0.58	0.33	0.25
Progression-free life years (undiscounted)	0.58	0.47	0.11
Life years (undiscounted)	1.36	0.92	0.44
Quality-adjusted life years (QALYs)	0.91	0.61	0.30
Cost per QALY gained			**3,784,673**

5.2 JNHB base case

5.2.1 Changes in assumptions in the JNHB base case scenario

- Jointly fitted Weibull curves were chosen as the base case parametric fitting for the OS comparison between Tibsovo and BSC.
- Utility weights depend on progression status.
- The medicine costs in the analysis account for wastage.
- A chemotherapy administration cost of 8,599 SEK for each intravenous infusion is assumed.
- Cost of genetic testing is included in the Tibsovo arm.

5.2.2 Results in the JNHB base case scenario

Table 12 JNHB base case results for Tibsovo vs BSC, SEK

	Tibsovo	BSC	Difference
Drug acquisition costs	1,380,979	0	1,380,979
Administration costs	0	0	0
Other direct costs	167,299	134,954	32,345
Total costs	1,548,278	134,954	1,413,324
Time on treatment (years, undiscounted)	0.63	0.22	0.41
Progression-free life years (undiscounted)	0.59	0.16	0.43
Life years (undiscounted)	1.23	0.64	0.59
Quality-adjusted life years (QALYs)	0.83	0.43	0.40
Cost per QALY gained			**3,538,770**

Table 13 JNHB base case results for Tibsovo vs FOLFOX, SEK

	Tibsovo	FOLFOX	Difference
Drug acquisition costs	1,269,481	3,766	1,265,715
Administration costs	0	74,085	-74,085
Other direct costs	174,220	145,624	28,596
Total costs	1,443,701	223,475	1,220,225
Time on treatment (years, undiscounted)	0.58	0.33	0.25
Progression-free life years (undiscounted)	0.58	0.47	0.11
Life years (undiscounted)	1.36	0.92	0.44
Quality-adjusted life years (QALYs)	0.91	0.63	0.29
Cost per QALY gained			**4,260,507**

5.2.3 JNHB sensitivity analyses

JNHB sensitivity analyses are presented in Table 14 and Table 15 below. A summary of justification for the sensitivity analyses can be found below the tables.

Table 14 JNHB sensitivity analyses for Tibsovo vs BSC, SEK

Sensitivity analyses		Incr. costs	Incr. QALYs	Cost/QALY
Base case		**1,413,324**	**0.40**	**3,538,770**
Discounting	0%	1,435,176	0.41	3,473,897
	5%	1,399,985	0.39	3,581,110
Age at model entry	65 years	1,413,324	0.40	3,539,215
	70 years	1,413,324	0.40	3,538,779
Extrapolation of PFS	Exponential	1,416,811	0.39	3,621,375
	Generalized gamma	1,413,689	0.40	3,547,259
	Weibull	1,416,795	0.39	3,620,988
Extrapolation of OS	Exponential	1,417,484	0.38	3,771,205
	Gompertz	1,418,210	0.41	3,469,682
Utility weights	+SD (PFS 0,74, PD 0,69)	1,413,324	0.41	3,442,268
	-SD (PFS 0,71, PD 0,62)	1,413,324	0.39	3,643,525
Extrapolation of TTD	PFS	1,317,915	0.40	3,300,562
	Gompertz	1,341,810	0.40	3,359,203
	Weibull	1,279,924	0.40	3,203,842
	Exponential	1,281,895	0.40	3,208,799
Disease management and monitoring costs	2x as many oncologist visits + blood tests	1,422,001	0.40	3,560,495
	3x as many oncologist visits + blood tests	1,430,677	0.40	3,582,220
Cost of genetic testing	Cost of genetic testing excluded	1,389,835	0.40	3,479,957
	Prevalence 9%	1,436,813	0.40	3,597,583
	Unit cost 14,352 SEK *(Massiv Parallellsekvensering (MPS) 200 NGS solida tumörer (DNA och RNA).*	1,469,569	0.40	3,679,598

Age at model entry: In the base case, age at model entry is 61. According to JNHB's clinical experts, patients could be older. 65 and 70 years are explored in a sensitivity analysis.
Extrapolation of PFS: In the base case, PFS is extrapolated with a log-normal distribution. More conservative distributions are explored in the sensitivity analysis. These have a limited impact on the cost-effectiveness results.
Extrapolation of OS: In the base case, OS is extrapolated with a Weibull distribution. One more conservative and one less conservative distribution are explored in the sensitivity analysis.
Utility weights: In the base case, the utility weights are 0,73 (PFS) and 0,66 (PD). The utility values are associated with uncertainties and are varied by the standard deviations in a sensitivity analysis.
Extrapolation of TTD: In the base case, TTD is extrapolated with a generalized gamma distribution. In sensitivity analyses, JNHB examines the impact on cost-effectiveness results when TTD with Tibsovo is extrapolated with more conservative distributions. JNHB also examines the impact on cost-effectiveness results when treatment duration is restricted by PFS.
Disease management and monitoring costs: In the base case, Servier's estimate of monitoring and disease management costs is used. Based on statements from JNHB clinical experts, higher costs are explored in a sensitivity analysis.
Cost of genetic testing: In the base case, the prevalence of IDH1 is assumed to be 18% and the unit cost is 4,228 SEK. According to Boscoe et al[7] the prevalence of IDH1 is between 9 and 18%. A prevalence of 9%, as well as a higher unit cost for testing, is explored in a sensitivity analysis.

[7] Boscoe, A.N., C. Rolland, and R.K. Kelley, Frequency and prognostic significance of isocitrate dehydrogenase 1 mutations in cholangiocarcinoma: a systematic literature review. J Gastrointest Oncol, 2019. 10(4): p. 751-765

Table 15 JNHB sensitivity analyses for Tibsovo vs FOLFOX, SEK

Sensitivity analyses		Incr. costs	Incr. QALYs	Cost/QALY
Base case		**1,220,225**	**0.29**	**4,260,507**
Discounting	0%	1,237,370	0.30	4,144,926
	5%	1,209,772	0.28	4,336,410
Age at model entry	65 years	1,220,225	0.29	4,261,247
	70 years	1,220,225	0.29	4,260,516
Extrapolation of PFS	Exponential	1,151,274	0.28	4,060,311
	Weibull	1,111,796	0.28	3,927,164
Extrapolation of OS	Gompertz	1,210,707	0.28	4,344,738
	Generalized gamma	1,224,369	0.30	4,130,866
	Lower CI for HR (0,327)	1,245,942	0.53	2,361,446
	HR=0,40	1,238,833	0.46	2,667,902
	HR=0,50	1,230,039	0.38	3,224,303
	HR=0,70	1,213,973	0.23	5,392,103
	HR=0,80	1,206,409	0.15	8,011,691
	Upper CI for HR (1,183)	1,179,259	-0.12	Dominated
Utility weights	+SD (PFS 0,74, PD 0,69)	1,220,225	0.30	4,082,552
	-SD (PFS 0,71, PD 0,62)	1,220,225	0.27	4,465,151
Disease management and monitoring costs	2x as many oncologist visits + blood tests	1,226,759	0.29	4,283,319
	3x as many oncologist visits + blood tests	1,233,292	0.29	4,306,132
Cost of genetic testing	Cost of genetic testing excluded	1,196,736	0.29	4,178,494
	Prevalence 9%	1,243,714	0.29	4,342,520
	Unit cost 14,352 SEK *(Massiv Parallellsekvensering (MPS) 200 NGS solida tumörer (DNA och RNA).*	1,276,470	0.29	4,456,889

All scenario descriptions as above.
Extrapolation of OS: In the base case, the constant HR used in extrapolation of OS is 0,62. Since the estimate from Servier's indirect treatment comparison is uncertain, the HR is varied by the lower and upper confidence interval in a sensitivity analysis.

5.3 Patient numbers

According to Servier the estimated number of patients eligible for treatment with Tibsovo are five in Finland and Norway respectively, 10 in Denmark and 17 in Sweden. This equals a total of 37 patients.

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Appendix 1 – Crossover-adjustment methodology

Crossover adjustment

Patients on placebo were allowed to cross over to the active treatment arm and receive Tibsovo (AG-120) after radiographic documented disease progression (as assessed by the Investigator and after consultation with the Sponsor Medical Monitor). Overall, 43/61 (70.5%) placebo patients received Tibsovo. The primary OS analysis was based on ITT set and included all OS data, including data after crossover. However, to adjust for the crossover effect from placebo to AG-120 on OS, an advanced modeling method such as rank preserving structural failure time (RPSFT) method, was pre-specified. RPSFT assumes that Tibsovo after the switch is acting by multiplying survival time by a given factor (acceleration factor) relative to placebo and assumes the treatment effect is the same for all subjects regardless of when treatment is received (common treatment effect).

From company's submission

The RPSFT model and assumptions (from ClarIDHy statistical analysis plan)

RPSFT assumes that the AG-120 after the switch is acting by multiplying survival time by a given factor (acceleration factor) relative to placebo, and assumes the treatment effect is the same for all subjects regardless of when treatment is received (common treatment effect).

Specifically, let U_i denote the latent survival time if subject i were assigned to the placebo arm, adhere to it and discontinue only after the event (also called counter-factual event time), $U_i = T_i{}^{off} + T_i{}^{on} \exp(\psi 0)$

where $T_i{}^{off}$ is the time that subject i is off treatment, and $T_i{}^{on}$ is the time that subject i is on treatment; $\exp(\psi 0)$ is the acceleration factor which denotes the amount by which a subject's survival time is 'increased' by the active treatment. A positive (negative) $\psi 0$ value corresponds to a harmful (beneficial) treatment effect. Specifically, for

- AG-120 subjects at randomization: $U_i(\psi 0) = T_i{}^{ag120} \exp(\psi 0)$;
- placebo subjects who crossed over to AG-120: $U_i(\psi 0) = T_i{}^{pbo} + T_i{}^{ag120} \exp(\psi 0)$;
- placebo subjects without crossover: $U_i(\psi 0) = T_i{}^{pbo}$.

In order to estimate $\psi 0$, we assume that U_i is independent of randomized treatment assignment and can be viewed as baseline characteristics. Thus, if we conduct a hypothesis test (such as logrank test) for the treatment difference on $Ui(\psi 0)$, we shall obtain a p-value close to 1 with a sufficiently large sample size. RPSFT works by reconstructing the survival time of subjects, as if they have never received active treatment. A grid search within a reasonable range will

then be performed in order to find the estimated $\psi 0$ with the largest p-value. The corresponding point estimate of HR between the two arms will be reported, with the 95% CI generated from bootstrapping method.

Re-censoring

Administrative censoring refers to the censoring where the event is not observed by the time of data cutoff. Unfortunately, its time scale cannot be adjusted in the same way as event, as potential bias could be introduced because censoring would be dependent on time spent on treatment and thus treatment arm (informative censoring). To overcome this problem, the counter-factual event times are re-censored by the minimum Ui that could have been observed for individuals (with and without events) across their possible treatment changes.

Let Ci be the potential censoring time for a subject i. The subject is then re-censored at the minimum possible censoring time:

$D_i^*(\psi 0) = \min(C_i , C_i \exp(\psi o))$.

If $D_i^* < U_i$, then U_i is replaced by D_i^* and the subject is censored. For treatment arm where switching didn't occur, re-censoring is not applied.

From company's response to the list of questions

Justification for the common treatment effect assumption

The RPSFT method relies on the "common/constant treatment effect" assumption, which implies that patients who are originally randomized to the intervention group will experience the same treatment effect as patients who switch treatment. In cases where treatment switching occurs after disease progression (as in this case) it may not be credible to assume that switchers – who now have more advanced disease – receive the same benefit from treatment as those in the experimental group who received the treatment from randomization.

However, the "common treatment effect" assumption cannot be formally tested quantitatively (31) so it is generally recommended that clinical opinion is sought regarding its plausibility. In the IQVIA analysis, the assumption was considered to hold, by comparing median survival times of switchers against patients originally assigned to ivosidenib. These were found similar, as shown in table below, thus there were not strong indications of violation of the common treatment effect assumption.

Table 16 Median OS for IVO and placebo switchers

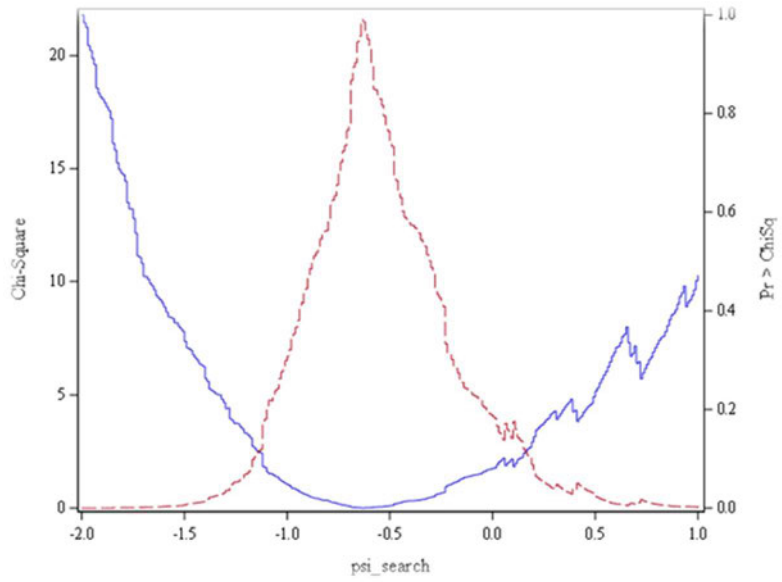
	N	Median OS (95% CI)
Tibsovo	126	10.3 (7.8, 12.4)
Placebo switchers	43	9.1 (5.4, 13.5)

The grid range searched

A grid search from -5 to 5 by 0.00001 was performed, in which the range was wide enough to allow for the possibility of extreme values and the grid was small enough to avoid potential local optimal solutions.

The estimated treatment effect parameter (with 95% CI), and g-estimation output

The plot shows distribution of the log-rank statistic (blue line) and the corresponding p-value (red line). A grid search within a range of (-5, 5) was performed to find the optimal point estimate Ψ with the largest p-value. In the plot, it shows the range of (-2, 1), the optimal point estimate Ψ is -0.63598.



Counterfactual survival times between randomized groups

The RPSFT method works by reconstructing the survival time of subjects as if they never received active treatment. Therefore, when calculating the counterfactual times, using the estimated acceleration factor, median survival times should be relatively similar. In the company's analysis the survival times were estimated post-adjustment as presented in table below:

Table 17 Survival times post-adjustment

Arm	N	Events	Median	95% CI
Tibsovo	126	100	5.2	(4.19, 6.76)
Placebo	61	49	4.9	(3.84, 8.45)

The limitations of the RPSFTM and the impact on the study's conclusions

The primary limitations of the RPSFTM involve the "common treatment effect" assumption and the randomization assumption. The latter should be reasonable in the context of an RCT. The former, is more problematic. If patients who switch on to the experimental treatment part way through the trial receive a different treatment effect compared to patients originally randomized to the experimental group, the RPSFTM estimate of the treatment effect received by patients in the experimental group will be biased. Therefore, the "common treatment effect" assumption may in some instances not be clinically plausible, as treatment switching is often permitted after disease progression, at which time the capacity for a patient to benefit may be different compared to pre-progression [5].

The use of RPSFTM is also problematic if the comparator treatment used in the RCT is active, i.e. it prolongs survival. The counterfactual survival model requires that patients are either "on" or "off" at any one time. If patients in the control group receive an active treatment followed by supportive care, then the "off" treatment category represents more than one type of treatment, and the counterfactual survival model is not appropriate unless additional causal parameters are added to the model. The "on-treatment" approach of RPSFTM method tries to handle this by assuming that the treatment effect is only received while a patient is "on" treatment, and it disappears as soon as treatment is discontinued. The "treatment group" approach, that was used in this case, ignores treatment discontinuation times and estimates the effect associated with being randomized to the experimental group, rather than the effect received

while taking the experimental treatment. This approach is more similar to a standard ITT analysis of randomized groups [5].

As stated above, re-censoring involves data being re-censored at an earlier time-point and is therefore associated with a loss of longer-term survival information. It also may lead to biased estimates of the "average" treatment effect in circumstances where proportional treatment effect assumptions do not hold, because longer term data on the effect of treatment may be lost.

Appendix 2 – Indirect treatment comparison (from Servier's submission and responses)

Systematic literature search

An SLR was conducted on January 30, 2024, to identify relevant clinical studies for evidence synthesis of efficacy and safety outcomes. The SLR was conducted in accordance with the general recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (158), the general principles of the CRD (University of York) guidance (159) for undertaking reviews in health care, PRISMA guidelines (160) and the methods for systematic reviews as specified by NICE (161).

A total of 6,023 references were identified from electronic databases searches (MEDLINE®: 1,212; Embase®: 3,860; CENTRAL®: 951). After removing duplicates, assessment for inclusion according to study eligibility criteria and identifying studies via hand searches 142 studies were identified. Following screening of the 142 included studies against the ITC eligibility criteria, 12 unique studies in total (including ClarIDHy) were included in the ITC feasibility assessment.

The target population was based on the population used in the clinical SLR, i.e., adults with unresectable, advanced or metastatic CCA. This population was selected in order to match as much as possible the population of the ClarIDHy study, which included subjects with histologically confirmed, advanced, *mIDH1* CCA who had progressed on previous therapy and had up to two previous treatment regimens for advanced disease. A wider scope was selected for the SLR (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* other than Tibsovo®.

The outcomes considered for this ITC analysis were PFS, OS, ORR, CR, SAEs and discontinuation due to adverse events (AEs).

Seven of the twelve studies were excluded due to varying definitions of the key outcomes (PFS) (Zhang 2021 (32), Larsen 2018 (33), Belkouz 2020 (34), Lin 2020 (35), Feng 2020 (36), Mizrahi 2018 (37) and Ueno 2021 (38)). Furthermore, given that REACHIN (39) did not report OS and therefore no comparative OS estimates could be derived for inclusion in the economic model, this study was excluded from the ITC. Lastly, based on the NCCN guidelines (40) and the feedback received from key opinion leaders that fluorouracil + leukovarin is not widely used in clinical practice Choi 2021 (41) was also excluded from the ITC. The two remaining studies (NIFTY (42) and ABC-06 (43)) were deemed eligible for inclusion in the ITC analysis in addition to ClarIDHy.

Matching adjusted-indirect comparison
MAIC is a non-parametric likelihood reweighting method of comparing treatment effects, while minimizing bias that results from prognostic or effect-modifying baseline characteristics that are imbalanced across study populations. MAICs can take the form of 'anchored' or 'unanchored' indirect comparisons depending on whether a common treatment comparator arm is used or not. Anchored MAICs can be used where the evidence is connected by a common comparator (e.g., study AB vs study AC, where common treatment A acts as the common comparator. Anchored approaches are preferred because they respect randomization within studies. Both anchored and unanchored MAICs were conducted in this instance.

Selection of variables for weighting
Effect modifiers and prognostic variables to be adjusted for in the MAIC were determined by a combination of factors:

- The characteristics adjusted for in the previous, relevant MAIC conducted in the NICE submission of pemigatinib for CCA were examined in order to inform the selection for the current MAICs.
- Selection was also determined through statistical testing of the ClarIDHy individual patient data (IPD), by adding them as predictors in a logistic regression model for the binary ORR outcome, or a Cox proportional hazards model for the OS and PFS outcomes and testing their statistical significance. The full list of variables is presented in Table 18, below.

Table 18 Variables considered for adjustment in the MAIC analyses.

Variable name	Available in ClarIDHy	Available in ABC-06	Included in pemigatinib NICE submission MAIC	Identified by statistical selection process		
				OS	PFS	ORR
Gender	+	+	+	+	+	
Age	+	+	+			
Previous LoT	+			+		
ECOG PS	+	+	+	+	+	+
CCA subtypes	+	+		+	+	
Extent of disease at screening	+	+		+	+	
Liver cirrhosis at screening	+					

Variable name	Available in ClarIDHy	Available in ABC-06	Included in pemigatinib NICE submission MAIC	Identified by statistical selection process		
				OS	PFS	ORR
IDH1 mutation	+					
CA19-9 concentration at baseline	+	+				
Platinum sensitivity		+				
Albumin levels		+	+			
Tumour site		+				
Histology		+				
Grade of differentiation		+				
Had previous surgery		+				
Previous cisplatin and gemcitabine		+				
Baseline carcinoembryonic antigen		+				
Baseline CA125		+				
Ethnicity						
Site of metastatic lesion						

Comparisons to ABC-06 were conducted on the subset of the ClarIDHy patient population that an ECOG of 0 or 1, and 1 previous LoT, to better match the eligibility criteria of the comparator study. In the unanchored MAIC of PFS and ORR, as well as the anchored MAIC of OS comparing ClarIDHy to ABC-06, age, sex, extent of disease at baseline, and ECOG status were adjusted for in the base case analyses. LoT did not need to be adjusted as it was fully similar due to the prior patient subsetting. CCA subtype was omitted in the base case matching process as it led to a large drop in the effective sample size (ESS), and hence greater uncertainty. Given that the association between CCA subtype and clinical outcomes is uncertain according to the current literature (44-46) it was decided to omit it in the base case analysis but include it in scenario analyses.

Table 19 Comparison of variables prior and after weighting. Adjustment for CCA (in orange) was only conducted for a sensitivity analysis.

Outcome	Analysis	Characteristic	ClarIDHy pre-adjustment	ClarIDHy post-adjustment	Comparator (ABC-06)
OS anchored MAIC	Base case	Age: ≥ 65 (%)	42.27	50.00	50.00
		Gender: Male (%)	34.02	49.38	49.38
		ECOG PS: 0 (%)	38.14	32.72	32.72
		Extent of disease at screening: Metastatic (%)	91.75	82.10	82.10
		CCA subtypes (%) iCCA	90.72	92.49	44.44
		CCA subtypes (%) eCCA	3.09	2.53	27.78
	Scenario	Age: ≥ 65 (%)	42.27	50.00	50.00
		Gender: Male (%)	34.02	49.38	49.38
		ECOG PS: 0 (%)	38.14	32.72	32.72
		Extent of disease at screening: Metastatic (%)	91.75	82.10	82.10
		CCA subtypes (%) iCCA	90.72	44.44	44.44
		CCA subtypes (%) eCCA	3.09	27.78	27.78
PFS unanchored MAIC	Base case	Age: ≥ 65 (%)	43.08	50.00	50.00
		Gender: Male (%)	32.31	53.09	53.09
		ECOG PS: 0 (%)	40.00	30.86	30.86
		Extent of disease at screening: Metastatic (%)	92.31	82.72	82.72
		CCA subtypes (%) iCCA	89.23	91.22	41.98
		CCA subtypes (%) eCCA	3.08	1.86	32.10
	Scenario	Age: ≥ 65 (%)	43.08	50.00	50.00
		Gender: Male (%)	32.31	53.09	53.09
		ECOG PS: 0 (%)	40.00	30.86	30.86
		Extent of disease at screening: Metastatic (%)	92.31	82.72	82.72
		CCA subtypes (%) iCCA	89.23	42.51	41.98
		CCA subtypes (%) eCCA	3.08	30.94	32.10
ORR unanchored MAIC	Base case	Age: ≥ 65 (%)	39.66	49.78	50.00
		Gender: Male (%)	29.31	53.28	53.09
		ECOG PS: 0 (%)	43.10	31.71	30.86
		Extent of disease at screening: Metastatic (%)	91.38	82.84	82.72
		CCA subtypes (%) iCCA	89.66	93.75	41.98
		CCA subtypes (%) eCCA	3.45	2.06	32.10
	Scenario	Age: ≥ 65 (%)	39.66	49.78	50.00
		Gender: Male (%)	29.31	53.28	53.09
		ECOG PS: 0 (%)	43.10	31.71	30.86
		Extent of disease at screening: Metastatic (%)	91.38	82.84	82.72
		CCA subtypes (%) iCCA	89.66	41.82	41.98
		CCA subtypes (%) eCCA	3.45	31.71	32.10

Distribution of rescaled weights after matching
In the base case, the rescaled weights after matching the ClarIDHy trial to ABC-06 population for OS and PFS were lower than three, suggesting that no patient was excessively upweighted in the matching process.

