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.

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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.

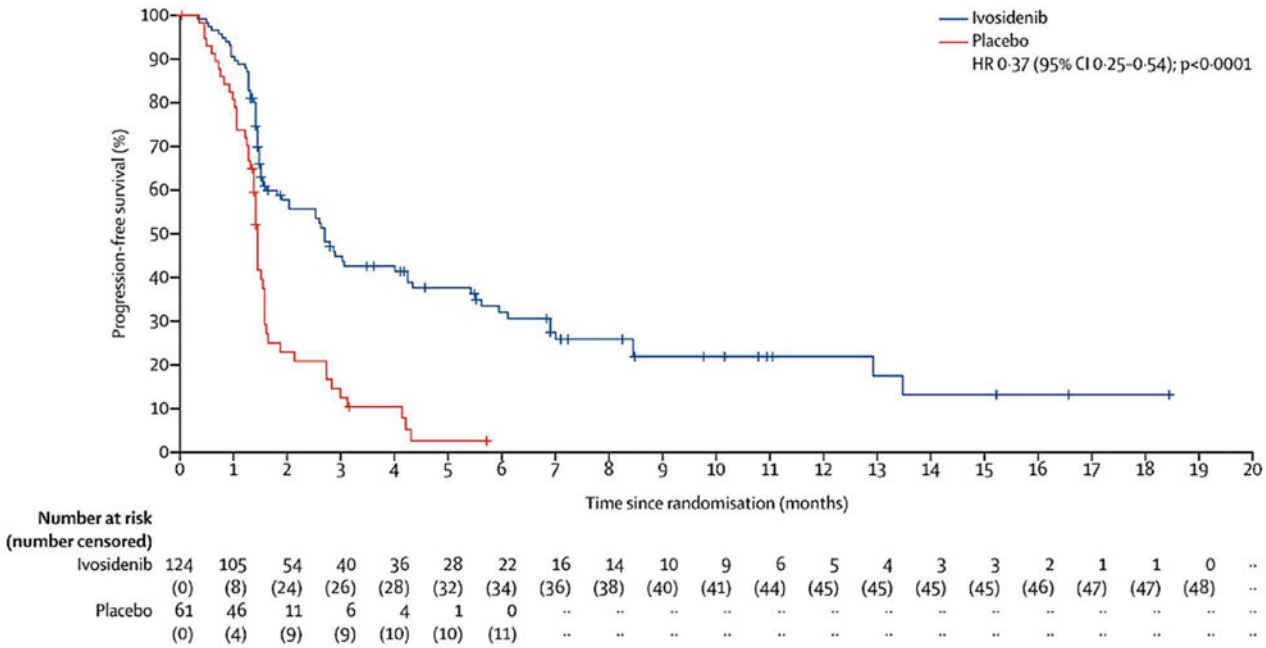


Figure 1 PFS KM curve for ClarIDHy, January 31, 2019 data cut off (9).