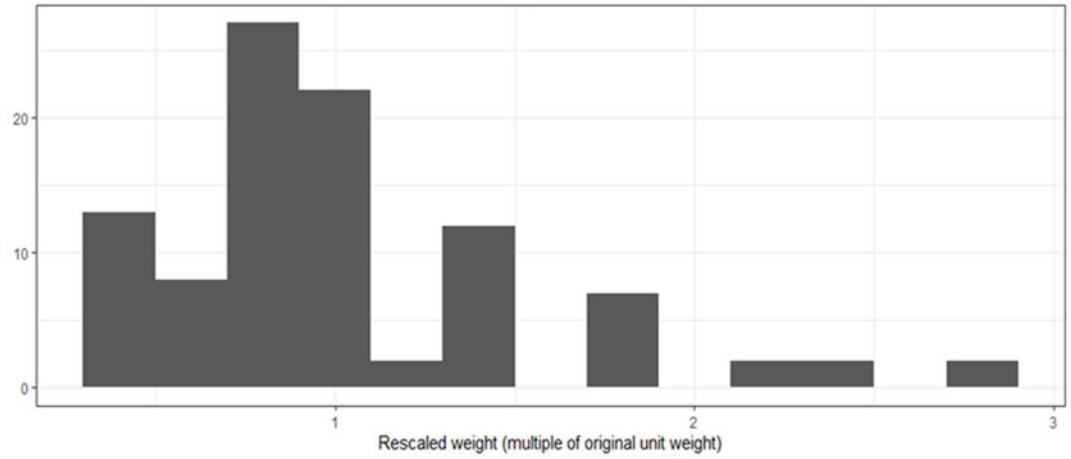


Figure 13 Distribution of rescaled weights after matching the ClarIDHy trial to ABC-06 population for OS: Base case

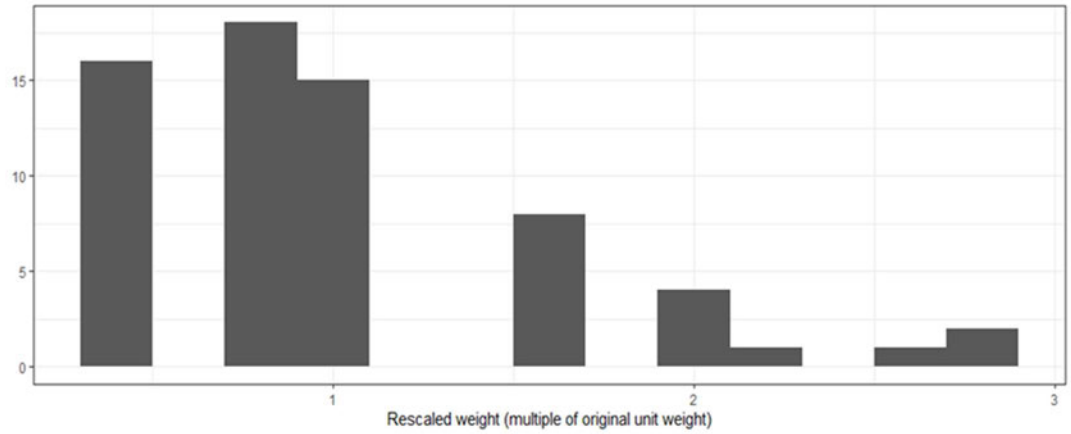


Figure 14 Distribution of rescaled weights after matching the ClarIDHy trial to ABC-06 population for PFS: Base case

Proportional hazard diagnostics

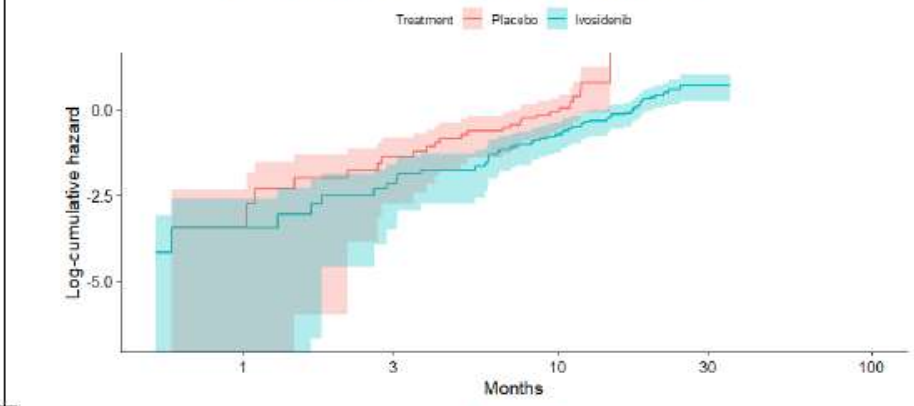
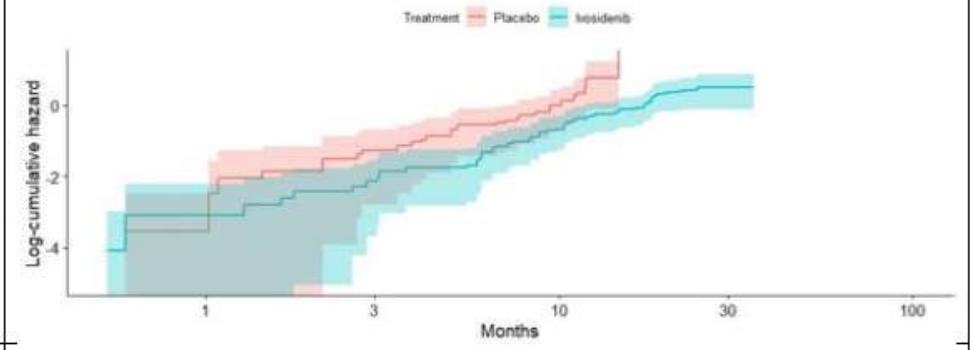
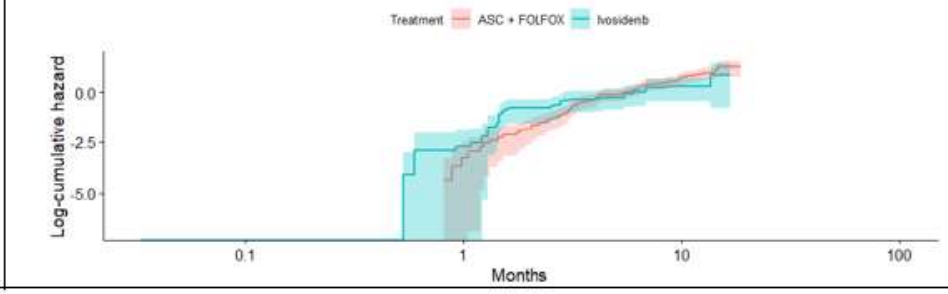
Comparison	Log-cumulative hazard vs log-time plot
OS – Tibsovo vs Placebo within ClarIDHy – Unadjusted	
OS – Tibsovo vs Placebo within ClarIDHy – Anchored MAIC adjusted – Base case analysis	
PFS – Tibsovo vs FOLFOX (ClarIDHy vs ABC-06) – Unanchored MAIC adjusted – Base case analysis	

Figure 15 Proportional hazard diagnostic plots

Results

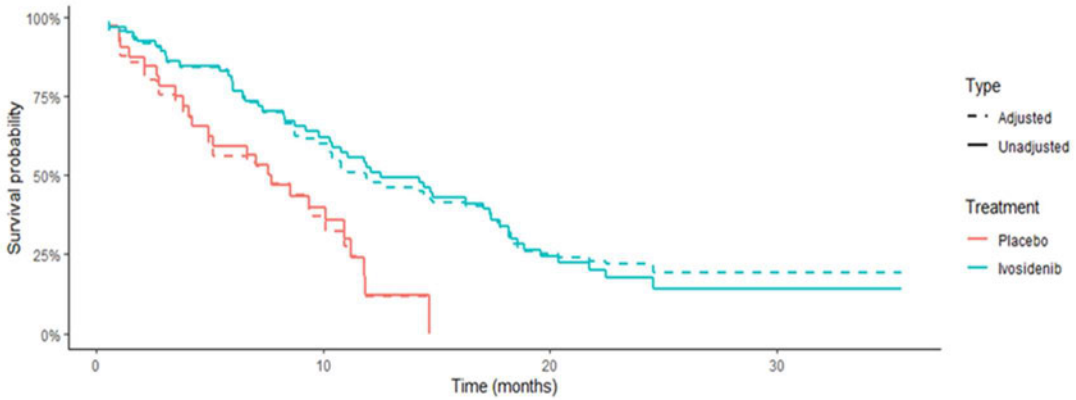
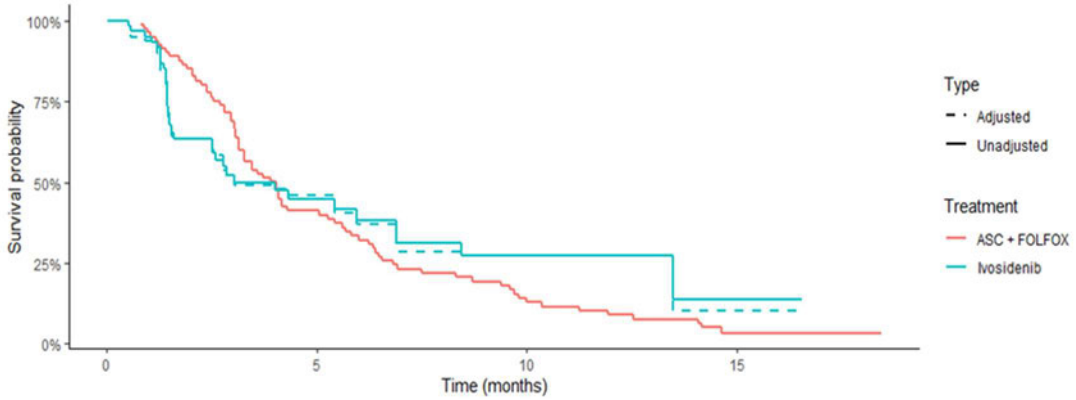


Figure 16 MAIC-adjusted vs unadjusted KM Curve for OS from ClarIDHy

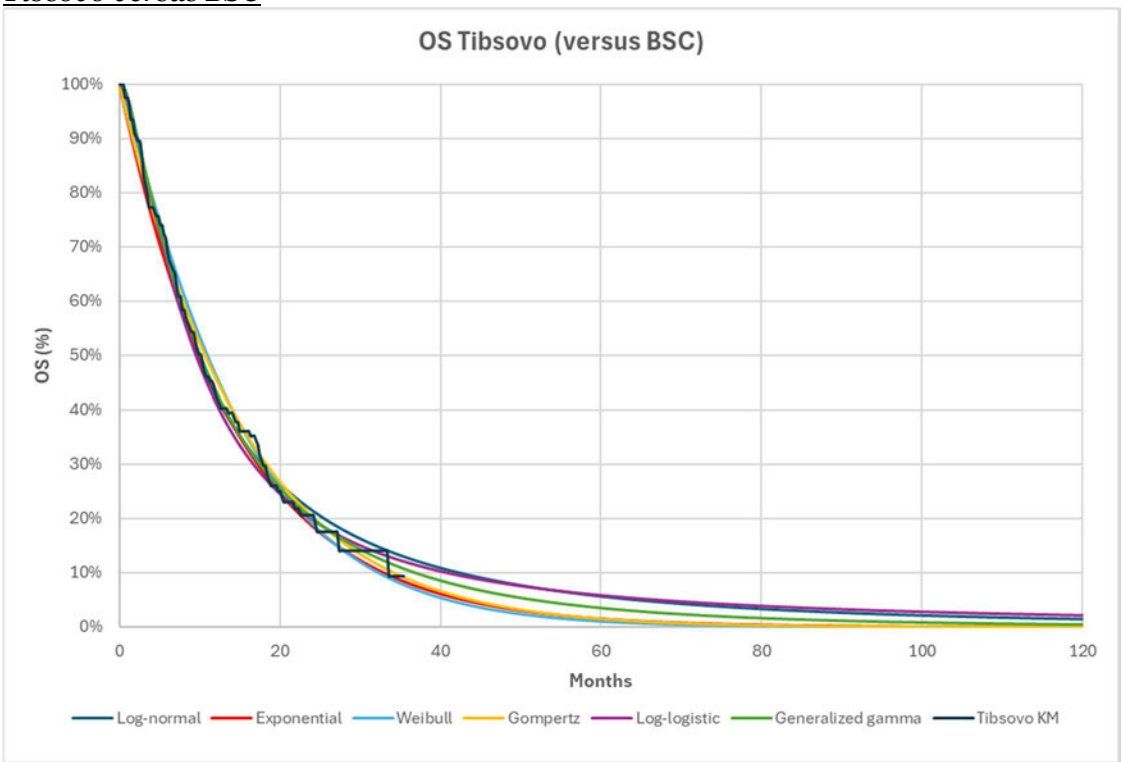


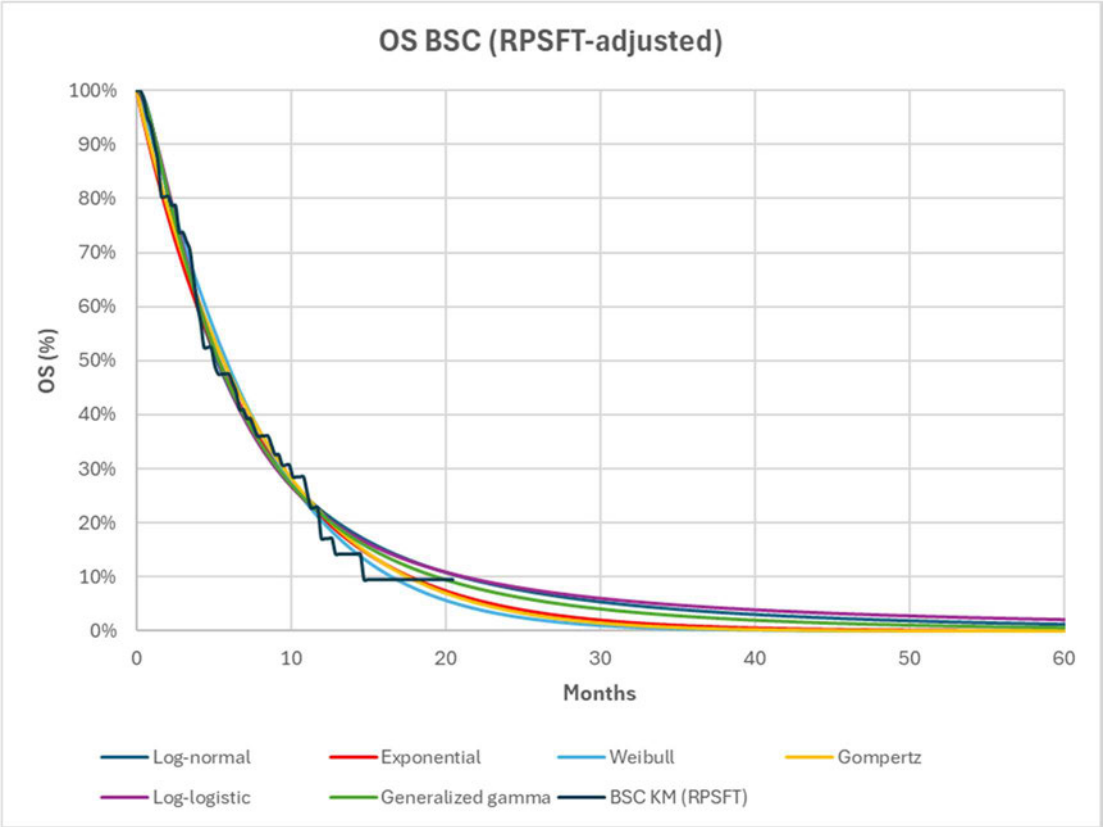
Abbreviations: ASC, Active symptom control; FOLFOX, Folinic acid, fluorouracil, and oxaliplatin; KM, Kaplan-Meier; PFS, Progression-free survival.

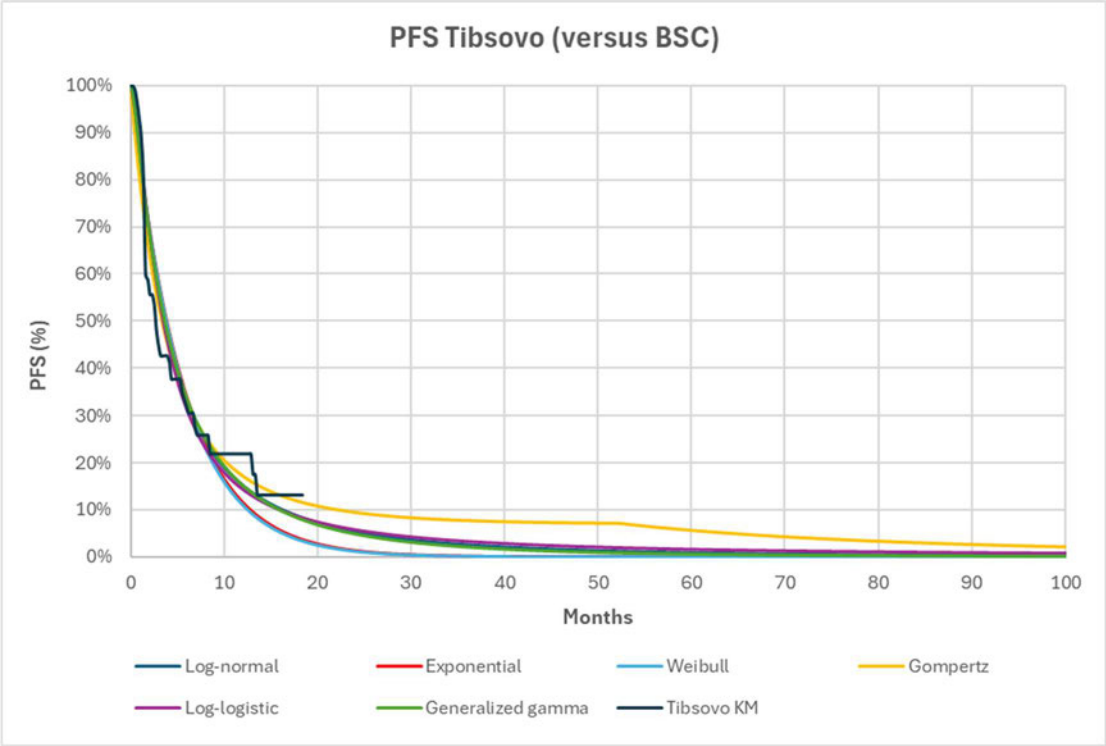
Figure 17 MAIC-adjusted vs unadjusted KM Curve for PFS: based on ClarIDHy and ABC-06

Appendix 3 – parametric fits, AIC/BIC and log-cumulative hazard plots

Tibsovo versus BSC




OS BSC (RPSFT-adjusted)
OS (%)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
10
20
30
40
50
60
Months
Log-normal
Exponential
Weibull
Gompertz
Log-logistic
Generalized gamma
BSC KM (RPSFT)


PFS Tibsovo (versus BSC)
PFS (%)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
10
20
30
40
50
60
70
80
90
100
Months
Log-normal
Exponential
Weibull
Gompertz
Log-logistic
Generalized gamma
Tibsovo KM

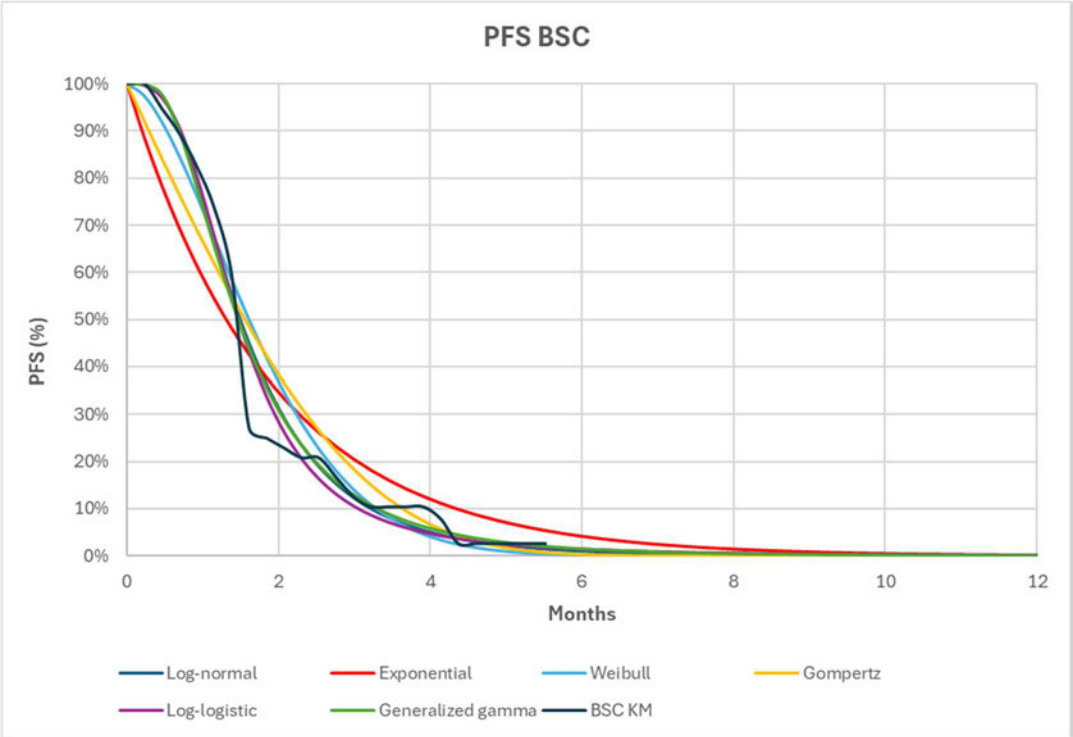


Table 4. AIC and BIC statistics for OS parametric fits (overall population)

Parametric	AIC			BIC		
	Tibsovo®	BSC	BSC (RPSFT)	Tibsovo®	BSC	BSC (RPSFT)
Exponential	745.10	351.10	303.00	747.90	353.20	305.10
Weibull	745.70	357.20	303.60	751.30	357.20	307.90
Log-logistic	743.60	356.20	302.30	749.20	356.20	306.50
Gompertz	747.00	352.50	304.80	752.70	352.50	304.80
Log-normal	**743.20**	**355.00**	**301.50**	**748.80**	**355.00**	**305.70**
Generalised gamma	744.10	359.00	303.30	752.60	359.00	309.70

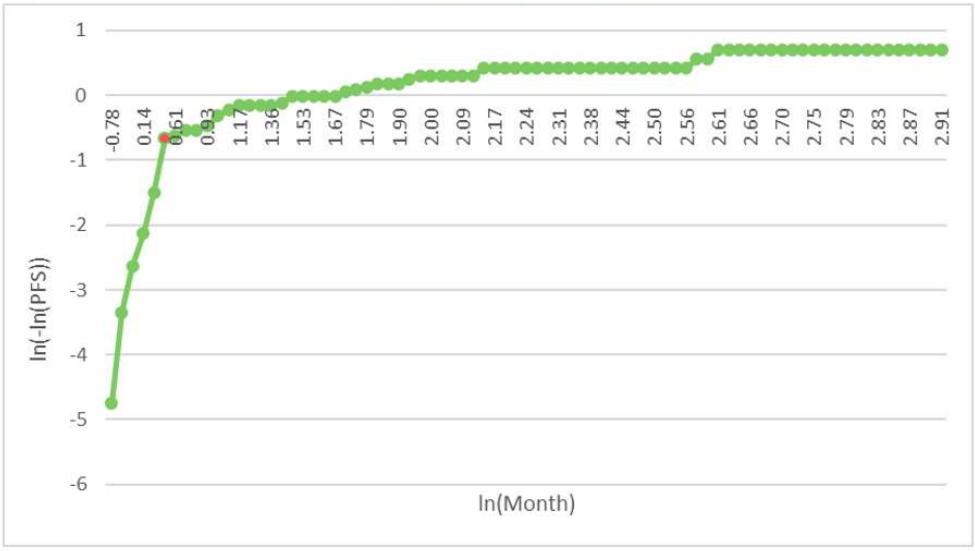
Abbreviations: AIC, Akaike information criterion, BIC, Bayesian information criterion; BSC, best supportive care; OS, overall survival, RPSFT, rank-preserved structural failure time

Table 5. AIC and BIC statistics for PFS parametric fits (overall population)

Parametric	AIC		BIC	
	Tibsovo®	BSC	Tibsovo®	BSC
Exponential	412.60	165.50	415.40	167.70
Weibull	414.60	148.10	420.20	152.40
Log-logistic	395.20	135.80	400.90	140.00
Gompertz	408.80	160.70	414.50	164.90
Log-normal	**391.40**	**135.50**	**397.00**	**141.70**
Generalised gamma	379.80	139.30	388.20	145.60

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

Figure 10. Cumulative log-hazard plot for Tibsovo® PFS in ClarIDHy

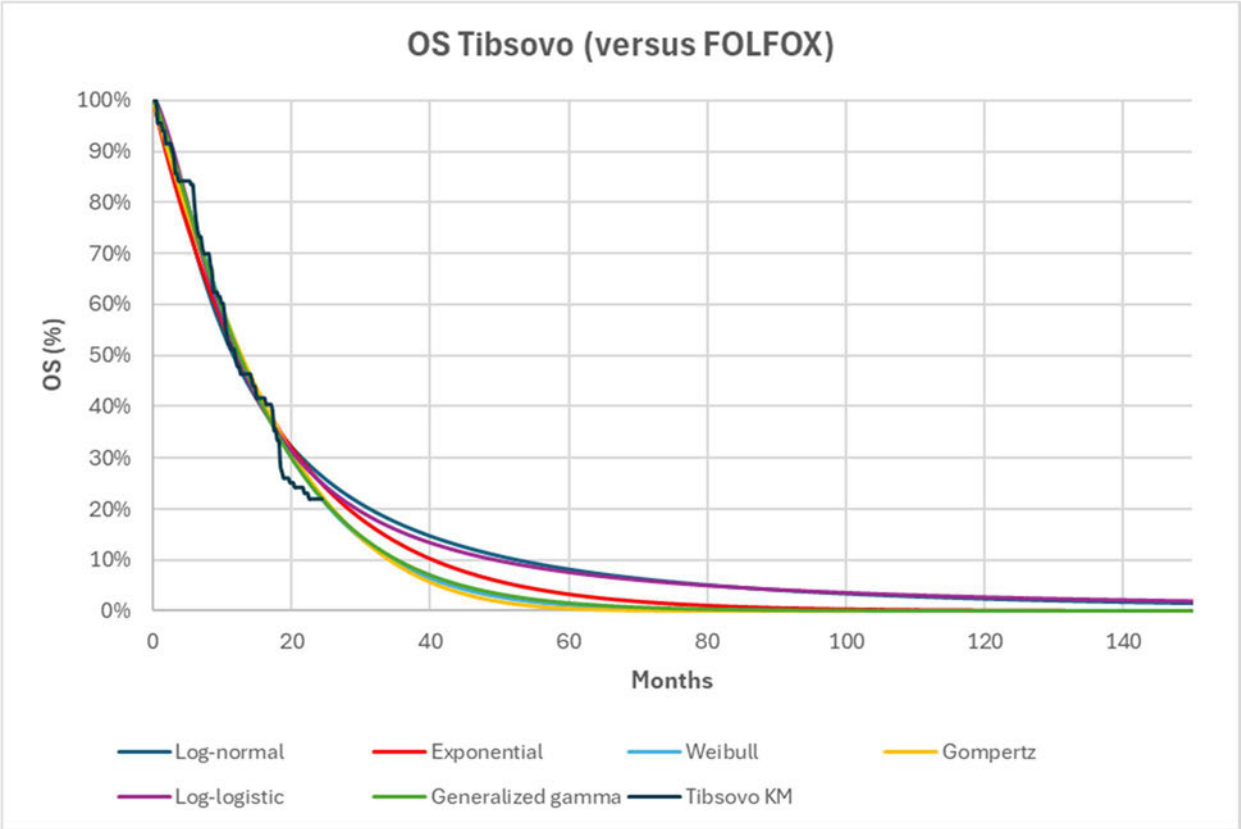


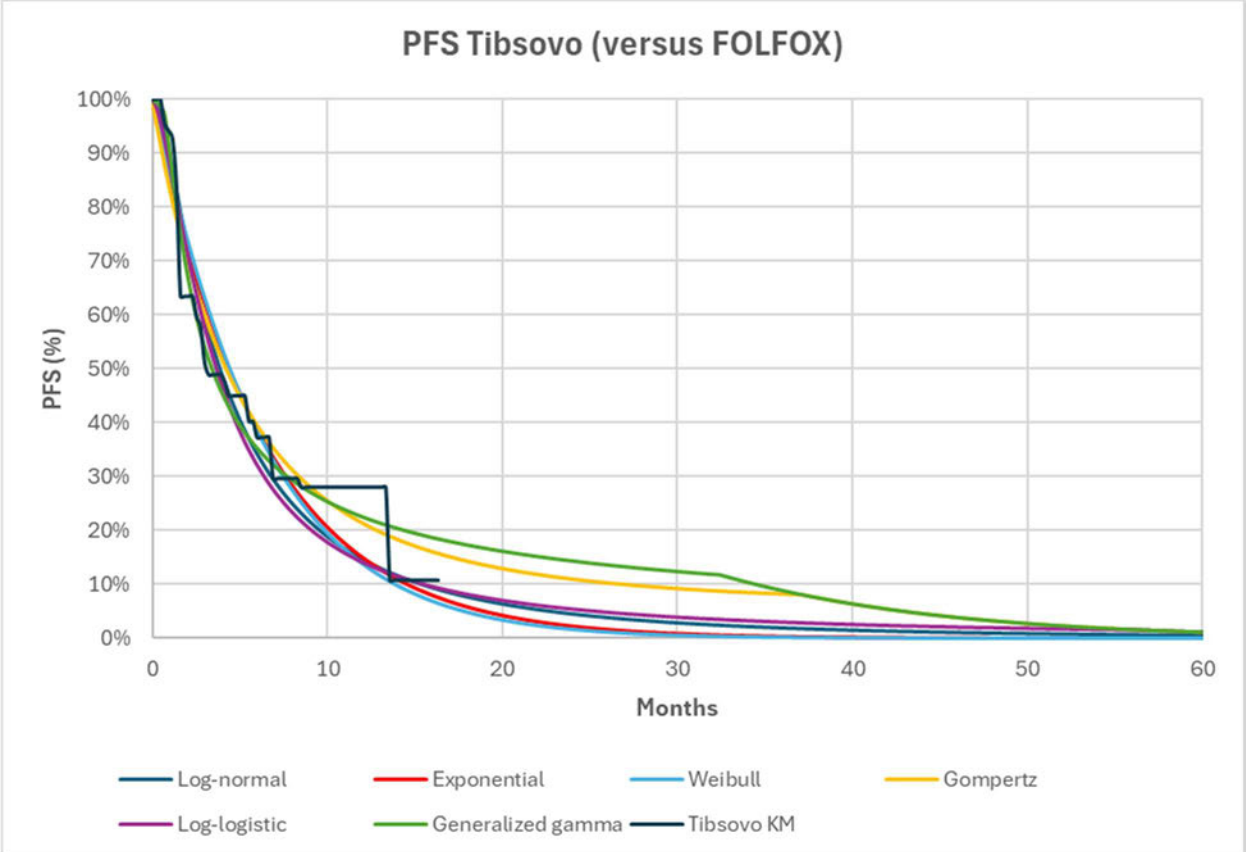
Abbreviations: PFS, progression-free survival

Figure 11. Cumulative log-hazard plot for BSC PFS in ClarIDHy

Abbreviations: BSC, best supportive care; PFS, progression-free survival

Tibsovo versus FOLFOX


OS Tibsovo (versus FOLFOX)
OS (%)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
20
40
60
80
100
120
140
Months
Log-normal
Exponential
Weibull
Gompertz
Log-logistic
Generalized gamma
Tibsovo KM


PFS Tibsovo (versus FOLFOX)
PFS (%)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
10
20
30
40
50
60
Months
Log-normal
Exponential
Weibull
Gompertz
Log-logistic
Generalized gamma
Tibsovo KM

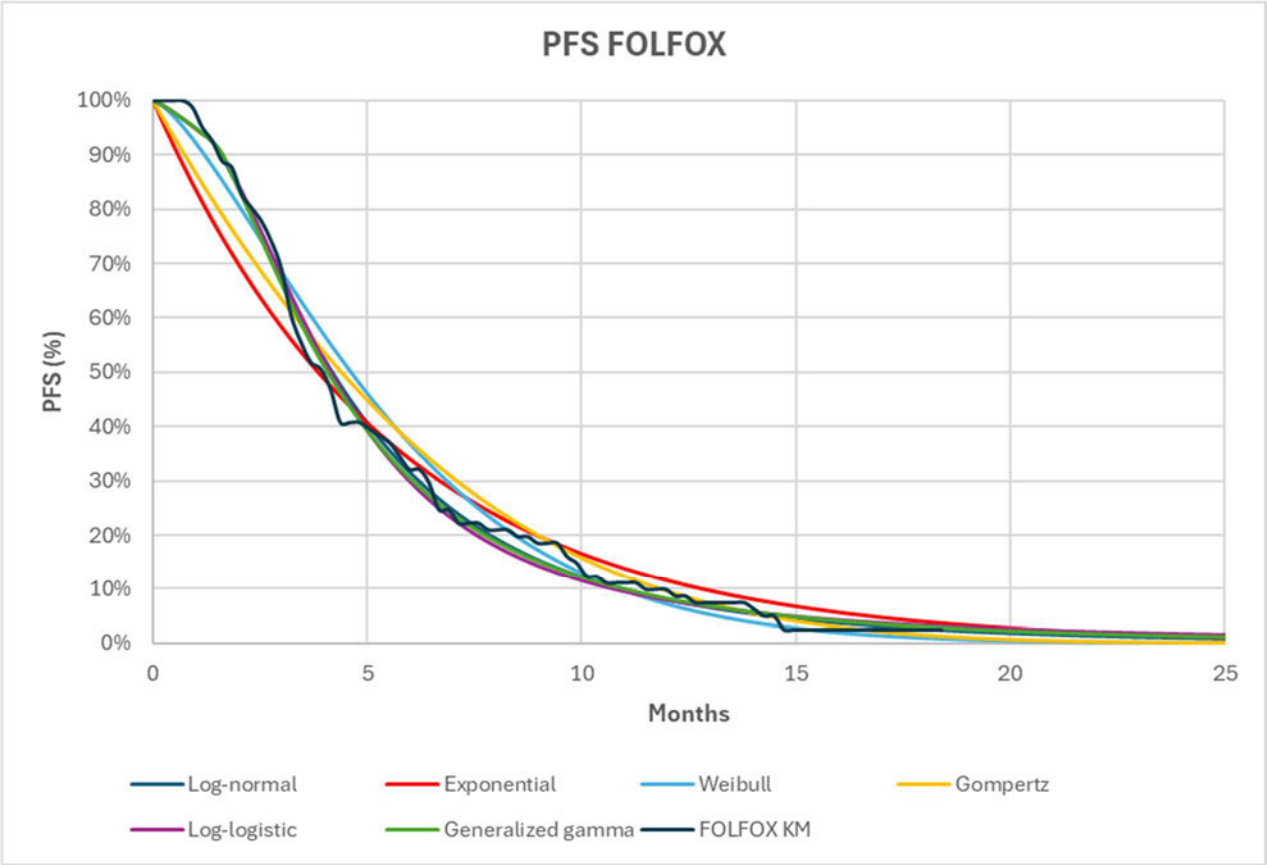


Table 30. AIC and BIC statistics for OS parametric fits (overall population)

Parametric	AIC		BIC	
	Tibsovo®	FOLFOX	Tibsovo®	FOLFOX
Exponential	318.24	483.88	320.41	486.28
Weibull	**318.50**	**479.09**	**322.85**	**483.88**
Log-logistic	319.23	475.65	323.57	480.44
Gompertz	319.47	484.05	323.82	488.84
Log-normal	321.77	473.29	326.12	478.08
Generalised gamma	320.44	475.20	326.96	482.38

Abbreviations: AIC, Akaike information criterion, BIC, Bayesian information criterion, OS, overall survival.

Table 10. AIC and BIC statistics for PFS parametric fits (overall population)

Parametric	AIC		BIC	
	Tibsovo®	FOLFOX	Tibsovo®	FOLFOX
Exponential	168.00	430.41	170.18	432.81
Weibull	169.87	419.15	174.22	423.94
Log-logistic	163.73	409.00	168.08	413.79
Gompertz	168.83	428.71	173.18	433.50
Log-normal	161.48	406.93	165.83	411.72
Generalised gamma	157.25	408.59	163.77	415.78

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

To JNHB: Comments from Servier of the preliminary report, CCA dnr 885/2024

Regarding confidential information placed on the Nordic websites by JNHB:
Our wish is that the yellow marked sections/figures in the preliminary report will be seen as confidential information, only relevant for the different authorities working groups and in line with our waiver of confidentiality.

Major:

- Page 17: We suggest a rephrasing of the sentence "Overall, the diagnostic test show an inconsistent picture. The lack of hazard proportionality *reduces the validity* of the application of a constant treatment effect..." to: "Overall, the diagnostic tests show an inconsistent picture; the uncertainty around the hazard proportionality *could question the validity* of the application of a constant treatment effect..."
- Page 23: We suggest that it should be mentioned that despite the clinical rationale to have the same 4-years estimate of survival rate, the log-normal distribution has the lowest AIC for both Tibsovo and BSC (see table 4 of the technical report). Therefore, we further suggest that a scenario using log-normal distributions should be presented.

Minor corrections/typos:

- Page 16: the HR for FOLFOX vs ASC should be 0.69 rather than 0.63 (see table 5 of the Q & A document submitted on June 12
- Table 5: We suggest rewording the title to "1-5-year *Tibsovo* survival rates" for clarity
- Page 20, section 4.2: There is an incorrect cross-reference to section 0.

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

19.12.2024
CAF/MBA

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.01.2025
Leverandør	Servier Sverige AB
Lægemiddel	Tibsovo (ivosidenib)
Ansøgt indikation	Behandling af cholangiocarcinom (CCA) med IDH1 (R132) mutation efter mindst én tidligere systemisk behandling
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel vurderet som en del af fælles nordisk proces i JNHB. To indikationer for Tibsovo behandles på samme Medicinrådsmøde.

Prisinformation

To indikationer cholangiocarcinom (CCA) og akut myeloid leukæmi (AML) for Tibsovo behandles på samme møde i Medicinrådet. Leverandøren har derfor givet tilsagn om forskellige tilbudspriser afhængigt af hvilke indikationer, som anbefales af Medicinrådet.

- Scenarie A: Hvis både CCA og AML anbefales af Medicinrådet eller udelukkende AML anbefales af Medicinrådet
- Scenarie B: Udelukkende CCA anbefales af Medicinrådet
- Scenarie C: Ingen af de to indikationer anbefales af Medicinrådet

Amgros har forhandlet følgende pris på Tibsovo (ivosidenib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Scenarie A - SAIP (DKK) (rabat ift. AIP)	Scenarie B - SAIP (DKK) (rabat ift. AIP)	Scenarie C - SAIP (DKK) (rabat ift. AIP)
Tibsovo	250 mg (60 stk.)	113.400	[redacted]	[redacted]	[redacted]

Prisenerne i scenarie A og B er betinget af Medicinrådets anbefaling, mens prisen i scenarie C ikke er betinget af Medicinrådets anbefaling.

Aftaleforhold

[redacted]

Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Konkurrencesituationen

Tabel 2 og tabel 3 viser lægemiddeludgiften per år per patient for henholdsvis scenarie A og scenarie B.

*Tabel 2: Lægemiddeludgift pr. patient – scenarie A**

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Scenarie A - Pris pr. pakning (SAIP, DKK)	Scenarie A - Lægemiddeludgift pr. år** (SAIP, DKK)
Tibsovo	250 mg (60 stk.)	500 mg 1 gang dagligt, oral	[redacted]	[redacted]

* Jævnfør Medicinrådets vurderingsrapport, er komparator enten *Best Supportive Care* (BSC) eller 5-Fluorouracil (5-FU) og oxaliplatin (FOLFOX). Udgiften for begge mulige komparatorer er minimal og er derfor ikke angivet i denne tabel.
** Median behandlingslængde var i ClarIDHy-studiet for Tibsovo (ivosidenib) på 2,8 måneder (min: 0,1 måned, max: 34,4 måneder).

*Tabel 3: Lægemiddeludgift pr. patient – scenarie B**

Læge-middel	Styrke (paknings-størrelse)	Dosering	Scenarie B - Pris pr. pakning (SAIP, DKK)	Scenarie B - Lægemiddeludgift pr. år** (SAIP, DKK)
Tibsovo	250 mg (60 stk.)	500 mg 1 gang dagligt, oral	[redacted]	[redacted]

* Jævnfør Medicinrådets vurderingsrapport, er komparator enten *Best Supportive Care* (BSC) eller 5-Fluorouracil (5-FU) og oxaliplatin (FOLFOX). Udgiften for begge mulige komparatorer er minimal og er derfor ikke angivet i denne tabel.
** Median behandlingslængde var i ClarIDHy-studiet for Tibsovo (ivosidenib) på 2,8 måneder (min: 0,1 måned, max: 34,4 måneder).

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering	En del af den fælles nordiske JNHB-proces. Afventer beslutning.	
England	Anbefalet		Link til anbefaling
Sverige	Under vurdering	En del af den fælles nordiske JNHB-proces. Afventer beslutning.	

Opsummering

[redacted]

QUANTIFY

QUANTIFY

Tibsovo®(ivosidenib) for the treatment of cholangiocarcinoma (CCA) patients with an isocitrate dehydrogenase 1 (IDH1) R132 mutation, previously treated by at least one prior line of systemic therapy

Medical dossier – Sweden (TLV)/FINOSE

Final version 1.0

Prepared for:

Jan Wahlberg

Servier

Date submitted:

2024-03-22

Authors:

Hannah Norman
Senior Project Leader
hannah.norman@quantifyresearch.com
+46 (0) 769 34 91 70

Marija Vasilevska
Senior Research Analyst
marija.vasilevska@quantifyresearch.com
+46 (0) 763 40 48 15

Zoltán Németh
Senior Research Analyst
zoltan.nemeth@quantifyresearch.com
+46 (0) 702 20 87 47

Quantify Research AB
Hantverkargatan 8
112 21 Stockholm
Sweden

info@quantifyresearch.com
+46 (0)70 736 5569

About Quantify

Quantify is an experienced partner in health economics, outcomes research, real-world evidence, and market access. Our goal is to continuously deliver high quality services, combining our scientific and quantitative skills with a solution-oriented mindset and business focus.

We have our roots in academia with a broad technical competence in value strategy, modeling, evidence generation, biostatistics, study design and analysis.

Through extensive experience within both the governmental and private sectors, we have acquired a dynamic and efficient work model, putting emphasis on communication and finding tailored solutions to fit our clients' needs.

QUANTIFY

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Tables and figures

List of tables

List of figures

List of abbreviations

Abbreviation	Definition
1L	First line
2-HG	2-hydroxyglutarate
2L	Second line
5-FU	5-fluorouracil
AE	Adverse events
AIC	Akaike information criterion
AML	Acute Myeloid Leukemia
AZA	Azacitadine
ASC	Active symptom control
BIC	Bayesian information criterion
BID	Twice a day
BSC	Best supportive care
BTC	Biliary tract carcinoma
CapOx	Oxaliplatin and capecitabine
CCA	Cholangiocarcinoma
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COS	Crossover Set
CR	Complete response
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
dCCA	Distal cholangiocarcinoma
DOR	Duration of response
DSU	Decision Support Unit
eCCA	Extrahepatic cholangiocarcinoma
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
ED	Emergency department
EEA	European Economic Area
EMA	European medicines agency
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ	European Organization for the Research and Treatment of Cancer core Quality of Life Questionnaire
EOT	End of treatment
EQ-5D-5L	EuroQol 5-dimensions 5-levels
ERCP	Endoscopic retrograde cholangiopancreatography
ESMO	European Society of Medical Oncology
ESS	Effective sample size
EU	European Union
FAS	Full analysis set
FOLFOX	Folinic acid, fluorouracil and oxaliplatin

Abbreviation	Definition
GBC	Gallbladder cancer
GC	Gemcitabine and cisplatin
GEM	Gemcitabine
GI	Gastrointestinal
GLM	Generalized linear models
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HCRU	Healthcare resource utilisation
HSC	Hematopoietic stem cell
iCCA	Intrahepatic cholangiocarcinoma
ICER	Incremental cost-effectiveness ratio
IDH	Isocitrate dehydrogenase
IDH1m	Isocitrate dehydrogenase 1 mutation
IPCW	Inverse-probability-of-censoring weighting
IPD	Individual patient data
IRC	Independent radiology center
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intra-venous
IVO	Ivosidenib
KM	Kaplan-Meier
KPS	Karnofsky performance status
LOT	Line of therapy
LS	Least squares
LVEF	Left ventricular ejection fraction
MAIC	Matching-adjusted indirect comparison
MMR	DNA mismatch repair
MSI	Micro-satellite instability
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not estimable
NGS	Next-generation sequencing
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ORR	Objective response rate
OS	Overall survival
PBO	Placebo
pCCA	Perihilar cholangiocarcinoma
PDT	Photodynamic therapy
PFS	Progression free survival
PGI-C	Patient Global Impressions of Change
PHQ-9	Patient Health Questionnaire 9
PK	Pharmacokinetics

Abbreviation	Definition
PPS	Per protocol set
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
QD	Once daily
QoL	Quality of life
QTc	Corrected QT interval
RANO	Response assessment in neuro-oncology criteria
RCT	Randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RPSFT	Rank preserving structural failure time
SAE	Serious adverse event
SAS	Safety analysis set
SD	Stable disease
SIC	Standard induction chemotherapy
SLR	Systematic literature review
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
US	United States
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment

1 Regulatory status and general information

1.1 Approved indications and pricing

On 4 May 2023, Tibsovo®(ivosidenib) received a marketing authorization by the European Medicines Agency's (EMA) valid throughout the European Union (EU) for the following indications (1):

1. As monotherapy, for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma (CCA) with an isocitrate dehydrogenase 1 (IDH1) R132 mutation who were previously treated by at least one prior line of systemic therapy
2. In combination with azacitidine (AZA), for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) with an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy (SIC)

This dossier aims to facilitate the FINOSE Joint Assessment, only discussing the CCA indication. A separate dossier for the AML indication is submitted in parallel to FINOSE. Simultaneously, dossiers adjusted to the national requirements are submitted to the corresponding national authorities for pricing and reimbursement negotiation. The requested reimbursement for Tibsovo® (film-coated tablets) in CCA is identical to the indication approved by EMA.

Tibsovo® is packaged in a bottle of 60 film-coated tablets containing 250mg each. The intended price for Tibsovo® in the FINOSE countries is presented in Table 1.

Table 1: Applied wholesale/pharmacy purchase prices of Tibsovo® in each country

Product	Vnr number	Package	Finland	Sweden	Norway	Denmark
Tibsovo	135124	60 tablets of 250 mg	[redacted]	[redacted]	[redacted]	[redacted]

1.2 General administrative information

Approval of marketing authorisation, approval of Nordic article number (135124) and the summary of product characteristics (SmPC) are appended to this submission. Additionally, a summary of the clinical assessment report is provided in Section 4.3.

2 Disease description

2.1 Aetiology /pathophysiology

Gastrointestinal (GI) cancers refers to malignant conditions of the GI tract and accessory organs of digestion, including the esophagus, stomach, biliary system, pancreas, small intestine, large intestine, rectum and anus (2). Among the GI cancers, biliary tract carcinomas (BTCs) are very infrequent (3). BTCs are malignancies that arise from the epithelium of the biliary system and include the following malignancies: CCA, gall bladder cancer (GBC), and ampulla of vater cancer (4) (Figure 1).

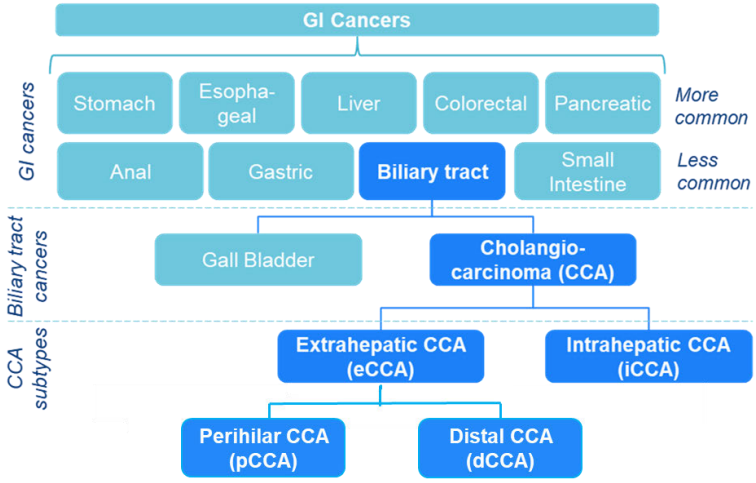


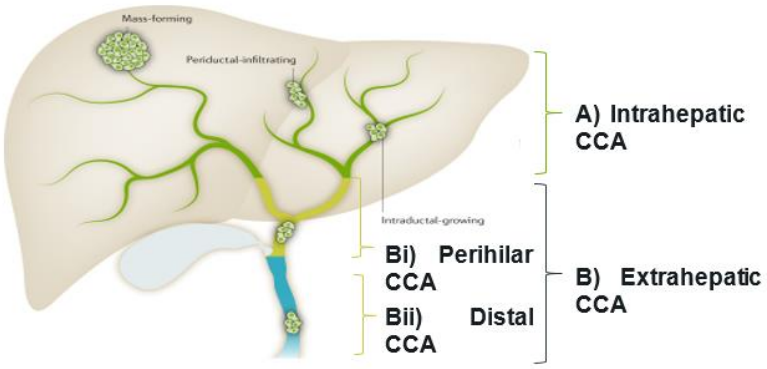
Figure 1. Overview of GI maligancies

Source: Adapted from Banales et al. 2020 (3).
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 (Figure 2) (6). The main types of CCA include (7, 8):

- **Intrahepatic CCA (iCCA) tumors:** originating from the biliary tree within the liver.
- **Extrahepatic CCA (eCCA) tumors:** originating outside the liver parenchyma and further subdivided based on their site of origin.
    - **Perihilar (pCCA):** also called Klatskin tumors 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.

Figure 2. CCA subtypes



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

2.1.1 IDH1 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 (9). These genetic alterations indicate the need for anti-cancer targeted biologic therapies in the treatment of CCA.

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 tumor-suppressor genes (10). IDH proteins play a role in several types of tumors, and exist as three isoforms: IDH1, IDH2, and IDH3 (11). IDH1 mutations are rare, occurring in 18% of iCCA patients and 1% of eCCA patients (12). 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 (13). IDH1 is found in the cytoplasm and peroxisomes (14, 15) and the gene encoding IDH1 is located on chromosome 2q33.3 (16). IDH proteins catalyze the oxidative decarboxylation of isocitrate to produce carbon dioxide and alpha-ketoglutarate (α-KG) (11).

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 (17-19). 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 (20-22). Thus, the cancer-associated IDH mutations block normal cellular differentiation and promote tumorigenesis via the abnormal overproduction of 2-HG (11). Inhibition of mutant IDH1 is expected to reduce 2-HG levels and restore cellular differentiation, thereby act as relevant therapeutic targets in CCA (23-25).

2.2 Clinical presentation

The clinical presentation depends upon tumor stage, location and growth pattern (26). Patients with iCCA often experience non-specific, gradual symptoms such as fever, weight loss, abdominal pain, nausea, and hypoxia (27, 28). Patients with eCCA often experience biliary obstruction, leading to dramatic, sudden symptoms such as; painless jaundice, weight loss, abdominal pain, fever and pruritus (29). The symptoms and clinical signs associated with CCA requires an invasive diagnostic work-up to identify the subtype of the disease (9). CCA often presents signs or symptoms in the later course of disease (29), leading to diagnosis at later stages, when the prognosis is poor (5, 26).

2.3 Disease diagnosing and testing

No specific screening methods are available to reliably detect CCA early enough, and most CCA cases are found only after the cancer has advanced to an incurable stage (30). Most patients (~70%) are diagnosed at late stages of disease progression due to lack of specific symptoms (5). In a European study with 2,234 CCA patients, nearly 60% had either locally advanced or metastatic disease at diagnosis (31), which further confirms delay in disease diagnosis. Additionally, CCA is frequently misdiagnosed as cancer of unknown primary origin (8, 32, 33) 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 (9).

Histologically advanced CCA often resembles metastatic disease to the liver which makes it challenging to diagnose (2, 34). 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 (28). For accurate diagnosis, it is important to distinguish between the tumor subtypes (iCCA, pCCA, dCCA or GBC) (30).

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. The ESMO Precision Medicine Working Group recommends routine Next Generation Sequencing (NGS) in all CCA patients with advanced disease suitable for systemic treatment. Furthermore, ESMO guidelines for BTC recommend NGS over single gene testing (35). While countries included in FINOSE's joint assessment adhere to ESMO guidelines, only Danish and Norwegian national guidelines or action programs explicitly address or recommend NGS testing (35-38). In Denmark, NGS testing is recommended for patients diagnosed with iCCA and exhibiting good general health (Performance Status [PS] 0-1). This testing is crucial and should be completed at the initiation of chemotherapy to ensure timely availability of results before initiating subsequent lines of treatment (LOTs) (37). The guidelines in Norway currently do not recommend any molecular analyses due to the limited availability of targeted treatments. However, the guidelines states that for patients with inoperable disease, molecular analyses can be performed to uncover biomarkers relevant to treatment selection, even though available treatments might not

be publicly funded. Similarly to the ESMO guidelines, the Norwegian guidelines recommend gene panels (i.e. NGS) over single-gene analyses (38).

2.4 Epidemiology of CCA

As noted in section 2.3, 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 (32). Challenges in the diagnosis and classification of CCA have historically made it difficult to quantify the true incidence (8, 32, 39).

Globally, the incidence of CCA ranged from 0.35 to 8.75 per 100,000 persons (5). In the European Orphanet, the incidence varies between 0.5 and 3.4 per 100,000 people (40). Notably, within the FINOSE countries, the incidence remains consistent, except in Sweden, where it is slightly elevated at approximately 4.4 per 100,000 people (41). iCCA has been found to account for 30% to 42% of all newly diagnosed CCA cases (42-44), whereas IDH1 mutations are estimated to occur in approximately 18% of iCCA patients (24). Notably, the incidence of iCCA in high income countries is rising and at a faster rate compared to eCCA (45, 46).

The incidence of CCA increases with age, thus, it is most frequent in the age group between 50 and 70 years (12, 37). According to the available data, the median age at diagnosis in the Scandinavian countries is slightly above 70 years (38, 42).

The CCA mortality represents ~2% of all cancer-related deaths worldwide annually (3). CCA patients experience aggravating symptoms and half of all untreated patients fail to survive past three to four months from presentation of symptoms (47). Data from the Finnish Cancer Registry indicates that the median time from diagnosis to death is 2.3 months among Finnish patients with CCA (42).

The prognosis of CCA is dismal owing to its silent clinical character, difficulties in early diagnosis and limited therapeutic approaches (24). Advanced stage diagnosis results in 30% of CCA patients being eligible for tumor resection (48) and poor survival outcomes among patients with CCA have been reported across multiple analyses covering various patient subgroups and clinical settings (49). The prognostic factors and the therapeutic approaches to CCA differ depending upon their location along the biliary tree (28).

Data on the prognostic significance of IDH1 mutations on clinical outcomes in patients with CCA are limited and most published studies have indicated no prognostic significance (13). A systematic literature review (SLR) published in 2019 analyzed eight relevant studies and found no statistically significant association between mutant isocitrate dehydrogenase 1 (mIDH1) and clinical outcomes for patients with iCCA (13).

The estimated number of newly diagnosed patients with mIDH1 iCCA per year in the FINOSE countries is presented in Table 2. It should however be noted that considering the second line indication of Tibsovo®, not all patients will be eligible for treatment with Tibsovo®.

Table 2. Estimated number of incident cases per year and country

	Denmark	Finland	Norway	Sweden
CCA incident cases per year	235	160	190	449
iCCA incident cases per year	108	59	57	190
IDH1m incident cases per year	19	11	10	34

Note: Estimated number of patients presented in this table were sourced from the national cancer registries or approximated using available data on incidence of histological types and mutations, as well as other information on share of patients per line of treatment (24, 37, 42, 43, 50-54).

Abbreviations: CCA, cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; IDH1m, isocitrate dehydrogenase 1 mutation.

2.5 Burden of disease of CCA

Due to delayed diagnosis and poor prognosis of CCA, a significant clinical, humanistic and economic burden is imposed on patients. The burden of CCA symptoms on daily lives, work productivity, QoL, mental health, and sexual function is immense (55). Early detection will not only benefit the patients in receiving broader treatment methods, but will aim to lessen the burden on the public health system (56). There is a lack of evidence pertaining to the burden of disease on caregivers and the wider society.

For the majority of patients with advanced or metastatic CCA there are limited treatment options beyond intravenously infused chemotherapy, which typically provides only modest survival benefits and substantial toxicity, contributing to the burden of illness in this patient population (57).

No studies on the burden of CCA in the FINOSE countries were identified. Thus, studies conducted in other geographical areas will be presented in this section.

2.5.1 Clinical burden

CCA poses a significant clinical burden, mostly due to associated signs and symptoms at an advanced stage of the disease, morbidity, and hospitalizations (57-60). Post-procedural infection of the bile duct system was the most common complication in CCA in patients following interventions such as endoscopic retrograde cholangiopancreatography (ERCP) and photodynamic therapy (PDT) (61, 62). The most frequent admissions for medical procedures entailed diagnostic imaging, with computerized axial tomography (45.7%), ultrasound (42.25%) and magnetic resonance imaging (15.3%) being the most common (58).

Based on a retrospective study of advanced CCA patients failing first-line therapy (GEM or 5-fluorouracil [5-FU] based regimen) from a US commercial and Medicare Advantage insurance claims database (n=1,298), the study indicated that the most common comorbidities of advanced CCA were hypertension (70.3%), liver disease (60.7%) and coronary heart disease (24.9%) (57). The study also highlighted that the existing

treatment option, chemotherapy, casuses substantial toxicity, contributing to the burden of illness in this patient population whilst only providing modest survival benefits %) (57).

However, robust evidence for clinical burden is required in patients with advanced, unresectable or metastatic CCA. Furthermore, there is a dearth of evidence on misdiagnosis, societal costs, sleep quality and productivity impact on CCA patients.

2.5.2 Humanistic burden

Maintaining HRQoL is one of the most important goals of treatment for patients with CCA. This is because the aggressive nature of the disease and the limited availability of effective treatment options mean that patients with CCA experience higher burden from disease-related symptoms and a rapid decline in health-related quality of life (HRQoL) (27, 63). A survey of patients with GI cancers (pancreatic cancer (n=656) or CCA (n=355) reported that 84% of patients felt that QoL was more important than longevity (57).

A survey conducted in the US included the EORTC QoL questionnaire CCA and GBC module (EORTC QLQ-BIL21), Patient Health Questionnaire 9 (PHQ-9), and Work Productivity and Activity Impairment (WPAI) instruments concluded negative impacts of illness on daily lives, work productivity, HRQoL and mental health due to the burden of CCA symptoms (55). Across all domains of the EORTC QLQ-BIL21 instrument, patients reported a substantial negative impact on QoL. Patients aged 18–44 years reported worse QoL scores across all domains with the exception of weight loss. The worst impacts were felt in the domains of anxiety (mean score = 52.9), tiredness (52.3) and treatment-related side effects (51.3). On the PHQ-9, nearly half of the patients (47%) reported symptoms that were consistent with severe depression. Depression was prevalent in all stages of disease (55).

Longitudinal data on HRQoL among patients with CCA are limited. The HRQoL values for patients with unresectable, advanced or metastatic CCA are not available in the published literature.

In summary, CCA is associated with substantial decline in HRQoL and highlights the need for effective and tolerable treatments that can maintain or improve HRQoL in patients with CCA (57).

2.5.3 Economic burden

Economic burden data in CCA is limited, but the available evidence suggest that management of CCA is associated with high health care resource use (HCRU) and costs, particularly from medical services and hospital admission charges (64).

A retrospective database study conducted based on the records of admissions due to iCCA in 23,315 patients in Spain between 2000 and 2018, indicates that the mean cost per admission in patients with metastatic iCCA was €6,061, corresponding to €8,444 per patient. The main hospital admission cost driver was costs from diagnostic procedures. A further 11% of total admissions related to chemotherapy injections or infusions (58).

3 Disease management and national guidelines for CCA

CCA is a rare and aggressive disease, and a majority of patients present with either locally advanced or metastatic disease at diagnosis (31, 42). Therefore, awareness surrounding diagnosis and earlier diagnosis are required. For these patients, treatment options are very limited, particularly in 2nd line (2L) treatment. Some patients with CCA are treated with best supportive care (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 are often older and more unwell) (65). Half of all untreated patients fail to survive past three to four months from presentation of symptoms (47), thus the goal of treatments is to increase overall survival (OS) and progression-free survival (PFS) (13).

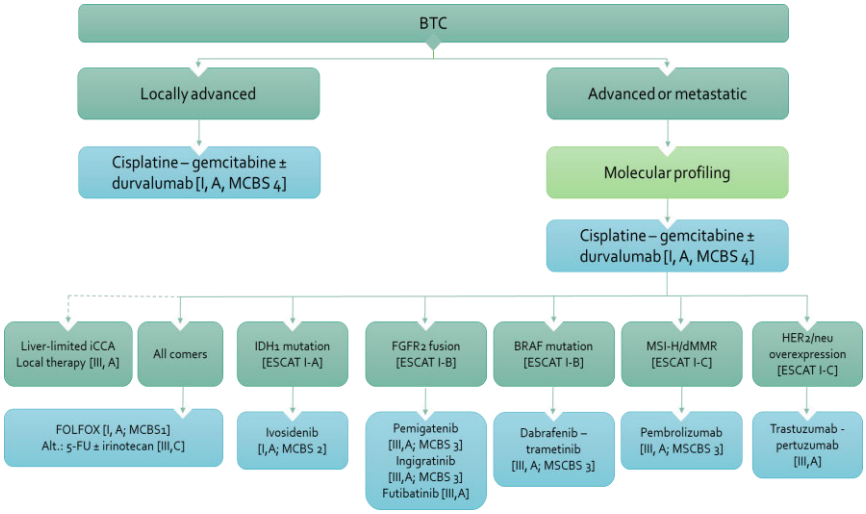
Currently, there is no cure for unresectable locally advanced or metastatic CCA, and due to a lack of symptoms, 70% of patients are diagnosed at late stages (3). At these late stages, when the disease is unresectable, the only option is palliative treatment (3). Therefore, controlling symptoms and improving patients' quality of life (QoL) are also treatment goals in unresectable CCA (66).

The European Society for Medical Oncology (ESMO), dedicated to enhancing the quality and accessibility of uniform cancer care, issues comprehensive guidelines for diagnosis, treatment, and follow-up, which often serve as a foundation for national treatment recommendations and clinical practice. In recent years, ESMO has shifted its focus towards targeted therapies, particularly in CCA patients with relevant mutations and these treatments are now recommended in both primary and subsequent LOTs. ESMO's proposed algorithm for the treatment of BTC is shown in Figure 3. Additionally, an ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) score has been provided for each of the recommended treatments. The ESMO-MCBS is intended to both assist oncologists in explaining the likely benefits of a particular treatment to their patient as well as to aid public health decision makers to prioritize therapies for reimbursement. It is currently incorporated in the ESMO Clinical Practice Guidelines and is being used as part of Health Technology Assessment (HTA) processes in many countries.

The 2023 ESMO guidelines are now recommending molecular testing before first line (1L) therapy especially for patients with CCA, particularly iCCA displaying small duct histology, being enriched for actionable targets. According to detected mutation a number of options are now available. For IDH1m CCA, Tibsovo® (ESMO-MCBS score 3 [updated in 2023]) is the only option available and recommended. As for all other patients with advanced or metastatic CCA without specific mutations, FOLFOX (ESMO-MCBS score 1) or 5-FU ± irinotecan is recommended as SoC in 2L setting.

Hence, the paradigm shift towards more personalized medicines, which was reflected in a more recent version of the NCCN guidelines in the US, has now been incorporated in the ESMO guidelines (67). However, the ESMO guidelines may be perceived as placing targeted therapies such as Tibsovo® next to non-targeted therapies such as FOLFOX, and therefore remains sub-optimal for patients with targetable mutations. Furthermore, although the minimal clinical benefit score (MCBS) was updated in early 2023 from 2 to 3 (denoting a higher magnitude of benefit) (68), the online and printed versions still reflect the lower MCBS of 2, rather than the newer MCBS of 3.

Figure 3. ESMO recommended treatment algorithm for advanced or metastatic BTC



Source: Vogel 2022 (67)

Note: Ivosidenib (Tibsovo®) MCBS score has been updated from 2 to 3 in 2023

Abbreviations: 5-FU, 5-fluorouracil; BTC, biliary tract cancer; dMMR, mismatch repair deficiency; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FGFR2, fibroblast growth factor receptor 2; FOLFOX, 5-fluorouracil–leucovorin–oxaliplatin; HER2, human epidermal growth factor receptor 2; IDH1, isocitrate dehydrogenase 1; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MSI-H, microsatellite instability-high.

All the FINOSE countries adhere to ESMO's guidelines for treatment of BTC. However, except for Denmark, their national treatment guidelines and action programs, have not been updated to reflect recent developments in treatment landscape and clinical practice. In Denmark, targeted therapies are recommended in 2L setting for CCA patients with specific gene mutations. However, non-targeted treatment remains the only available option for all other patients with advanced or metastatic CCA.

Generally, there seems to be a lack of treatment options for unresectable, locally advanced, or metastatic CCA, especially for patients with IDH1 mutations in later LOTs. Table 3 provides a brief overview of the recommended treatment options in 2L setting for patients with metastatic or locally advanced CCA in each of the FINOSE countries. The national treatment guidelines are described in more detail in the following sections.

Table 3. Recommended 2L treatment for patients with metastatic or locally advanced CCA

Country	2L treatment recommendations
Denmark	Pemigatinib for FGFR mutations
	PD-1/PD-L1-inhibitors for MSI
	FOLFOX for all other/ no gene mutations
Finland	No standardised cytostatic treatment, depends on what is given in 1L
	ASC is sometimes the only viable option
	In clinical practice FOLFOX and CapOx are sometimes used in 2L*
Norway	No established 2L treatment.
	5-Fluorouracil/Leucovorin and Irinotecan (FLIRI) can be an option, but regimen depends on what is given in 1L.
Sweden	No standardised cytostatic treatment, it depends on what was given as a first line.
	If appropriate, clinical trials should also be offered as 2L

Abbreviations: 1L, first line ; 2L, second line; ASC, active symptom control; CapOx, capecitabine and oxaliplatin; FOLFOX, folinic acid, fluorouracil and oxaliplatin; FGFR, fibroblast growth factor receptor; MSI, microsatellite instability, PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

*Informal communication with clinical expert

3.1 Denmark

In 2023, the Danish Liver Cancer and Biliary Cancer Group has published a second version of their clinical guidelines for investigation and treatment of CCA. According to the guidelines, despite advancements in treatment landscape, surgical treatment remains the sole potentially curative option for most types of CCA. However, only approximately one-third of cases are resectable at the time of diagnosis (37). Therefore, neoadjuvant chemotherapy is recommended for 2-3 months for downstaging and subsequent resectability assessment.

Chemotherapy is considered as 1L treatment typically involving a cytostatic regimen of gemcitabine and cisplatin for patients exhibiting good overall health conditions (Performance Status [PS] 0-1). For those with a favourable PS (0-1), genomic tumour profiling is recommended to explore potential biologically targeted therapies in the 2L setting (37). Biologically targeted therapies based on specific predictive gene alterations is theoretically possible in many patients with CCA, including in up to 70% of patients with iCCA (37, 69). Notably, targeted therapies such as pemigatinib for fibroblast growth factor

receptor (FGFR) gene mutations and PD-1/PD-L1 checkpoint inhibitors for microsatellite instability (MSI) are available options in the 2L setting for patients with these specific gene mutations. However, for the remaining patients, FOLFOX stands as the sole available treatment option in 2L setting (37).

3.2 Finland

In Finland, while there are no national treatment guidelines, Tampere University Hospital has issued treatment guidelines for CCA in 2006. These guidelines acknowledge that iCCA is rarely amenable to surgical resection, and the efficacy of chemotherapy for patients with advanced CCA remains poor. Gemcitabine, fluorouracil, anthracyclines, or cisplatin are among the treatment options mentioned in the guidelines, but according to information received in recent informal correspondence with a clinical expert, FOLFOX (leucovorin, fluorouracil and oxaliplatin) and CapOx (capecitabin and oxaliplatin) are sometimes used as 2L treatment. However, the guidelines also state that active symptom control (ASC) is often the only available option (70).

Notably, Tampere University Hospital is an active member of EUROCAN, the European Reference Network (ERN) dedicated to rare adult solid cancers. Their clinical practice guidelines for BTC are aligned with the ESMO's guidelines (67, 71).

3.3 Norway

Treatment guidelines are published by the Norwegian Directorate of Health (38). The treatment depends primarily on the size of the cancer, its location and whether it has metastasized. In addition, the general condition of patients with CCA plays a crucial role in determining the treatment. Standard treatment for patients with CCA consists of surgery, chemotherapy and radiotherapy, in addition to symptom-relieving treatments. Surgery is the only curative treatment, and it is attempted using resection, for patients whose disease status allows it, and only for patients in good general condition (WHO-ECOG status 0/1) (38).

Preoperative chemotherapy for down-staging/downsizing should be considered e.g. at resectability against. Chemotherapy is mainly given as palliative treatment option for advanced disease, if the patients is in a good general condition (ECOG 0-2). Chemotherapy is not recommended for routine use as adjuvant therapy, since there is no documented effect in terms of prolonged overall survival with chemotherapy beyond 1L treatment (38).

Combination chemotherapy is considered standard treatment for locally advanced disease, metastatic disease or inoperable local recurrences (38). There are several chemotherapy regimens recommended as 1L therapy in Norway today (with similar overall survival, OS), including Gemcitabine-Oxaliplatin (GemOx), Gemcitabine-Cisplatin (GemCis) and Gemcitabine-Capecitabine (GemCap). The guidelines clearly state that there is no established 2L treatment, but 5-Fluorouracil/Leucovorin and Irinotecan (FLIRI) is mentioned as treatment for consideration, but the choice of regimen depends on what

was given in 1L. Immunotherapy (PD-1 inhibitor) is mentioned but not yet recommended at is being assessed in Nye Metoder. Additionally, targeted therapies are listed in the guidelines but at the time of publication of guidelines (January 2023), only entrectinib is approved for use in Norway. The guidelines mention ivosidenib, referring to the results of the ClarIDHy trial (38).

3.4 Sweden

The Regional Cancer Centre published the treatment guidelines for gallbladder and BTC in 2019. The treatment guidelines aim to contribute to more uniformed care by providing guidelines for investigations, treatment, and follow-up (72).

For iCCA, curative treatment is attempted using resection, for patients whose disease status allows it. For unresectable CCA the only curative treatment option is transplantation, however this is not indicated for iCCA, only pCCA (72). In 2009-2020, 26% of patients with CCA had received curative treatment, the corresponding number for iCCA was 25% (73).

Neoadjuvant treatment is currently not recommended for patients with resectable CCA. The guidelines however describe the need to improve survival outcomes after curative surgery, with adjuvant therapy, as about half the patients with CCA experience disease recurrence with distal metastases following such procedure (72).

In the palliative stage, the patient's condition and the balance between toxicity and expected efficacy determines the treatment path and the use of single or combination cytostatic treatment. The cytostatic treatment options include gemcitabine, capecitabine, oxaliplatin, cisplatin, and fluoropyrimidines. For 2L there is no standardised cytostatic treatment, it depends on what was given as a first line. If appropriate, clinical trials should also be offered as 2L (72).

The 2019 guidelines state that there is a rapid development of targeted therapies and immunotherapies, however none are yet to be implemented in standard care (72).

3.5 Other national guidelines

Similar to the international guidelines, gemcitabine and cisplatin (GC) is the most common 1st LOT option in the country-specific guidelines identified followed by GEM-oxaliplatin combination therapy (74-77). However, there is less alignment between countries regarding 2nd line treatments. Guidelines for Germany, France and Spain all recommend FOLFOX as 2nd line treatment (74-77).

In addition to FOLFOX, Germany, France and Spain also recommend targeted treatments in patients with the relevant genetic alterations (74-77). Larotrectinib (NTRK gene-fusion positive tumors), entrectinib (NTRK gene-fusion positive tumors) and Tibsovo® (IDH1 positive tumors) are recommended for patients with the relevant genetic alterations in several countries i.e., Germany (LOT unclear, all three targeted therapies are recommended) and France (2nd LOT, only larotrectinib and Tibsovo® are recommended) (74, 78). Pemigatinib is a common targeted therapy (in FGFR2 fusions/rearrangements

positive tumors) recommended in the UK and Germany (LOT of targeted therapies are unclear in both sets of guidelines) (74, 76, 78). The German, French and Spanish guidelines separate targeted from non-targeted therapies in their recommendations (74-77).

3.6 Unmet need in CCA

CCA often presents signs or symptoms at a later stage of disease (29). As a result of the delayed presentation, patients are frequently diagnosed at an advanced/metastatic stage when the disease is incurable with ~70% being ineligible for tumor resection (5, 13, 30, 79). At present, there is no effective SoC for advanced/metastatic patients who are ineligible for resection and do not respond to 1L. Furthermore, during the course of the disease, patients experience aggravating and non-specific symptoms (e.g., jaundice, weight loss and abdominal pain) 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 (29, 55).

Advanced/metastatic CCA is associated with a poor prognosis and an increased mortality rate (average 5-year OS is 9 - 10%) (57-60, 80). Half of all untreated patients fail to survive past 3-4 months from presentation of symptoms (47). A US study found that the median OS was seven months in the overall CCA group, four months in the iCCA subgroup, and eight months in the eCCA subgroup (49). The US study also found that the mortality rate increases with each stage of disease (49, 81); the 5-year mortality rate for CCA at stage I was 74.17% compared to 79.47% at stage II, 87.94% at stage III, and 97.13% at stage IV (49).

There is also a high clinical and economic burden in CCA due to associated hospitalizations (27, 57-60). A study in Spain found that there were 31,760 hospital admissions for iCCA[1] from January 2000 to December 2018, with 67.1% admissions identified as urgent (58). Given the CCA incidence of 0.5 per 100,000 people in Spain, a high rate of hospitalizations amongst patients indicates an increased clinical burden for these patients (40). Additionally, the mean cost per admission to hospital with metastatic iCCA was estimated at €6,061 and the cost in combination with the increased urgent admissions can result in a high economic burden (58).

The modest benefit with cytotoxic chemotherapy regimens has been a driver towards developing targeted therapies (82). In recent years, molecular profiling has become more common and there has been a paradigm shift towards targeted therapies for the treatment of CCA (83-85). Molecular profiling must be completed as early as possible post diagnosis to ensure that these targeted treatments can be considered as potential treatment options (86). IDH mutations (the target mutations of Tibsovo®) have little to no overlap with NTRK, MSI-H, and FGFR2 alterations which are targeted by entrectinib/larotrectinib, pembrolizumab and pemigatinib respectively (87). Consequently, existing targeted treatments are not indicated in CCA patients with IDH1 mutations.

[1] Data was not available for eCCA

3.7 How Tibsovo® fulfils the unmet medical need in CCA

For product information, please refer to section 4.3. Under the current treatment paradigm, CCA patients with mIDH1 are treated based on their age, performance status, disease stage, previous treatment and other clinical and pathological factors (88, 89). First line SoC in locally advanced or metastatic CCA is combination chemotherapy; however, 2L SoC is ill-defined (90).

In 2L CCA, current chemotherapy demonstrates a limited clinical benefit vs. ASC / placebo and limits patients' QoL due to the poor safety profile (91).

Molecular profiling has led to the development of targeted therapies. In the EU, pemigatinib is the only approved targeted therapy based on findings from biliary tract / CCA trials and is indicated for patients with FGFR2 mutations in 2L and locally advanced or metastatic CCA.

Tibsovo® is a targeted treatment that provides a significant clinical benefit in patients with mutated IDH1 (131). In CCA, the FGFR-2 mutations targeted by pemigatinib rarely co-occur with the IDH1 mutations targeted by Tibsovo® (approximately 2%) (12). Hence, there is not a significant overlap between the eligible populations for pemigatinib and Tibsovo®. The proposed position of Tibsovo® is in the 2L for locally advanced or metastatic CCA in patients with an IDH1 mutation to address the aforementioned unmet need.

Tibsovo® is also the only mutated IDH1 targeted treatment focused on advanced/metastatic CCA that has completed a pivotal phase III study (ClarIDHy) (44). The ClarIDHy trial demonstrated that Tibsovo® had an improved mOS, QoL and safety profile compared with ASC and thus may help to address the high unmet need in advanced/metastatic CCA (44). The ClarIDHy trial is discussed in more detail in section 4.1.

3.8 Relevant comparators

Based on the treatment guidelines, the main comparator is best supportive care (BSC; referred to in the model as "placebo"), as this is the comparator considered in the ClarIDHy trial (44, 92), and given the lack of an established SoC specifically for the treatment of IDH1 mutated patients with CCA in the FINOSE countries. At a pre-meeting with the Norwegian Medicines Agency (NoMA; 2023-03-30) where the choice of comparator was discussed, NoMA suggested that in addition to BSC an active treatment comparator should also be added. Given the lack of established treatments in the specific patient population and based on available data for relative efficacy FOLFOX was deemed as a second comparator. The choice of comparator was confirmed at a later meeting with FINOSE (2023-11-22).

Denmark is the only FINOSE country where FOLFOX is recommended in the treatment guidelines for treatment of patients with metastatic or locally advanced CCA, who are not harbouring FGFR and MSI gene mutations. In the remaining FINOSE countries, there is no clear SoC, but clinical practice implies that due to lack of treatment options, FOLFOX is used to some extent in 2L setting for this specific patient population.

4 Clinical efficacy

4.1 ClarIDHy - Key clinical trial evaluating Tibsovo® in IDH-mutant CCA

ClarIDHy (NCT02989857; AG120-C-005) was a Phase III pivotal study [completed], investigating Tibsovo® as a targeted treatment for CCA. The main aim of this study was to evaluate the efficacy, safety and QoL of patients treated with Tibsovo® (93). An overview of the main characteristics of the ClarIDHy trial is presented in Table 4.

Table 4: ClarIDHy study characteristics

Study	ClarIDHy
Sample size (n)	187 randomised patients: • 126 to ivosidenib arm • 61 to placebo arm
Study design	Multicentre, randomized, double-blind, placebo-controlled phase III study
Patient population	Patients with unresectable, locally advanced or metastatic CCA and an IDH1 mutation previously treated with a GEM- or 5-FU containing regimen.
Intervention(s)	Ivosidenib 500 mg oral once daily (provided as 250 mg strength tablets)
Comparator(s)	Placebo once daily in continuous 28-day cycles
Follow-up period	
Is the study used in the health economic model?	Yes
Reasons for use of the study in model	Best available evidence
Primary endpoints reported	<u>PFS</u> - Median: 2.7 months vs 1.4 months in placebo group (HR, 0.37; 95% CI, 0.25 to 0.54; p < 0.0001) - 12-month rate: 22% vs NE for placebo Further information in section 4.1.4.

Study	ClarIDHy
Other outcomes reported	• <u>OS</u> - Median: ○ 10.3 months vs 7.5 months in the placebo arm (HR, 0.79; 95% CI, 0.56 to 1.12; p = 0.093) before adjusting for crossover ○ 10.3 months vs 5.1 months in the placebo arm (HR, 0.49; 95% CI, 0.34 to 0.70; p < 0.0001) after adjusting for crossover using the RPSFT method - 12-month rate: 43% vs 36% for placebo Further information in section 4.1.4. • AEs: see section 4.1.4.4 • Other secondary outcomes are presented in Appendix 10.1.3

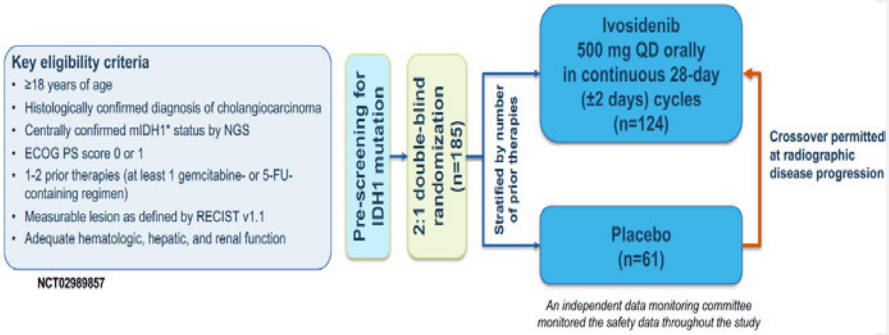
Abbreviations: 5-FU, 5-fluorouracil; AE, adverse event; CCA, cholangiocarcinoma; CI, confidence interval; GEM, gemcitabine; HR, hazard ratio; IDH1, isocitrate dehydrogenase 1, ; OS, overall survival; NE, not estimable; PFS, progression free survival; RPSFT, rank preserving structural failure time.

ClarIDHy is also used to inform the cost-effectiveness model and will be presented closer in the following sections. In addition, NCT02073994 (AG120-C-002) is an ongoing Phase I dose-escalation and expansion study. The main aim of this study is to evaluate the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) in patients with advanced solid tumors treated with Tibsovo®. This study is described in appendix 10.2.

4.1.1 Study design

ClarIDHy was a multicenter, randomized, double-blind, placebo-controlled phase III study to evaluate Tibsovo® in patients with unresectable, locally advanced or metastatic CCA and an IDH1 mutation previously treated with a gemcitabine or 5-fluorouracil (5-FU) containing regimen. The patient population in ClarIDHy was representative of the real-world population (41, 94-96). The chosen comparator was placebo, due to no available evidence supporting second-line chemotherapy (12). Patients were randomized in a 2:1 ratio to Tibsovo® and placebo arms, and patients in each arm were further stratified by number of prior systemic treatment regimens for advanced disease (1 or 2) (41). All patients enrolled in the ClarIDHy study continued with their assigned study treatment until withdrawal and/or study completion as per protocol (93). An overview of the ClarIDHy study design is illustrated in Figure 4.

Figure 4. ClarIDHy study design



Source: Abou-Alfa 2019 (97)
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.

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. 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, as there are no approved drugs in CCA after first line and second-line therapy is ill-defined (98). Thus, allowing crossover in the trial was an ethical approach and ensured that patient needs were central to trial design (41, 99, 100).

Rank preserving structural failure time (RPSFT) is a suitable technique to correct for crossover in small trials, with relatively little information on covariates, and for trials where a large proportion of patients crossover (101-110). The RPSFT model is a commonly used and accepted method by the EMA and NICE (101-107, 111-114). Moreover, it has been used in a large number of previous oncology HTAs (101-105, 107, 111-113). In cases where RPSFT has been presented alongside alternative methods such as inverse-probability-of-censoring weighting (IPCW), the NICE appraisal committee have used the RPSFT results as a basis for decision making (115, 116). In addition to RPSFT, sensitivity analyses using other crossover adjustment methodology were conducted and results were found to be consistent with RPSFT outcome confirming robustness of ClarIDHy data. This, and further description of statistical analyses is further described in appendix 10.1.3.2.

Dose modifications of Tibsovo® 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, Tibsovo® or placebo dose was reduced to 250 mg. Re-escalation was allowed with approval from the medical monitor (41).

Several prespecified subgroup analysis were performed. These are described further in appendix 10.1.3.1.

4.1.2 Trial endpoints

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 center (IRC) per response evaluation criteria in solid tumors (RECIST) v1.1, or date of death due to any cause (117, 118).

The key secondary endpoints included (117, 118):

- Secondary efficacy endpoints:
    - OS, defined as the time from date of randomization to date of death.
- Safety and tolerability:
    - AE, serious adverse events (SAEs), AEs leading to discontinuation or death.
- HRQoL as assessed by validated instruments:
    - Health economic outcomes as assessed by the EQ-5D-5L.

4.1.3 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 5. A full list of inclusion and exclusion criteria is presented in appendix 10.1.1.

Table 5. 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

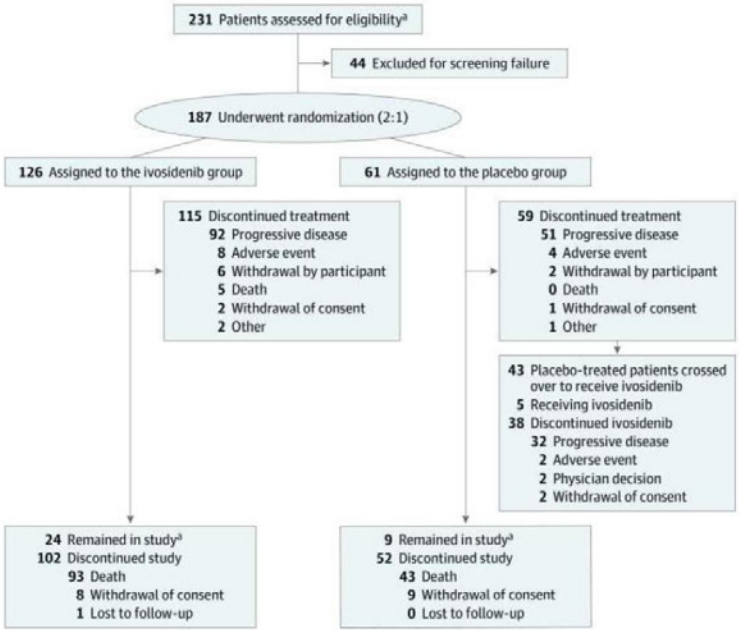
Source: ClinicalTrials.gov (ClarIDHy) (117).
Abbreviations: ECOG, Eastern Cooperative Oncology Group; GEM, gemcitabine; 5-FU, 5-fluorouracil; IDH, isocitrate dehydrogenase; IDH1, isocitrate dehydrogenase 1; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

4.1.4 Study results

4.1.4.1 Baseline demographics and disease characteristics

The patient disposition is illustrated in Figure 5.

Figure 5. ClarIDHy - CONSORT diagram



Source: Zhu 2021 (44).
a. As of the cutoff date (31 May 2020)

At the time of secondary analysis (May 31, 2020 data cut-off date), the median age was 61 years, 35% were male, 90% had iCCA and 93% presented with metastatic disease at screening in the Tibsovo® arm (119). In the placebo arm, median age was 63 years, 39% were male, 95% had iCCA, and 92% presented with metastatic disease at screening (120). Median follow-up duration was 8.6 months (95% CI, 7.4 to 10.6) for the Tibsovo® arm and 9.1 months (95% CI, 5.2 to 11.4) for the placebo arm (120). Demographic and baseline characteristics of patients in the ClarIDHy study are presented in Table 6.

Table 6. ClarIDHy: patient demographics and baseline characteristics (May 31, 2020 data cut off)

Parameter	Tibsovo® (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)

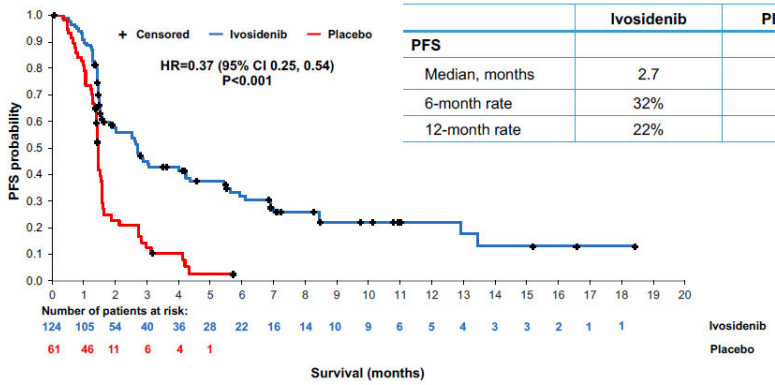
Abbreviations: ECOG, Eastern Cooperative Oncology Group; IDH1, isocitrate dehydrogenase 1.

4.1.4.2 PFS

PFS based on IRC review was analyzed at the time of primary analysis (January 31, 2019 data cut-off). Tibsovo® 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 Tibsovo® vs. 1.4 months for patients who received placebo (HR, 0.37; 95% CI, 0.25 to 0.54; $p < 0.0001$) (41, 121). No patients in the placebo group were free from progression for ≥ 6 months (41). The 6-month PFS rate was 32% and the 12-month PFS rate was 22% for the Tibsovo® group. PFS rates in the placebo group were not estimable (NE) (41).

Figure 6 presents the KM analysis of PFS for the Tibsovo® and placebo arms. The observed PFS benefit in the Tibsovo® arm compared to placebo was generally consistent across key patient subgroups (see appendix 10.1.3).

Figure 6. ClarIDHy: Tibsovo® vs. placebo – PFS (overall) (January 31, 2019 data cut-off)



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

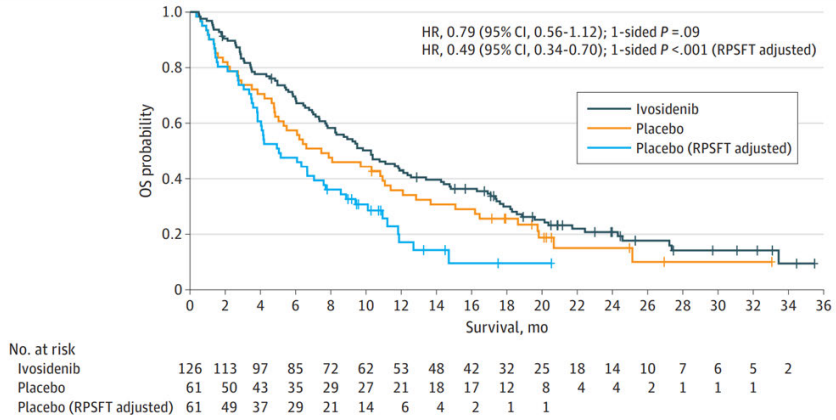
Source: Abou-Alfa 2020 (41).
Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression free survival.

4.1.4.3 OS

Based on the secondary analysis (May 31, 2020 data cut-off), ClarIDHy enrolled 187 patients with IDH1-mutant CCA, with 126 patients in the Tibsovo® arm and 61 patients in placebo arm (44). Of the 61 patients in the placebo arm, 43 patients (70.5%) crossed over to open-label Tibsovo® upon radiographic disease progression and unblinding. Median OS was 10.3 months in the Tibsovo® 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 7). The 6-month OS rate was 69% for Tibsovo® and 57% for placebo, and the 12-month OS rate was 43% for Tibsovo® and 36% for placebo (44, 121).

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). The subgroup analyses are presented in appendix 10.1.3.

Figure 7. ClarIDHy: Tibsovo® vs. placebo – OS (May 31, 2020 data cut-off)



Source: Zhu 2021 (44).
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; RPSFT, rank-preserving structural failure time.

4.1.4.4 Safety and tolerability

At the time of final database lock (June 21, 2021), the median treatment duration was 2.8 months (range, 0.1 to 45.1) in the Tibsovo® arm, both including and excluding patients who crossed over (93). A total of 26 patients (15.7%) remained on Tibsovo® for ≥ 12 months. The median treatment duration for patients in the placebo arm was 1.6 months (range, 0 to 6.9) (93).

Tibsovo® had a favorable safety profile over placebo (93). The most common (>15%) TEAEs among all patients who received Tibsovo® (including those who crossed over) were nausea (38.6%), diarrhea (33.1%), fatigue (28.9%), abdominal pain (22.3%), cough (21.7%), decreased appetite (21.7%), vomiting (20.5%), ascites (19.9%), anemia (18.7%), peripheral edema (15.7%), and constipation (15.1%) (see Table 7) (93).

Tibsovo® patients reported few severe TEAEs. Grade ≥3 TEAEs were reported in 89 patients (53.6%) in the Tibsovo® arm vs. 22 patients (37.3%) in the placebo arm (93). The most common TEAEs of grade ≥ 3 (all patients who received Tibsovo® vs. placebo) were ascites (9.0% vs. 6.8%), anemia (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 Tibsovo® vs. none receiving placebo (93). TEAEs leading to discontinuation were less common in the Tibsovo® arm when compared to the placebo arm (6.6% vs. 8.5%). No event of IDH differentiation syndrome was identified in patients with CCA (93).

Eight patients (4.8%) in the Tibsovo® arm experienced a TEAE leading to death, none of which were assessed by the investigator as being associated with Tibsovo® and were considered to be complications associated with the underlying disease or comorbid

conditions (93). Serious TEAEs were reported for 43 patients (35.0%) receiving Tibsovo® 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 Tibsovo® 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 Tibsovo® group vs. none in the placebo group (93).

The observed safety profile of Tibsovo® at the time of final database lock (June 21, 2021) was consistent with the secondary analysis (May 31, 2020 data cut-off date) (93). Also, the overall safety profile of Tibsovo® in ClarIDHy trial was similar to that observed in the multicenter single-arm open-label phase I AG120-C-002 study that enrolled patients with advanced solid tumors and an IDH1 mutation (including 73 patients with CCA) (41, 122).

Table 7. ClarIDHy: most common (≥ 15%) TEAEs (June 21, 2021 database lock)

Adverse Event, n (%)	Tibsovo® (n=123)	Placebo (n=59)	After Crossover to Tibsovo® (n=43)	Total Tibsovo®[1] (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 Tibsovo® group includes 43 patients initially assigned to placebo who had crossed over to Tibsovo® upon radiographic disease progression.
Source: AG120-C-005 – CSR Addendum. Database lock: June 21, 2021 [Data on file] (93), Zhu et al. 2021 (44, 121).
Abbreviation: n, number; TEAE, treatment-emergent adverse event.

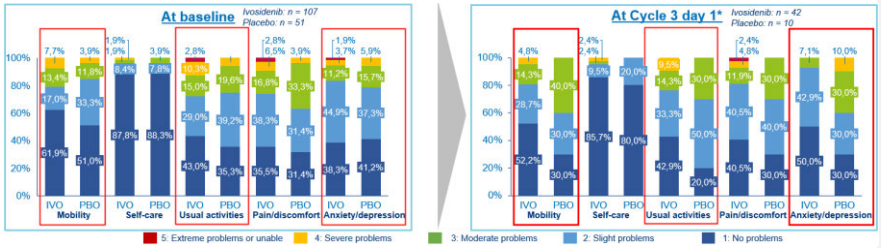
4.1.4.5 Patient reported outcomes measures

HRQoL was measured using several validated instruments. This section presents the key results from the generic health status instrument EQ-5D-5L, as these results were used to inform the CEM. Results for the other patient reported outcomes measures are presented in appendix 10.1.3.2.

A trend in emotional functioning was demonstrated by descriptive results from the EQ-5D-5L. Tibsovo® 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 (41, 123) (Figure 8). Compared to baseline, Tibsovo® increased the proportion of patients that

experienced no or slight grade mobility problems (Tibsovo®: +3.2%, placebo: -24%), no or slight problems with anxiety or depression (Tibsovo®: +9.7%, placebo: -18.5%), and no or slight problems in usual activities (Tibsovo®: +4.2%, placebo: -4.5%) at cycle 3 day 1 (123) (Figure 8).

Figure 8. 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 (123).
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.

In addition to the patient reported outcome measures reported above, it provides an added advantage to the patients to self-manage their disease since Tibsovo® 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, Tibsovo® helps the patients to maintain a better daily routine and enhance QoL (124).

4.2 Indirect treatment comparison in CCA

Tibsovo®, as described previously (see section 4.1) has demonstrated significant clinical benefit in patients with advanced or metastatic CCA with an IDH1 mutation who were previously treated with at least one prior line of systemic therapy compared with placebo in the ClarIDHy trial. Existing treatment options are very limited in 2L advanced/metastatic CCA and as a result, there is no established SoC (38). One treatment option for these patients is FOLFOX (see section 3). However, at the time of ClarIDHy initiation the results from FOLFOX ABC-06 trial we not available. Thus, as no head-to-head evidence was available to compare survival outcomes for Tibsovo® and FOLFOX, an indirect treatment comparison (ITC) was conducted (125), following a SLR to identify relevant trials for evidence synthesis. The methodology is presented in detail in appendix 10.3. Following the SLR, the ABC-06 trial (91) was deemed eligible for inclusion in the ITC. This trial investigated modified FOLFOX regimen as 2L chemotherapy vs. active symptom control for advanced BTC. To assess the relative treatment effect of FOLFOX compared to ivosidenib, certain factors need to be considered. ClarIDHy included almost

exclusively iCCA patients (41), while ABC-06 included all BTC patients, of which, less than half were diagnosed with iCCA (44%) (91).

Tibsovo® was compared to FOLFOX through a Bayesian NMA as it could form a network through their comparison with placebo/ASC. However, due to data unavailability for PFS and overall/objective response rate (ORR) of the ASC arm in ABC-06 (91), a matching-adjusted indirect comparison (MAIC) was considered appropriate for these outcomes, whereas the comparison for the OS (that is reported in both arms) could take the form of an ITC adopting an anchored MAIC (presented in base-case) or Bucher approach (available for scenario analyses). A comparison for complete remission (CR) between the two trials was not feasible as only one patient achieved CR in ABC-06 (91) and none in ClarIDHy (41).

The FINOSE base case cost-effectiveness model (CEM) includes a base case analysis using the results of the anchored MAIC analyses vs ABC-06 (except for PFS, which was obtained from unanchored MAIC). An anchored indirect treatment comparison was not feasible matching the ClarIDHy trial to the population of the ABC-06 study for PFS because there was no PFS data for the ASC arm in ABC-06. Therefore, only an unanchored MAIC was feasible for this endpoint (see section 4.2.1.1.2.1).

In this section, key results from the anchored and unanchored MAIC indirect comparison are presented. For more information on methodology, population matching processes and additional results, see section 10.3.

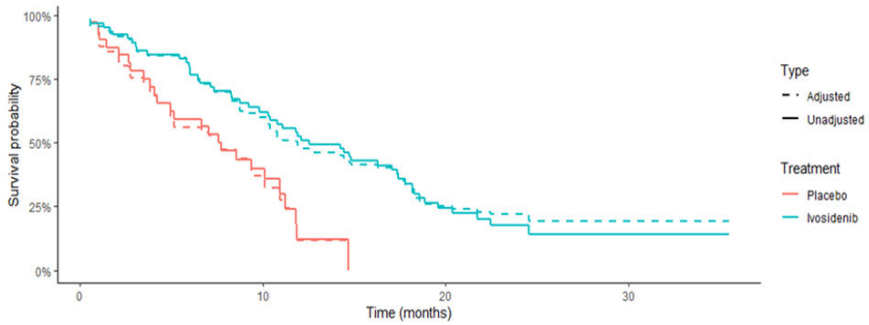
4.2.1.1 Results from indirect treatment comparison

4.2.1.1.1 *Results from* MAIC (anchored)

4.2.1.1.1.1 OS

An anchored indirect treatment comparison was feasible matching the ClarIDHy trial to the population of the ABC-06 study for OS. The digitized OS data from ABC-06 against the unadjusted and adjusted KM data from the ClarIDHy trial are shown in Figure 9 and Figure 10 for the base case and scenario analysis (including CCA subtype for the MAIC) respectively. Any subtle differences observed in the number of patients at risk at each timepoint between the presented ABC-06 KM curve and the one in the original publication (91) are attributable to the digitization process.

Figure 9. KM Curve for OS: Base case of ClarIDHy



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

Figure 10. KM Curve for OS: Scenario analysis of ClarIDHy

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

Table 8 contains the median PFS times (in months) of the ClarIDHy trial before and after matching and also of the pseudo-IPD of ABC-06 per scenario analysis.

Table 8. Median OS times (in months) of ClarIDHy before and after matching to ABC-06 (anchored MAIC)

Analysis, N/ESS	Trial	Treatment arm	Median OS times (in months) (95% CI)
Published results (91)	ABC-06	FOLFOX + ASC	iCCA: 5.7 months (4.1-7.4) eCCA: 6.2 months (4.0-7.9)
Published results (41)	ClarIDHy	Tibsovo®	10.3 months (7.8-12.4)
Naïve, n=97	ClarIDHy (unadjusted)	Tibsovo®	[redacted]
Base Case, ESS=75	ClarIDHy (adjusted)	Tibsovo®	[redacted]
Scenario Analysis, ESS=14		Tibsovo®	[redacted]

Note: Naïve results from ABC-06 are different from the published ones as the KM curve that was used for digitization was not specific for CCA patients and included also BTC patients
Abbreviations: ASC, Active symptom control; BTC, Biliary tract cancer; eCCA, Extrahepatic cholangiocarcinoma; ESS, Effective sample size; FOLFOX, folinic acid, fluorouracil and oxaliplatin; iCCA, Intrahepatic cholangiocarcinoma; MAIC, Matching-adjusted indirect comparison; N, Number; OS, Overall survival.

The relative treatment effect of Tibsovo® compared to FOLFOX + ASC was presented in the form of a constant hazard ratio, utilizing both the MAIC relative effect of Tibsovo® vs placebo and the published HR comparing FOLFOX + ASC vs ASC.

HR estimates of the naïve (unadjusted) and matching-adjusted comparisons of Tibsovo® vs FOLFOX + ASC along with the corresponding 95% CIs are presented in Table 9 per scenario analysis. For the base case, the MAIC relative effect for the unadjusted data was HR [redacted] while after the matching process in the adjusted base case analysis, the HR was equal to [redacted]. For the scenario analysis, the MAIC relative effect for the unadjusted data was HR, [redacted], while after the matching process in the adjusted base case analysis, the HR was equal to [redacted]

HR lower than 1 indicates that Tibsovo® is numerically better than FOLFOX + ASC in the base case and the unadjusted scenario analysis. However, no statistically significant differences were observed given that HR=1 is included in the confidence intervals around the point estimates. The adjusted scenario analysis suggested that FOLFOX + ASC performs better than Tibsovo®, however, the results of the scenario analysis should be interpreted with caution due to the significantly decreased effective sample size (ESS).

Table 9. Constant hazard ratios of OS (anchored MAIC)

Analysis	HR (95% CI)	P-value
Base case		
Unadjusted	[redacted]	[redacted]
Adjusted	[redacted]	[redacted]
Scenario analysis		
Unadjusted	[redacted]	[redacted]
Adjusted	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival.

Figure 11. Hazard ratio estimates of OS for Tibsovo® (ivosidenib) compared to FOLFOX + ASC: All scenario analyses

Abbreviations: ASC, active symptom control; CI, confidence interval; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HR, hazard ratio; OS, overall survival.

4.2.1.1.2 Results from MAIC (unanchored)

4.2.1.1.2.1 PFS

Only an unanchored indirect treatment comparison was feasible matching the ClarIDHy trial to the population of the ABC-06 study for PFS. The digitized PFS data from ABC-06 against the unadjusted and adjusted KM data from the ClarIDHy trial are shown in Figure 12 and Figure 13 for the base case and scenario analysis, respectively. Any subtle differences observed in the number of patients at risk at each timepoint between the presented ABC-06 KM curve and the one in the original publication (91) are attributable to the digitization process.

Figure 12. KM Curve for PFS: Base case of ClarIDHy versus ABC-06

Abbreviations: ASC, Active symptom control; FOLFOX, Folinic acid, fluorouracil, and oxaliplatin; KM, Kaplan-Meier; PFS, Progression-free survival.

Figure 13. KM Curve for PFS: Scenario analysis of ClarIDHy versus ABC-06

Abbreviations: ASC, Active symptom control; FOLFOX, Folinic acid, fluorouracil, and oxaliplatin; KM, Kaplan-Meier; PFS, Progression-free survival.

Table 10 contains the median PFS time (in months) of the ClarIDHy trial before and after matching and also of the pseudo-IPD of ABC-06 per scenario analysis.

Table 10. Median PFS times (in months) of ClarIDHy before and after matching to ABC-06 (unanchored MAIC)

Analysis, N/ESS	Trial	Treatment arm	Median PFS times (in months) (95% CI)
Published results (91)	ABC-06	FOLFOX + ASC	[redacted]
Naïve, n=81	ABC-06 (unadjusted)	FOLFOX + ASC	[redacted]
Published results (41)	ClarIDHy	Tibsovo®	[redacted]
Naïve, n=65	ClarIDHy (unadjusted)	Tibsovo®	[redacted]
Base Case, ESS=46	ClarIDHy (adjusted)	Tibsovo®	[redacted]
Scenario Analysis, ESS=8		Tibsovo®	[redacted]

Note: Naïve results from ABC-06 are different from the published ones as the KM curve that was used for digitization was not specific for CCA patients and included also BTC patients
Abbreviations: ASC, active symptom control; BTC, biliary tract cancer; eCCA, extrahepatic cholangiocarcinoma; ESS, effective sample size; FOLFOX, folinic acid, fluorouracil and oxaliplatin; iCCA, intrahepatic cholangiocarcinoma; MAIC, matching-adjusted indirect comparison; N, number; PFS, progression-free survival.

The relative treatment effect of Tibsovo® compared to FOLFOX + ASC was presented in the form of a constant hazard ratio, derived from Cox proportional hazards models.

HR estimates of the naïve (unadjusted) and matching-adjusted comparisons of Tibsovo® vs FOLFOX + ASC along with the corresponding 95% CIs are presented in Table 11 per scenario analysis. The MAIC relative effect for the unadjusted data was HR, [redacted], while after the matching process in the adjusted base case analysis, the HR was equal to [redacted]. HR lower than 1 indicates that Tibsovo® is numerically better than FOLFOX + ASC in the unadjusted analysis. [redacted]

Table 11. Constant hazard ratios of PFS time (unanchored MAIC)

Analysis	HR (95% CI)	P-value
Unadjusted	[redacted]	[redacted]
Adjusted	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival.

Figure 14. Hazard ratio estimates of PFS for Tibsovo® (ivosidenib) compared to FOLFOX + ASC: Scenario analysis

Abbreviations: ASC, active symptom control; CI, confidence interval; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HR, hazard ratio; PFS, progression-free survival.

4.2.1.1.2.2 ORR

ORR is a beneficial outcome, and it is measured using odds ratios (OR). The interpretation is the opposite of the hazard ratios, that are used in the survival outcomes, thus, values higher than 1 indicate a benefit of Tibsovo® versus FOLFOX + ASC.

Table 12 summarises the results of the indirect comparisons – including outcomes of the naïve (unadjusted) comparison – of Tibsovo® versus FOLFOX + ASC, as well as the within-trials estimates. The MAIC relative effect between the treatments was OR: [redacted] in the base case and [redacted] in scenario analysis. As in the naïve comparison, the analysis suggested numerically unfavourable results for Tibsovo® versus FOLFOX + ASC, indicating – on average – a lower probability of achieving ORR. None of the results were statistically significant. Especially for the analysis with more matching variables included (scenario analysis), the 95% CI appeared wide around the point estimate, suggesting higher uncertainty in the results.

Table 12: Summary of relative ORR estimates of Tibsovo® vs FOLFOX + ASC comparison (all analyses)

	Type	Odds Ratio (CI 95%)	Log-Odds Ratio (CI 95%)	Standard Error
ClarIDHy	Unadjusted	[redacted]	[redacted]	[redacted]
	Adjusted (Base Case)	[redacted]	[redacted]	[redacted]
	Adjusted (Scenario Analysis)	[redacted]	[redacted]	[redacted]
ABC-06	-	[redacted]	[redacted]	[redacted]
ClarIDHy vs ABC-06	Naïve	[redacted]	[redacted]	[redacted]
	MAIC (Base Case)	[redacted]	[redacted]	[redacted]
	MAIC (Scenario Analysis)	[redacted]	[redacted]	[redacted]

Abbreviations: ASC, active symptom control; CI, confidence interval; FOLFOX, folinic acid, fluorouracil and oxaliplatin; MAIC, matching adjusted indirect comparison; ORR, overall/objective response rate.

Figure 15: ORR odds ratios for the Tibsovo® (ivosidenib) vs FOLFOX + ASC: All analyses

Abbreviations: ASC, active symptom control; CI, confidence interval; FOLFOX, folinic acid, fluorouracil and oxaliplatin; MAIC, matching adjusted indirect comparison; OR, odds ratio; ORR, overall/objective response rate.

4.3 Clinical assessment report

Tibsovo® was granted a marketing authorization in the EU on 4 May 2023 (1). The assessment report by EMA's Committee for Medicinal Products for Human Use (CHMP) is attached to this application. Tibsovo® was granted orphan medicine designation, in its approved indication.

As described in the report, AG120-C-005 (ClarIDHy) was found to support the efficacy of Tibsovo® monotherapy in treating adult patients with locally advanced or metastatic CCA with an IDH1 R132 mutation who have previously received systemic therapy (126). Tibsovo® have shown efficacy in terms of reduction in risk of disease progression or death and durability of stable disease (126). Taking into account the recommendations implemented to minimize the risk of QT prolongation, the safety profile is considered

manageable (126). Given the poor prognosis of the disease, the limited treatment options to chemotherapy and the high medical need in this patient population, the benefit of Tibsovo® was considered established (126). Thus, the CHMP concluded that the overall benefit/risk balance of Tibsovo® is positive, subject to conditions outlined in the report (126).

5 Tibsovo® – product information

Tibsovo® was developed for the targeted treatment of haematological and solid malignancies harbouring IDH1 mutations, including r/r AML, CCA, and glioma. Tibsovo® (ivosidenib; previously known as AG-120) is a first-in-class, non-cytotoxic, selective, orally active small-molecule inhibitor of mutated IDH1 making it a highly targeted therapeutic agent for the treatment of patients with IDH1-mutated cancers, including AML and CCA (12, 127, 128). Tibsovo® has received EMA orphan drug designation for both indications, AML in 2016 and CCA in 2018 (129, 130).

5.1 Indications

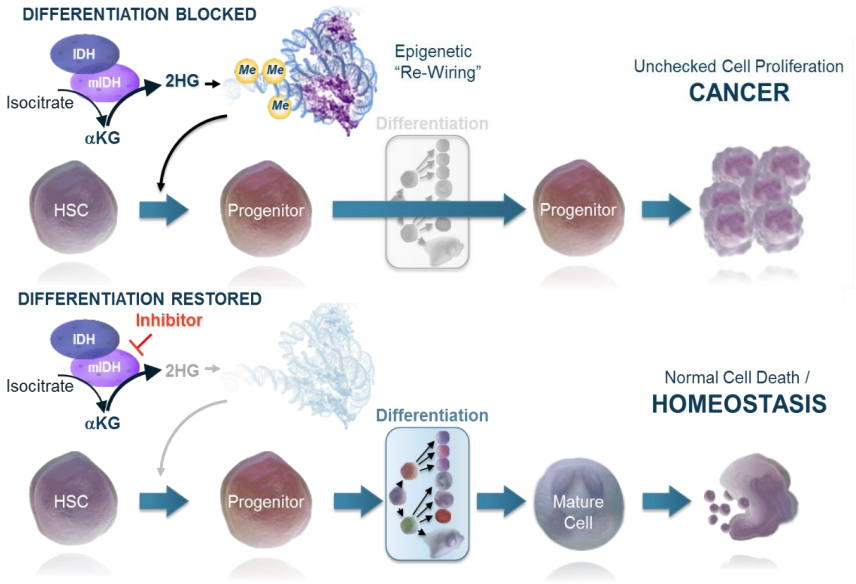
In the EU , Tibsovo® has received a marketing authorization from the EMA for the following two indications (1):

- As monotherapy for the treatment of adult patients with locally advanced or metastatic CCA with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy.
- In combination with AZA for the treatment of adult patients with newly diagnosed AML with an IDH1 mutation who are not eligible to receive SIC.

5.2 Mechanism of action

Tibsovo® is a small-molecule inhibitor that targets the mutant IDH1 enzyme. Mutant IDH1 converts α-KG to 2-HG. Increased 2-HG levels results in epigenetic alterations that impairs myeloid differentiation, increases proliferation of myeloblast and blocks cellular differentiation (11, 124, 131). Inhibition of the mutant IDH1 enzyme by Tibsovo® led to decreased 2-HG levels and restored cellular differentiation, as illustrated in Figure 16 (11, 131-133).

Figure 16. Mechanism of action of Tibsovo®



Abbreviations: αKG, alpha-ketoglutarate; 2-HG, 2-hydroxyglutarate; HSC, hematopoietic stem cells; IDH, isocitrate dehydrogenase; mIDH, mutant isocitrate dehydrogenase.
Source: Cairns 2013 (131)

5.3 Recommended dosage

Before taking Tibsovo®, patients must have confirmation of an IDH1 mutation using an appropriate diagnostic test (127). The recommended dose of Tibsovo® is 500 mg (2 x 250 mg tablets) taken orally once daily as long as clinical benefit is observed or until treatment is no longer tolerated by the patient (124).

A recommended dose has not been determined for patients with severe renal or hepatic impairment. Tibsovo® should be used with caution in patients with severe renal or hepatic impairment and this patient population should be closely monitored (124).

5.4 Monitoring

An electrocardiogram (ECG) should be performed prior to treatment initiation. ECGs should be monitored at least weekly during the first three weeks of therapy and then at least once monthly for the duration of therapy. Any abnormalities should be managed promptly (127).

6 Treatment costs

6.1 Treatment cost of Tibsovo®

Tibsovo® is packaged in a bottle, containing 60 film-coated tablets, each with a strength of 250 mg. The recommended dose is 500 mg ivosidenib (2 x 250 mg tablets) taken orally once daily (124). The wholesale prices of Tibsovo® set to the prices previously presented under Section 1.1 were used to derive the appropriate intervention prices for each country specific cost-effectiveness analysis. Drug acquisition costs for Tibsovo®, per pack and treatment cycle of 7 days, in each of the FINOSE countries are presented in Table 13.

Table 13 Treatment cost of Tibsovo® in each country

Country	Price per package	Price per 7-day cycle
Denmark	[redacted]	[redacted]
Finland	[redacted]	[redacted]
Norway	[redacted]	[redacted]
Sweden	[redacted]	[redacted]

6.2 Treatment cost of comparators

Drug acquisition costs for the comparator, per pack and treatment cycle of 7 days, in each of the FINOSE countries are presented in the tables below.

Table 14. Treatment cost of comparators in Denmark

Drug	Dosing	Strength & package	Wholesale price per pack	Cost per 7-day cycle
BSC	n/a	n/a	n/a	n/a
Fluorouracil	400 mg/m2 bolus injection + 2400 mg/m2 continuous infusion over 46 hours (2.8g total every 2 weeks)	50 mg/mL, 100 mL	[redacted]	[redacted]
Oxaliplatin	0.085 g/m2 (every 2 weeks)	5 mg/mL, 20 mL	[redacted]	[redacted]
Calcium folinate	0.35 g (every 2 weeks)	10 mg/mL, 35 mL	[redacted]	[redacted]

Source: Laegemiddelstyrelsen, 2023 (134)
Treatment costs per 7-day cycle presented in this table are estimated assuming no wastage.

Table 15. Treatment cost of comparators in Finland

Drug	Dosing	Strength & package	Wholesale price per pack	Cost per 7-day cycle
BSC	n/a	n/a	n/a	n/a
Fluorouracil	400 mg/m2 bolus injection + 2400 mg/m2 continuous infusion over 46 hours (2.8g total every 2 weeks)	50 mg/mL, 100 mL	[redacted]	[redacted]
Oxaliplatin	0.085 g/m2 (every 2 weeks)	5 mg/mL, 20 mL	[redacted]	[redacted]
Calcium folinate	0.35 g (every 2 weeks)	10 mg/mL, 50 mL	[redacted]	[redacted]

Source: Kela's Medicinal Products Database, 2024 (135)
Note: Treatment costs per 7-day cycle presented in this table are estimated assuming no wastage.

Table 16. Treatment cost of comparators in Norway

Drug	Dosing	Strength & package	Wholesale price per pack	Cost per 7-day cycle
BSC	n/a	n/a	n/a	n/a
Fluorouracil	400 mg/m2 bolus injection + 2400 mg/m2 continuous infusion over 46 hours (2.8g total every 2 weeks)	50 mg/mL, 100 mL	[redacted]	[redacted]
Oxaliplatin	0.085 g/m2 (every 2 weeks)	5 mg/mL, 20 mL	[redacted]	[redacted]
Calcium folinate	0.35 g (every 2 weeks)	10 mg/mL, 10 mL	[redacted]	[redacted]

Source: Statens Legemiddelverk, 2023 (136)
Note: Treatment costs per 7-day cycle presented in this table are estimated assuming no wastage.

Table 17. Treatment cost of comparators in Sweden

Drug	Dosing	Strength & package	Wholesale price per pack	Cost per 7-day cycle
BSC	n/a	n/a	n/a	n/a
Fluorouracil	400 mg/m2 bolus injection + 2400 mg/m2 continuous infusion over 46 hours (2.8g total every 2 weeks)	50 mg/mL, 20 mL	[redacted]	[redacted]
Oxaliplatin	0.085 g/m2 (every 2 weeks)	5 mg/mL, 20 mL	[redacted]	[redacted]
Calcium folinate	0.35 g (every 2 weeks)	10 mg/mL, 25 mL	[redacted]	[redacted]

Source: Region Stockholm, 2023 (137)
Note: Treatment costs per 7-day cycle presented in this table are estimated assuming no wastage.

7 Treatment duration

In the ClarIDHy trial, the median duration of Tibsovo treatment was 2.8 months (95% CI: 0.1 – 34.4) and 1.6 months (95% CI: 0 – 6.9) for BSC (2.7 [95% CI: 0.3 – 29.8] for BSC with crossover) (93).

8 Patient numbers

Based on the CCA incidence numbers, the assumption of 19.1% prevalence of mIDH1 in iCCA patients (138) and patient distribution across LOTs, Table 18 displays the estimated number of patients eligible for treatment with Tibsovo® in each of the FINOSE countries.

Table 18. Number of CCA patients eligible for treatment with Tibsovo® per country

	Denmark	Finland	Norway	Sweden
CCA patients eligible for treatment with Tibsovo®	9	5	5	19

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10 Appendices

10.1 ClariDHy

10.1.1 ClarIDHy patient eligibility criteria

Table 19 ClarIDHy patient eligibility criteria

Inclusion criteria	Exclusion criteria
Subjects must have met all of the following criteria to be enrolled in the study:	Subjects who met any of the following criteria were not to be enrolled in the study:
1. ≥18 years of age.	1. Received a prior IDH inhibitor.
2. Had a histopathological diagnosis (fresh or banked tumor biopsy sample, preferably collected within the last 3 years) consistent with nonresectable or metastatic CCA and were not eligible for curative resection, transplantation, or ablative therapies.	2. Received systemic anticancer therapy or investigational agent <2 weeks prior to Day 1 (washout from prior immune based anticancer therapy was 4 weeks). In addition, the first dose of study treatment should not have occurred before a period ≥5 half-lives of the investigational agent has elapsed.
3. Had documented IDH1 gene-mutated disease (from a fresh tumor biopsy or the most recent banked tumor tissue available) based on central laboratory testing (R132C/L/G/H/S mutation variants tested).	3. Received radiotherapy to metastatic sites of disease <2 weeks prior to Day 1.
4. Had an ECOG PS score of 0 or 1.	4. Underwent hepatic radiation, chemoembolization, and radiofrequency ablation <4 weeks prior to Day 1.
5. Had an expected survival of ≥3 months.	
6. Had at least one evaluable and measurable lesion as defined by RECIST v1.1. Subjects who had received prior local therapy (including but not limited to embolization, chemoembolization, radiofrequency ablation, or radiation therapy) were eligible provided measurable disease fell outside of the treatment field or within the field and had	5. Had known symptomatic brain metastases requiring steroids. Subjects with previously diagnosed brain metastases were eligible if they had completed their treatment and had recovered from the acute effects of radiation therapy or surgery prior to study entry, had discontinued corticosteroid treatment for these metastases for at least 4 weeks and had radiographically stable disease for at

Inclusion criteria	Exclusion criteria
shown ≥20% growth in size since post-treatment assessment. 7. Had documented disease progression following at least 1 and no more than 2 prior systemic regimens for advanced disease (nonresectable or metastatic). Subjects had to receive at least 1 gemcitabine- or 5-FU-containing regimen for advanced cholangiocarcinoma. Systemic adjuvant chemotherapy was considered a line of treatment if there was documented disease progression during or within 6 months of completing the therapy. 8. Had recovered from toxicities associated with prior anticancer therapy to baseline unless stabilized under medical management. 9. Had adequate bone marrow function as evidenced by: a. Absolute neutrophil count ≥1,500/mm3 or 1.5 ×109 /L b. Hemoglobin ≥8 g/dL c. Platelets ≥100,000/mm3 or 100 × 109 /L 10. Had adequate hepatic function as evidenced by: a. Serum total bilirubin ≤2 × ULN, unless considered due to Gilbert's disease b. AST and ALT ≤5 × ULN 11. Had adequate renal function as evidenced by: a. Serum creatinine <1.5 × ULN OR b. Creatinine clearance ≥50 mL/min based on the Cockcroft-Gault glomerular filtration rate estimation: (140 − Age) ×	least 3 months prior to study entry. Note: up to 10 mg per day of prednisone equivalent was allowed. 6. Had a history of another primary cancer, with the exception of: a) curatively resected non-melanoma skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary solid or liquid tumor with no known active disease present that, in the opinion of the Investigator, did not affect subject outcome in the setting of current cholangiocarcinoma diagnosis. 7. Underwent major surgery within 4 weeks of Day 1 or had not recovered from post-surgery toxicities. 8. Were pregnant or breastfeeding. 9. Were taking known strong CYP3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window, unless they could have been transferred to other medications within ≥5 half-lives prior to dosing.

Inclusion criteria	Exclusion criteria
(weight in kg) × (0.85 if female)/72 × serum creatinine 12. Was able to understand and willing to sign the informed consent form and to comply with scheduled visits, treatment plans, procedures, and laboratory tests, including serial peripheral blood sampling and urine sampling, during the study. A legally authorized representative could have consented on behalf of a subject who was otherwise unable to provide informed consent if acceptable to and approved by the site's **Institutional Review Board** / **Independent Ethics Committee**. (Subjects who did not speak one of the languages that the QLQ-C30, QLQ-BIL21, PGI-C, PGI-S, or EQ-5D-5L were provided in at this time were permitted to enroll and not complete these HRQOL/health economic outcome instruments, assuming all other eligibility criteria were met.) 13. Female subjects with reproductive potential had to have a negative serum pregnancy test prior to the start of therapy, or a confirmation from an obstetrician in case of equivocal serum pregnancy results. Females of reproductive potential were defined as sexually mature women who had not undergone a hysterectomy, bilateral oophorectomy, or tubal occlusion or who had not been naturally postmenopausal (i.e., who had not menstruated) for at least 24 consecutive months (i.e., did not have menses at any time in the preceding 24 consecutive months). Women of reproductive potential, as well as fertile men and their partners who were female with reproductive potential, had to agree to use 2 effective forms of contraception (including at least 1 barrier form) from the time of giving informed consent throughout the study and for 90 days (both	

Inclusion criteria	Exclusion criteria
females and males) following the last dose of study drug. Effective forms of contraception were defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, intrauterine hormone-releasing systems, bilateral tubal ligation, condoms with spermicide, or male partner sterilization.	

10.1.2 ClarIDHy statistical analysis

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

- 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 (Tibsovo® 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 Tibsovo® 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 (41, 139).

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 Tibsovo® upon radiographic disease progression (41).

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 (140). Consequently, the ICER could misrepresent the true cost-effectiveness of the experimental treatment. Whilst the ITT approach is a useful method of analysis, National Institute for Health and Care Excellence (NICE) advises that it is likely inappropriate in the presence of treatment switching (140). In order to mitigate the bias, NICE appraises the use of crossover (141).

For the ClarIDHy study, different crossover adjustment methods were explored (e.g., simple pooling, RPSFT, IPCW and propensity score matching) (106). Ultimately, the RPSFT model was used to preserve the trial randomization, especially as the crossover rates were as high as 70%. Findings from a methodological review showed that in instances of a large proportion of crossover in small trials, the RPSFT method is preferable (106). The RPSFT model is a commonly used and accepted method and has been used in a large number of previous technology appraisals (TA) (142-147). The RPSFT method was used to reconstruct the survival curve (prespecified exploratory analysis) for patients receiving placebo, as if crossover had never occurred (148).

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 (149). Key assumptions of this method include the 'common treatment effect' (99). The RPSFT method assumes 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. 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 (99).

The major strengths of RPSFT method include: maintains original randomized group definitions, thus produces randomization-based effect estimators (99) and uses the complete dataset of the trial and ranking of the observed time-to-event data is preserved after adjustment (106). The limitations of the RPSFT method include: "common treatment effect" cannot be tested and may not be clinically plausible as the magnitude of treatment effect is dependent on extent of disease progression (150), does not use information on covariates which may affect the probability of crossover (106), and assumption that mortality decreases constantly during the time that the investigational drug is received may not reflect reality (106).

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 Tibsovo® 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 (41). 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 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) (59, 151). 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 done with statistical analysis software, version 9.4.

10.1.3 ClarIDHy additional results

10.1.3.1 Subgroup analysis

The prespecified subgroups included (119):

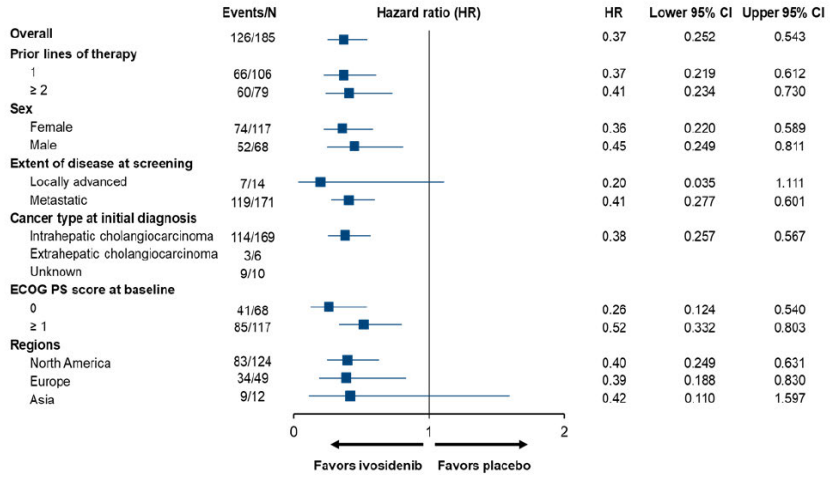
- The actual number of prior line of therapies in advanced setting (1 vs. ≥2)
- Gender (female vs. male)
- Extent of disease at screening (locally advanced vs. metastatic)
- CCA type (intrahepatic vs. extrahepatic)
- ECOG at baseline (0 vs. ≥1[2])
- Regions (North America vs. Europe vs. Asia)

10.1.3.1.1 PFS

The observed PFS benefit in the Tibsovo® arm compared to placebo was generally consistent across key patient subgroups (Figure 17). In general, most of the subgroups favored Tibsovo® 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 (41).

[2] '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.

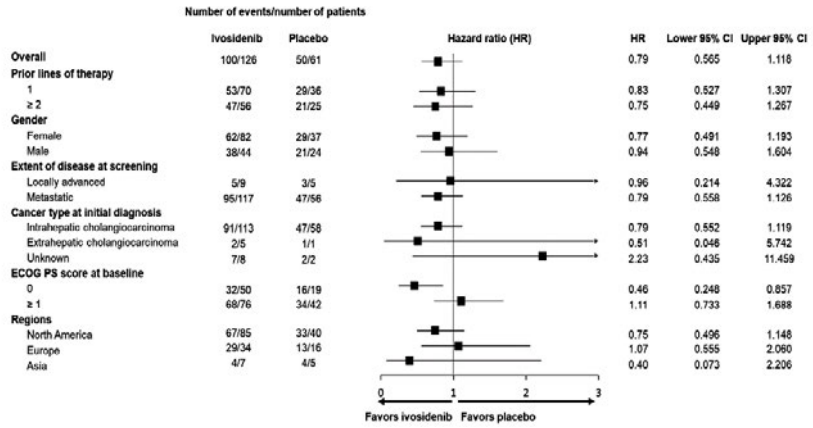
Figure 17. ClarIDHy: Tibsovo® vs. placebo by subgroup – PFS (January 31, 2019 data cut-off)



10.1.3.1.2 OS

The subgroup analyses for OS are presented in Figure 18 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 (44).

Figure 18. ClarIDHy: Tibsovo® vs. placebo by subgroup – OS (May 31, 2020 data cut-off)



10.1.3.2 Patient reported outcomes measures

QoL was well-maintained in the Tibsovo® arm compared to the placebo arm by better preserving physical and emotional functioning and limiting symptom worsening (e.g., pain, dyspnea, tiredness), as measured by EORTC metrics (93).

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 (93). Tibsovo® 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 (93). 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 (93).

A clinically meaningful decline in physical functioning was observed via EORTC QLQ-C30 in the placebo arm compared to Tibsovo® arm (93):

- Cycle 2 Day 1: Difference of 11.0 points; 95% CI, 4.23 to 17.71; p = 0.001
  - Tibsovo® 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
  - Tibsovo® 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. Tibsovo® based on EORTC QLQ-C30 (93):

- Cycle 2 Day 1: Difference of 13.8 points; 95% CI, 6.08 to 21.43; p = <0.001
  - Tibsovo® 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
  - Tibsovo® 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 (93):

- Cycle 2 Day 1: Difference of 13.2 points; 95% CI, -22.67 to -3.77; p = 0.006
  - Tibsovo® 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
  - Tibsovo® arm: LS mean [SE]: -5.3 [2.65]
  - Placebo arm: LS mean [SE]: -1.4 [5.67]

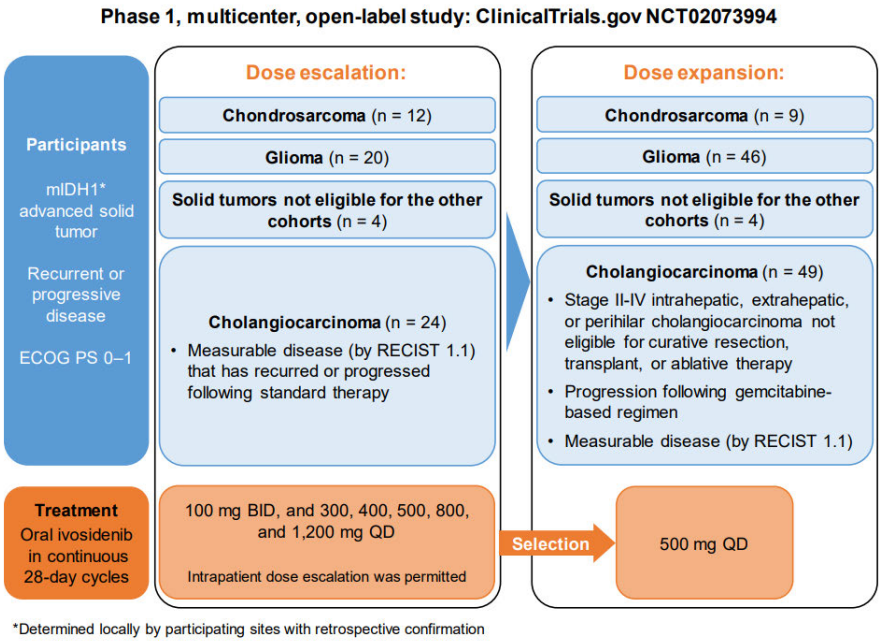
Furthermore, Tibsovo® continued to demonstrate a sustained QoL for 14 cycles (one year). A clinically meaningful physical functional decline was only observed in the placebo arm (41). Patients in the placebo arm reported a larger decline in physical, cognitive, and emotional functioning from baseline to cycle 2, day 1 compared with those in the Tibsovo® arm based on the QLQ-C30 functional subscales (physical, p = 0.002; cognitive, p = 0.029; emotional, p < 0.001) (121). Similar preservation of physical and emotional functioning was also observed for Tibsovo® 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 Tibsovo® 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 Tibsovo® arm based on the EORTC QLQ-BIL21 (121).

10.2 AG120-C-002

10.2.1 Study design and endpoints

AG120-C-002 is an ongoing multicenter, single-arm, open-label phase I study to evaluate Tibsovo® in patients with advanced solid tumors and an IDH1 mutation (117). Tibsovo® is being evaluated in three cohorts of patients with CCA (n=73), non-enhancing gliomas (n=35), and chondrosarcoma (n=21) (122, 152-155). Tibsovo® is administered continuously as a single agent dosed orally on Days 1 to 28 of a 28-day cycle. An overview of the AG120-C-002 study design is illustrated in Figure 19.

Figure 19. AG120-C-002: study design



Source: Lowery et al 2019 (122)
Abbreviations: BID, twice a day; ECOG, Eastern Cooperative Oncology Group; mg, milligram; mIDH1, mutant isocitrate dehydrogenase 1; PS, performance status; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

10.2.1.1 Study treatments

Dose escalation phase

The first part of the study is a dose escalation phase where cohorts of patients received ascending oral doses (200–1,200 mg daily in 28-day cycles) of Tibsovo® to determine MTD and/or the RP2D (122, 152-155).

For dose escalation, a standard design of three to six patients per dose is used and continued until two or more patients experience dose-limiting toxicities. Dose-limiting toxicities are evaluated during cycle 1 of this phase and defined as any grade 3 or higher event reported to be related or possibly related to Tibsovo®. In this phase, dose reduction in multiples of 50 mg and further to starting dose or an intermediate dose is permitted with medical monitor approval.

Dose expansion phase

The second part of the study is a dose expansion phase where four arms of patients receive the selected dose of Tibsovo® based on PK, pharmacodynamic, safety, and

activity data from dose escalation. Safety, tolerability, and clinical activity of the recommended phase II dose are further evaluated in this phase (122, 152-155).

In expansion, treatment is continued until disease progression, unacceptable toxicity, confirmed pregnancy, death, withdrawal of consent, or loss to follow-up. In the event of grade 1 or 2 toxicities, dose reduction to 250 mg and further to the starting dose or an intermediate dose is permitted with medical monitor approval.

10.2.1.2 Inclusion and exclusion criteria

Patients aged at least 18 years with documented mIDH1 gene based on local evaluation and who were amenable to serial peripheral blood sampling, urine sampling, and biopsies during the study were eligible for this study. The key inclusion and exclusion criteria are summarized in Table 20.

Table 20. Eligibility criteria for AC120-C-002 study

Inclusion criteria	Exclusion criteria
• ≥ 18 years of age • Documented IDH1 gene-mutated disease based on local test evaluation • Amenable to serial peripheral blood sampling, urine sampling, and biopsies during the study • ECOG PS 0 to 1 • Expected survival ≥ 3 months • Adequate bone marrow function as evidenced by absolute neutrophil count ≥ $1.5x10^9$/L, hemoglobin > 9 g/dL (transfusion allowed), and platelets ≥ $75x10^9$/L • Adequate hepatic function as evidenced by serum total bilirubin ≤ 1.5x upper limit of normal and aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase ≤ 2.5x upper limit of normal • Adequate renal function as evidenced by serum creatinine ≤ 2.0x upper limit of normal or creatinine clearance > 40 mL/min	• Received systemic anticancer therapy or radiotherapy < 21 days prior to their first day of study drug administration • Received an investigational agent < 14 days prior to their first day of study drug administration • Sensitive cytochrome P450 3A4 substrate medications • Taking p-glycoprotein transporter-sensitive substrate medications • Potentially curative anticancer therapy is available • Active severe infection that required anti-infective therapy or unexplained fever > 38.5°C during screening visits or first day of drug administration • Known hypersensitivity to any components of Tibsovo® • Patients with New York Heart Association class III or IV congestive heart failure or LVEF < 40% • History of myocardial infarction within the last 6 months • Unstable or uncontrolled angina pectoris • History of severe or uncontrolled ventricular arrhythmias

Inclusion criteria	Exclusion criteria
• • Dose escalation stage: • Histologically or cytologically confirmed, IDH1 gene-mutated advanced solid tumors that have recurred, progressed, or not responded following standard therapy • Must have evaluable disease (RECIST v1.1) • • Dose expansion stage: CCA • Histologically confirmed diagnosis of IDH1 gene mutated CCA stage II, III, or IV that is ineligible for curative resection, transplantation, or ablative therapies • Progressed following gemcitabine-based regimen • Radiographically measurable disease in at least one site not previously treated with radiation, chemoembolization, radioembolization, or other local ablative procedures	• Patients with heart-rate corrected QTc ≥ 450 ms or with other factors that increase the risk of QT • Taking medications that are known to prolong QTc • Known infection with HIV or active hepatitis B or hepatitis C • Known dysphagia, short-gut syndrome, gastroparesis, or other conditions limiting gastrointestinal absorption of oral drugs • Brain metastases that are untreated, symptomatic, or require therapy to control symptoms, within two months of first dose • History of grade 4 astrocytoma

Source: Lowery et al 2019 (122)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HIV, Human immunodeficiency virus; IDH1, isocitrate dehydrogenase 1; LVEF, left ventricular ejection fraction; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors.

10.2.1.3 Study endpoints

Safety measures and endpoints (156):

- Monitoring of AEs, including determination of dose-limiting toxicities (DLTs), SAEs, and AEs leading to treatment discontinuation. The severity of AEs is assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (version 4.03).
- Monitoring of safety laboratory parameters, physical examination findings, vital signs, 12-lead ECGs, evaluation of LVEF, and ECOG PS.

PK and pharmacodynamic measures and endpoints (156):

- Serial blood sampling at specified time points for determination of plasma concentration-time profiles and PK parameters of Tibsovo®.

- Blood and urine sampling, and tumor biopsies, at specified time points for determination of 2-HG levels to characterize the pharmacodynamic effects of Tibsovo®.
- Sampling of cerebrospinal fluid (glioma patients only) to assess IDH1 gene mutation status, 2-HG levels, metabolic profiling, and gene expression.

Clinical activity measures and endpoints (156):

- Serial radiographic evaluations (CT or MRI) to determine response to treatment based on RECIST v1.1 for patients without glioma or by response assessment in neuro-oncology criteria (RANO) or RANO LGG (expansion portion patients only) criteria for patients with glioma.
- Endpoints of clinical activity included ORR, DOR, PFS, OS (for CCA patients only), and time to response.

For other exploratory endpoints refer to the CSR (156) for further details.

10.2.1.4 Statistical analysis

Based on the planned dose escalation scheme, it was estimated that approximately 170 patients would be enrolled in the study overall (approximately 45 in the dose escalation phase and 125 in the expansion phase). The chance of observing at least one AE would be 99.5% based on 50 patients in the CCA expansion cohort, with a true underlying event rate of 10%, and 92.3% with a true underlying event rate of 5%. The chance of observing at least one AE would be 92.8% based on 25 patients in the expansion cohort, with a true underlying event rate of 10%, and 72.3%, with a true underlying event rate of 5%. Additionally, considering about 50 patients in the CCA expansion cohort and an exact binomial distribution, the maximum width of the 95% CI around the proportion of patients achieving an objective response would be 0.289 for the secondary endpoint of preliminary anti-tumor activity (122).

Safety data was reported for the safety analysis set, comprising all patients with CCA who were enrolled and received at least one dose of Tibsovo® in the dose escalation and dose expansion cohorts, classified according to the actual treatment received. All other analyses were reported for the full analysis set, comprising all patients who were enrolled and received at least one dose of study treatment, classified according to the assigned dose. Descriptive statistics were reported for safety outcomes and other clinical, PK, and pharmacodynamic parameters. Time-to-event endpoints (PFS and OS) were estimated using KM methods, and the median with associated 95% CI produced (122). Statistical analyses were done with statistical analysis software version 9.3 or higher.

10.2.1.5 Patient disposition

At the primary analysis cut-off date (May 12, 2017), the study included 168 patients with a variety of mIDH1 solid tumors (73 CCA patients, 43%; 66 glioma patients, 39%; 21 chondrosarcoma patients, 13%; and eight other, 5%) (46). As of the latest data cut-off (January 16, 2019), 146 patients (86.9%) had discontinued treatment and 22 patients (13.1%) remained on treatment. Reasons for on-study treatment discontinuation were PD in 123 patients (73.2%), followed by clinical progression (defined as clinical deterioration,

without evidence of radiographic PD) in 11 patients (6.5%). Overall median treatment duration was 3.7 months (range 0.4 to 50.5 months) (157).

10.2.1.6 Baseline demographics and disease characteristics

Given that enrolment in Study AG120 C 002 had been completed at the time of the data cut-off date for the primary CSR, demographic data and other baseline characteristics were unchanged between the primary CSR data cut-off date and the latest CSR addendum data cut-off date. As of the May 12, 2017 data cut-off, a total of 168 patients across all tumour types were treated (60 in dose escalation and 108 in the four dose expansion arms) (26). The results for patients in the three cohorts are reported individually (122, 152-154).

There were 73 patients with CCA treated with Tibsovo® in the dose escalation (n=24) and dose expansion cohorts (n=49), with 12 remaining on treatment (122). The median age in the CCA cohort was 60 years, 24 patients (32.9%) were male, and 49 patients (67.1%) were female; 89% had iCCA. Six patients received <500 mg Tibsovo® QD, 62 patients received 500 mg Tibsovo® QD, and five patients received >500 mg Tibsovo® QD. The demographics and baseline characteristics of patients are shown in

Table 21.

Table 21. AG120-C-002: Demographics and baseline characteristics of patients with CCA

Parameter	Patients (n=73)
Age in years, median (range)	60 (32 to 81)
Female/male, n	49/24
ECOG PS at screening, n (%)	
0	26 (36)
1	47 (64)
Subtype, n (%)	
Intrahepatic	65 (89)
Extrahepatic	8 (11)
Prior systemic therapies, median (range)	2 (1 to 5)
Prior gemcitabine-based, n (%)	71 (97)
mIDH allele, n (%)	
R132C	56 (77)
R132L	8 (11)
R132G	5 (7)
R132H	2 (3)
R132S	2 (3)

Source: Lowery 2019 (122)
Abbreviations: ECOG, Eastern Cooperative Oncology Group; mIDH1, mutant isocitrate dehydrogenase 1; PS, performance status

10.2.1.7 Results

Product efficacy

The ORR among patients with CCA was 5.5% (four PRs). In addition, 56.2% of patients had SD (157). Median PFS among patients with CCA was 3.8 months (95% CI, 3.6 to 7.3). The 6-month PFS rate was 40.2% and the 12-month PFS rate was 20.8% (Table 22). Median OS was 12.2 months (95% CI, 9.2 to 20) (Table 23) (157).

Table 22. Kaplan-Meier analysis of PFS by dose group and overall for patients with CCA (FAS)

Parameter	<500 mg (n=6)	500 mg (n=62)	>500 mg (n=5)	Overall (n=73)
PFS (months)[1]				
Number of Events (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of Censored (%)[2]	[redacted]	[redacted]	[redacted]	[redacted]
25th Percentile (median) [95% CI][3]	[redacted]	[redacted]	[redacted]	[redacted]
50th Percentile (median) [95% CI][3]	[redacted]	[redacted]	[redacted]	[redacted]
75th Percentile (median) [95% CI][3]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan-Meier Survival Rate (%)[4]				
3 Months	[redacted]	[redacted]	[redacted]	[redacted]
6 Months	[redacted]	[redacted]	[redacted]	[redacted]
9 Months	[redacted]	[redacted]	[redacted]	[redacted]
12 Months	[redacted]	[redacted]	[redacted]	[redacted]

Source: AG120-C-002 – CSR Addendum. Data cut-off: January 16, 2019 [Data on file] (157).
Abbreviations: CI, confidence interval; FAS, full analysis set; Max, maximum; Min, minimum; NE, not evaluable; PFS, progression-free survival.
Note: FAS was defined as all patients who were enrolled and received at least 1 dose of study treatment, classified to dose assigned. Percentages were based on the number of patients in the FAS in each column (denominator).
[1]PFS = (earliest date of progressive disease or death, whichever was earlier – first dose start date +1)/30.4375.
[2]Patients with no post-baseline assessment were censored at first dose date; no progression/death by data cut-off date were censored at the last adequate assessment date; alternative anticancer therapy started before progression/death were censored at the last adequate assessment prior to the alternative anticancer therapy; progression/death following a long gap (≥2 consecutive scheduled assessments missing) were censored at date of last adequate assessment prior to the gap.
[3]Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[4]Based on Survival Distribution Function estimates from product-limit method.

Table 23. Kaplan-Meier analysis of OS by dose group and overall for patients with CCA (FAS)

Parameter	<500 mg (n=6)	500 mg (n=62)	>500 mg (n=5)	Overall (n=73)
Overall Survival (months)[1]				
Number of Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of Censored[2], n (%)	[redacted]	[redacted]	[redacted]	[redacted]
25th Percentile (median) [95% CI][3]	[redacted]	[redacted]	[redacted]	[redacted]
50th Percentile (median) [95% CI][3]	[redacted]	[redacted]	[redacted]	[redacted]
75th Percentile (median) [95% CI][3]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan-Meier Survival Rate (%)[4]				
3 Months	[redacted]	[redacted]	[redacted]	[redacted]
6 Months	[redacted]	[redacted]	[redacted]	[redacted]
9 Months	[redacted]	[redacted]	[redacted]	[redacted]
12 Months	[redacted]	[redacted]	[redacted]	[redacted]

Source: AG120-C-002 – CSR Addendum. Data cut-off: January 16, 2019 [Data on file] (157).
Abbreviations: CI, confidence interval; FAS, full analysis set; Max, maximum; Min, minimum; NE, not evaluable; OS, overall survival.
Note: FAS was defined as all patients who were enrolled and received at least 1 dose of study treatment, classified to dose assigned. Percentages were based on the number of patients in the FAS in each column (denominator).
1 OS = months from the date of the first dose start date to the date of death due to any cause.
2 Patients without documentation of death at the time of the data cut-off for analysis were censored at the date the subject was last known to be alive, or the data cut-off date, whichever was earlier.
3 Quartile estimates from product-limit (Kaplan-Meier) method. Confidence Intervals from Brookmeyer and Crowley method with log-log transformation.
4 Based on Survival Distribution Function estimates from product-limit method.

Overview of product safety and tolerability

Tibsovo® was well tolerated and had an acceptable safety profile (153). Median duration of treatment at the time of latest data cut-off (January 16, 2019) was 3.7 months (range 0.4 to 50.5 months) (153). A total of 109 (64.9%) of the 168 patients in the safety analysis set (SAS) experienced at least one TEAE. The most common TEAEs (≥ 5%) included fatigue (19%), nausea (17.3%), diarrhea (14.9%), vomiting (8.9%), ECG QT prolonged and decreased appetite (6.5% each), and anemia (5.4%) (157).

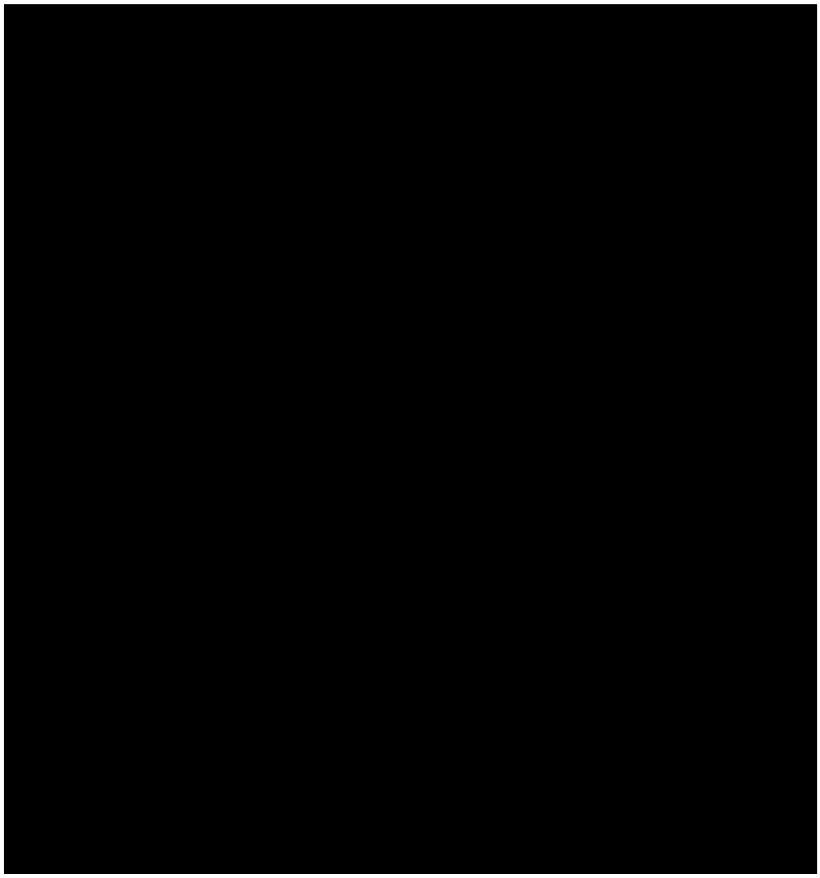
10.3 Comparative effectiveness

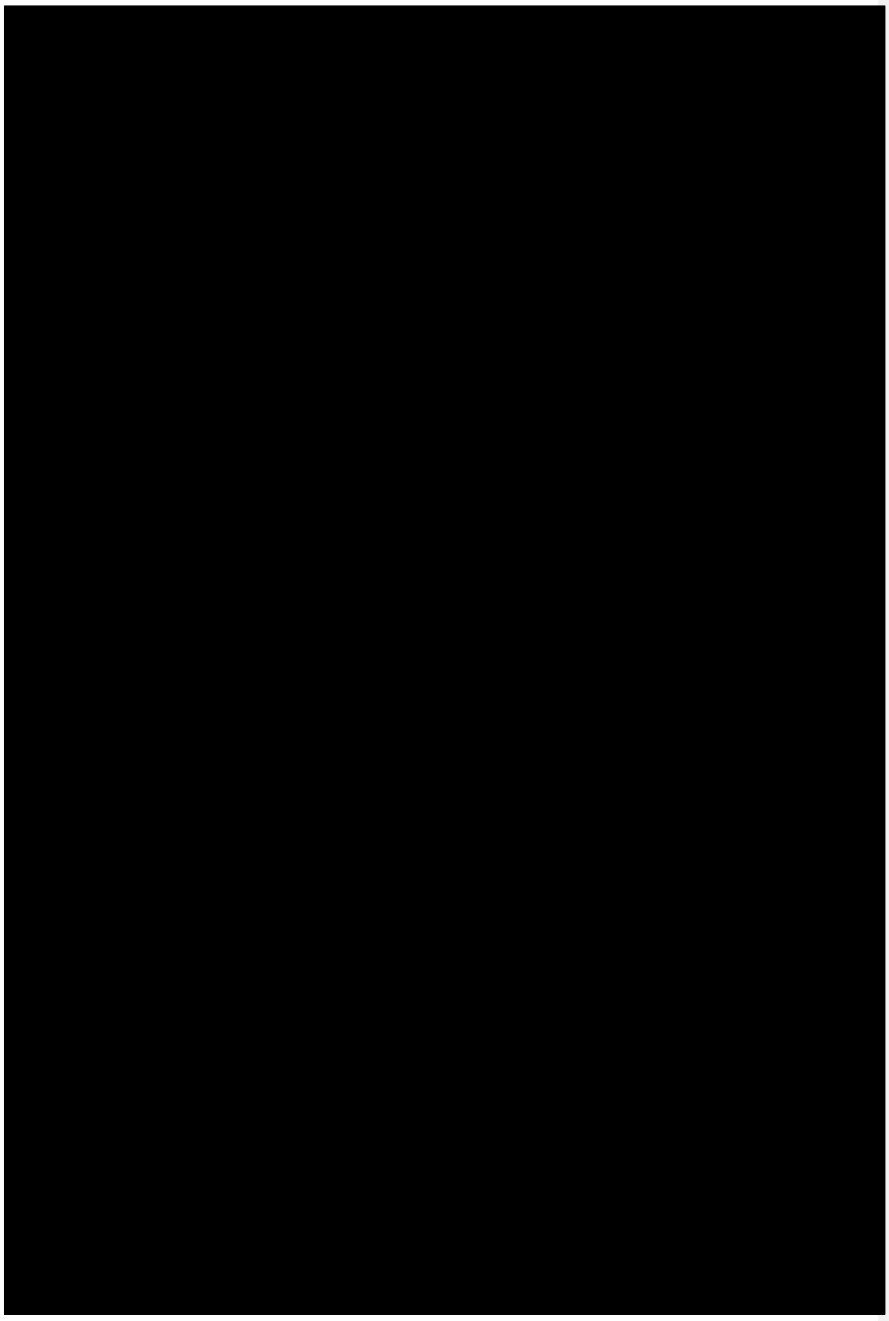
10.3.1 Evidence base and included studies

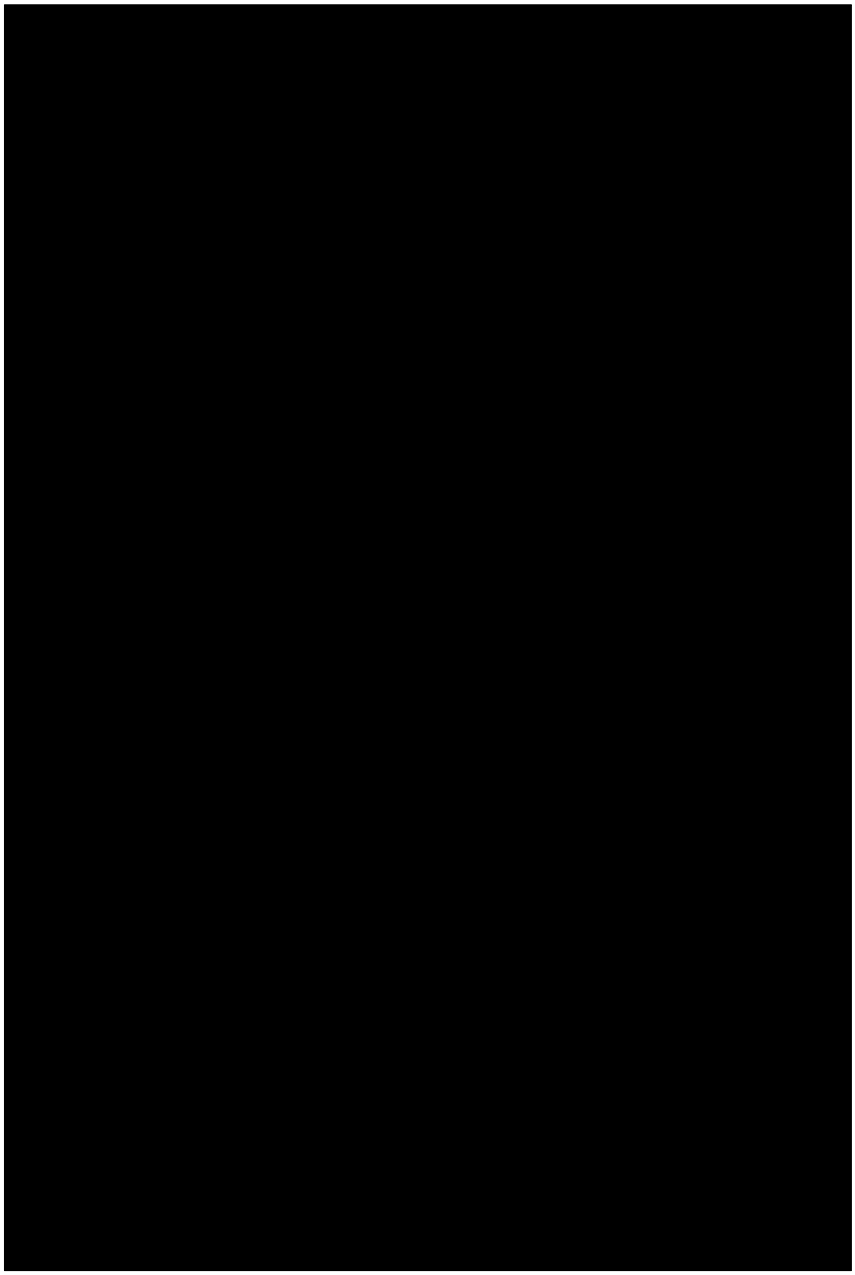
An SLR was conducted to identify relevant clinical studies for evidence synthesis of efficacy and safety outcomes. The SLR was conducted in accordance with the general recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (158), the general principles of the CRD (University of York) guidance (159) for undertaking reviews in health care, PRISMA guidelines (160) and the methods for systematic reviews as specified by NICE (161).

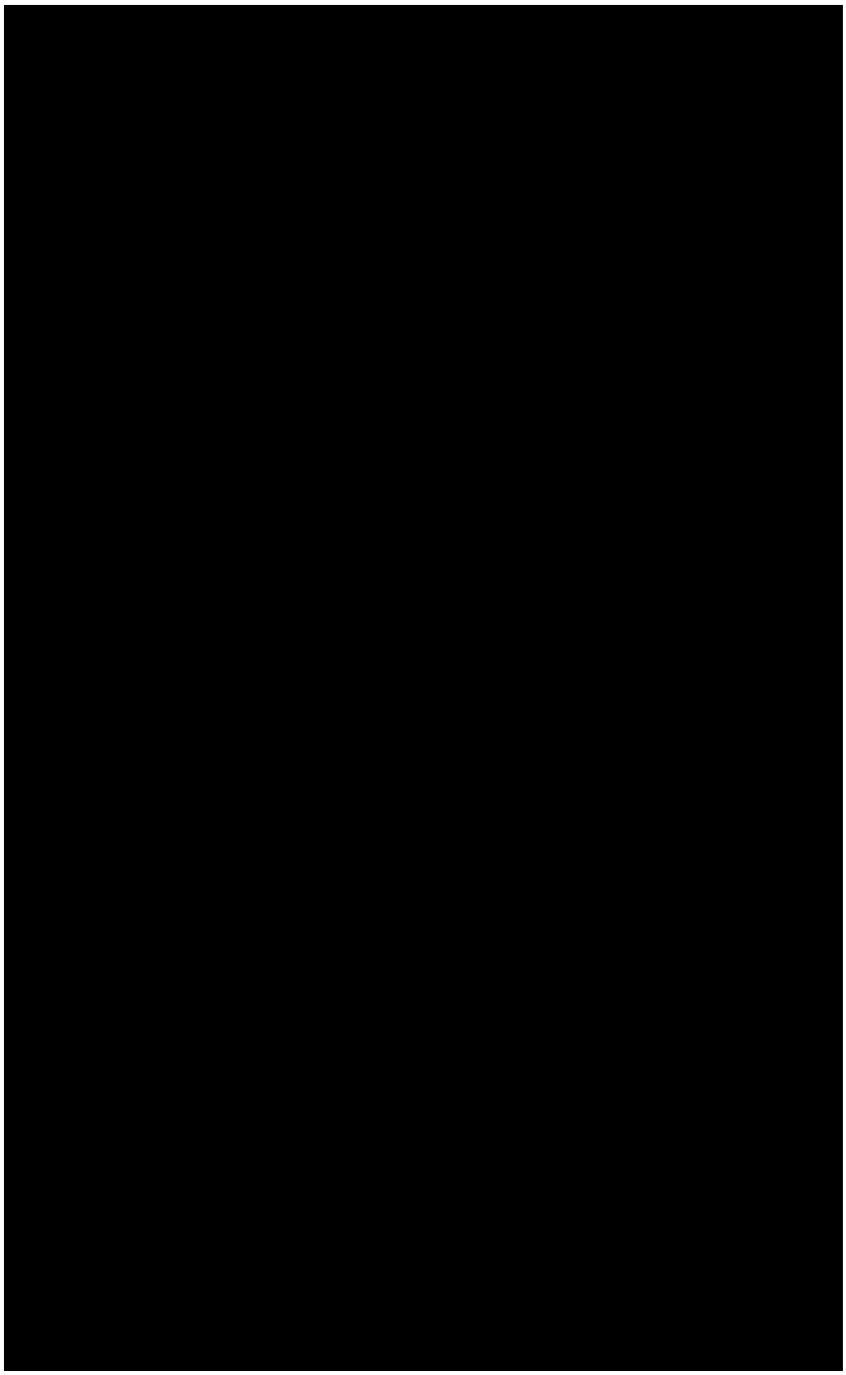
A total of 6,023 references were identified from electronic databases searches (MEDLINE®: 1,212; Embase®: 3,860; CENTRAL®: 951). After removing duplicates, assessment for inclusion according to study eligibility criteria and identifying studies via hand searches 142 studies were identified. Following screening of the 142 included studies against the ITC eligibility criteria, 12 unique studies in total (including ClarIDHy) were included in the ITC feasibility assessment.

10.3.2 ITC feasibility assessment









[redacted]

10.3.3 Additional outcomes

10.3.3.1 [redacted]

10.3.3.1. [redacted]

[redacted]

Table 24. Baseline characteristics in the ClarIDHy trial before and after matching to ABC-06 population for OS (anchored MAIC)

Analysis	Baseline characteristic	ClarIDHy IPD pre-matching	ClarIDHy IPD post-matching	ABC-06
BC	Age: ≥65 (%)	[redacted]	[redacted]	[redacted]
	Gender: Male (%)	[redacted]	[redacted]	[redacted]
	ECOG PS: 0 (%)	[redacted]	[redacted]	[redacted]
	Extent of disease at screening: Metastatic (%)	[redacted]	[redacted]	[redacted]
SA	Age: ≥65 (%)	[redacted]	[redacted]	[redacted]
	Gender: Male (%)	[redacted]	[redacted]	[redacted]
	ECOG PS: 0 (%)	[redacted]	[redacted]	[redacted]
	Extent of disease at screening: Metastatic (%)	[redacted]	[redacted]	[redacted]
	CCA subtypes (%) iCCA	[redacted]	[redacted]	[redacted]
	CCA subtypes (%) eCCA	[redacted]	[redacted]	[redacted]

Abbreviations: BC, base case; CCA, cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; IPD, individual patient data; OS: overall survival; SA, scenario analysis.

The weights assigned to patients in the ClarIDHy trial were rescaled to aid interpretation and were represented by histograms as shown in Figure 20 and Figure 21.

In the base case, the rescaled weights were lower than three, suggesting that no patient was excessively upweighted in the matching process. In the scenario analysis, the distribution of the rescaled weights is skewed to the right, with several patients having been assigned a rescaled weight of more than ten, while the majority had an assigned weight close to zero. This disproportion in weights explains the difference in the ESS between the two scenarios. The starting sample was XXX and the ESS was estimated to be [redacted] and [redacted] corresponding to [redacted] and [redacted] of the starting sample sizes for base case and scenario analysis, respectively.

Figure 20. Distribution of rescaled weights after matching the ClarIDHy trial to ABC-06 population for OS: Base case

Abbreviation: OS, Overall survival.

Figure 21. Distribution of rescaled weights after matching the ClarIDHy trial to ABC-06 population for OS: Scenario analysis

Abbreviation: OS, Overall survival.

10.3.3.2 MAIC (unanchored)

10.3.3.2.1 Population matching process

[redacted]

Table 25. Baseline characteristics in the ClarIDHy trial before and after matching to ABC-06 population for PFS (unanchored MAIC)

Analysis	Baseline characteristic	ClarIDHy IPD pre-matching	ClarIDHy IPD post-matching	ABC-06
BC	Age: ≥65 (%)	[redacted]	[redacted]	[redacted]
	Gender: Male (%)	[redacted]	[redacted]	[redacted]
	ECOG PS: 0 (%)	[redacted]	[redacted]	[redacted]
	Extent of disease at screening: Metastatic (%)	[redacted]	[redacted]	[redacted]
SA	Age: ≥65 (%)	[redacted]	[redacted]	[redacted]
	Gender: Male (%)	[redacted]	[redacted]	[redacted]
	ECOG PS: 0 (%)	[redacted]	[redacted]	[redacted]
	Extent of disease at screening: Metastatic (%)	[redacted]	[redacted]	[redacted]
	CCA subtypes (%) iCCA	[redacted]	[redacted]	[redacted]
	CCA subtypes (%) eCCA	[redacted]	[redacted]	[redacted]

Abbreviations: BC, base case; CCA, cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; IPD, individual patient data; PFS: progression-free survival; SA, scenario analysis.

Table 26. Baseline characteristics in the ClarIDHy trial before and after matching to ABC-06 population for ORR (unanchored MAIC)

Analysis	Baseline characteristic	ClarIDHy IPD pre-matching	ClarIDHy IPD post-matching	ABC-06
BC	Age: ≥65 (%)	[redacted]	[redacted]	[redacted]
	Gender: Male (%)	[redacted]	[redacted]	[redacted]
	ECOG PS: 0 (%)	[redacted]	[redacted]	[redacted]
	Extent of disease at screening: Metastatic (%)	[redacted]	[redacted]	[redacted]
SA	Age: ≥65 (%)	[redacted]	[redacted]	[redacted]
	Gender: Male (%)	[redacted]	[redacted]	[redacted]
	ECOG PS: 0 (%)	[redacted]	[redacted]	[redacted]
	Extent of disease at screening: Metastatic (%)	[redacted]	[redacted]	[redacted]

Analysis	Baseline characteristic	ClarIDHy IPD pre-matching	ClarIDHy IPD post-matching	ABC-06
	CCA subtypes (%) iCCA	[redacted]	[redacted]	[redacted]
	CCA subtypes (%) eCCA			

Abbreviations: BC, base case; CCA, cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; IPD, individual patient data; PFS: progression-free survival; SA, scenario analysis.

The weights assigned to patients in the ClarIDHy trial were rescaled to aid interpretation and were represented by histograms as shown in Figure 22.

In the base case, the rescaled weights were lower than [redacted] for both PFS and ORR, suggesting that no patient was excessively upweighted in the matching process. In the scenario analysis, the distribution of the rescaled weights is skewed to the right, with several patients having been assigned a rescaled weight of more than [redacted], while the majority had an assigned weight close to zero. This disproportion in weights explains the difference in the ESS between the two scenarios. The starting sample was [redacted] for PFS, and the ESS was estimated to be [redacted] corresponding to [redacted] and [redacted] of the starting sample sizes for base case and scenario analysis, respectively. Similarly, for ORR the starting sample was [redacted], and the ESS was estimated to be [redacted] ([redacted] of the starting sample sizes) for base case and scenario analysis, respectively.

Figure 22. Distribution of rescaled weights after matching the ClarIDHy trial to ABC-06 population for PFS: Base case

[redacted]

Abbreviation: PFS, Progression free survival.

Figure 23. Distribution of rescaled weights after matching the ClarIDHy trial to ABC-06 population for ORR: Base case

[redacted]

Abbreviation: ORR: Overall/objective response rate.

Figure 24. Distribution of rescaled weights after matching the ClarIDHy trial to ABC-06 population for PFS: Scenario analysis

Abbreviation: PFS, Progression free survival.

Figure 25. Distribution of rescaled weights after matching the ClarIDHy trial to ABC-06 population for ORR: Scenario analysis

Abbreviation: ORR: Overall/objective response rate.

10.3.3.3 Bucher analysis

10.3.3.3.1 OS

The primary analysis of OS followed the intent-to-treat principle, which does not account for the effect of crossover adjustment (41). 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 Tibsovo® is the same for all individuals, regardless of when treatment is received (177-179). Table 27 shows the results for OS before and after crossover adjustment.

Table 27. Bucher analysis results for OS

Analysis	HR (95% CI)	P-value
Unadjusted		
ClarIDHy (Tibsovo® vs Placebo)	[redacted]	[redacted]
ABC-06 (FOLFOX + ASC vs ASC)	[redacted]	[redacted]
Tibsovo® vs FOLFOX +ASC	[redacted]	[redacted]
Crossover adjustment		
ClarIDHy (Tibsovo® vs Placebo)	[redacted]	[redacted]
ABC-06 (FOLFOX + ASC vs ASC)	[redacted]	[redacted]
Tibsovo® 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.

[redacted]

10.3.4 ITC limitations

The main limitation of this analysis is the lack of IDH1-specific outcome data and baseline characteristics as well as the inclusion of BTC patients in the baseline characteristics of ABC-06. Furthermore, even though these trials provided CCA-specific results for the endpoints of interest (PFS, OS and ORR) the KM curves available from ABC-06 were not specific to CCA patients and included BTC patients. For this reason an additional subgroup analysis will be conducted containing KM curves with CCA patients only, in order to address this limitation. Moreover, the MAICs have some limitations, both intrinsic to the methodology and specific to these analyses. Unanchored MAICs rely on the assumption of constancy of the absolute effects, which is much stronger than the assumption imposed by anchored MAICs, the latter of which was only feasible for the OS comparison between ClarIDHy and ABC-06 (i.e., constancy of the relative effects) (181).

The implication is that in unanchored MAICs all prognostic variables and effect modifiers must be known, observed, and adjusted for to obtain unbiased relative effect estimates (172). This assumption is generally regarded as infeasible and, given that a MAIC cannot adjust for unobserved or unknown variables, results are likely to be affected by bias and should be interpreted with caution. Additionally, regarding the Bucher analysis, 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 EMs (i.e., study and patient characteristics that have an independent influence on treatment outcome).

Although population matching was successful, a considerable amount of the derived weights assigned to patients was extreme – often above 10 –, thus making these patients highly influential and leading to very low effective sample sizes in all scenarios. In addition, due to the relatively low sample size in ClarIDHy the matching processes generally resulted in low effective sample sizes (with sample size reductions ranging from 23% to 88%). As a result, wide confidence intervals were observed, and statistically significant results were only found in one analysis (OS outcome in the anchored comparison versus ABC-06). Therefore, the results of these analyses should be interpreted with caution in light of the uncertainty surrounding the point estimates.