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

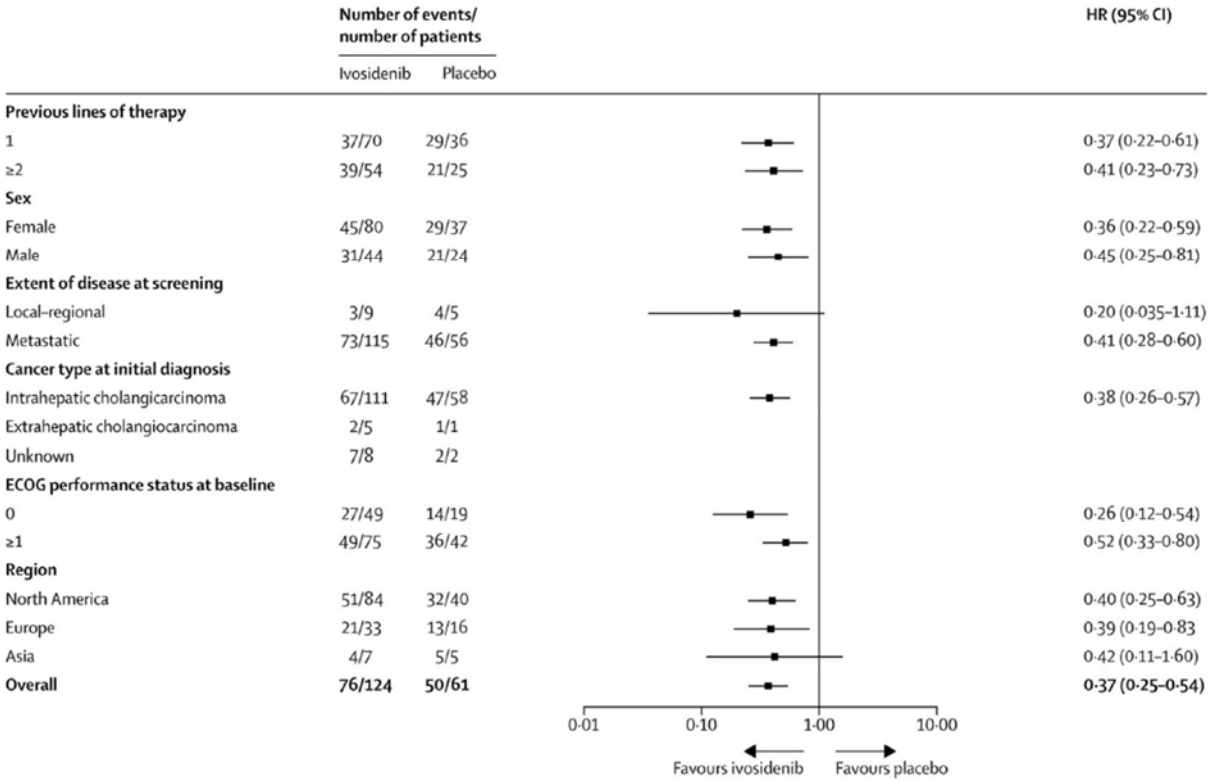


Figure 2 Forest plot of PFS HRs for key subgroups from ClarIDHy, January 31, 2019 data cut off (9).

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.

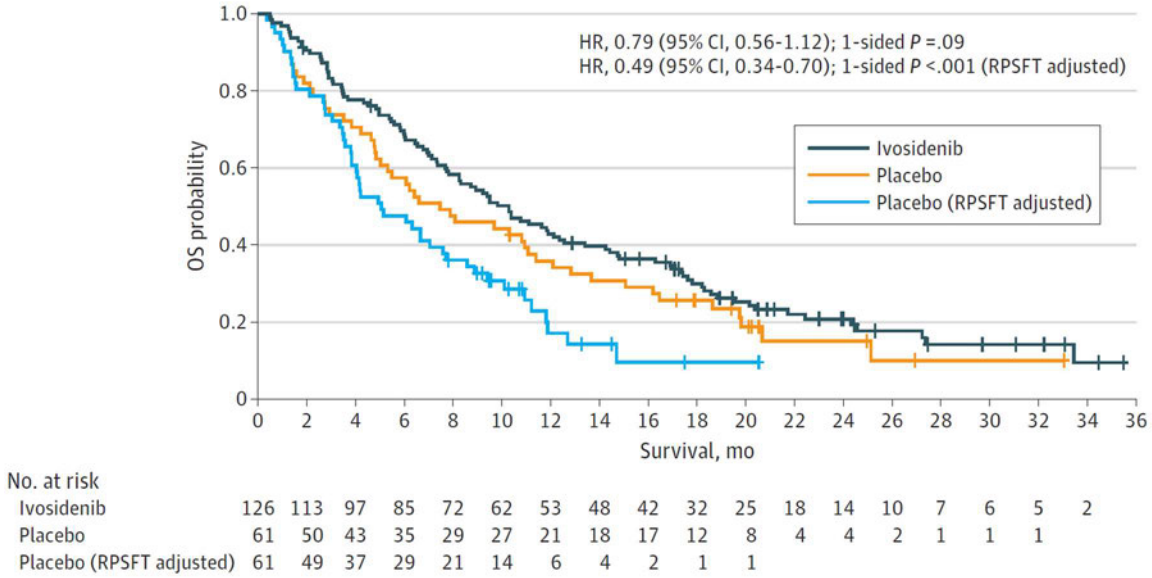


Figure 3 OS KM curve for ClarIDHy, May 31, 2020 data cut off (8).

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.

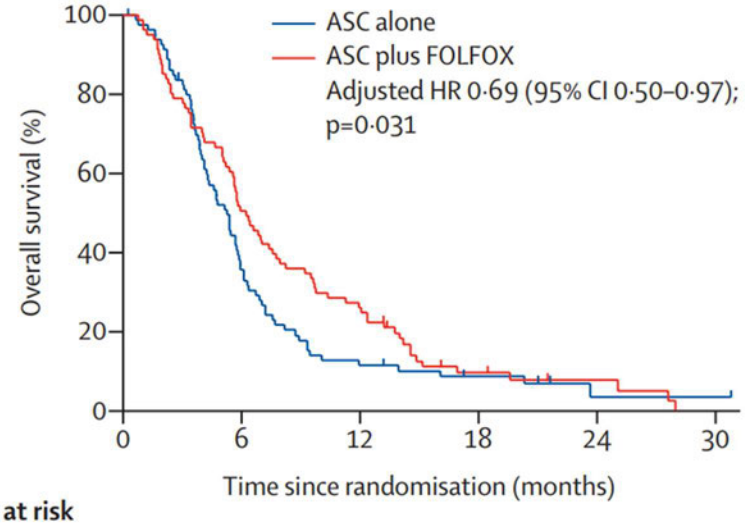
3.3 Indirect comparisons of Tibsovo vs. FOLFOX

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.

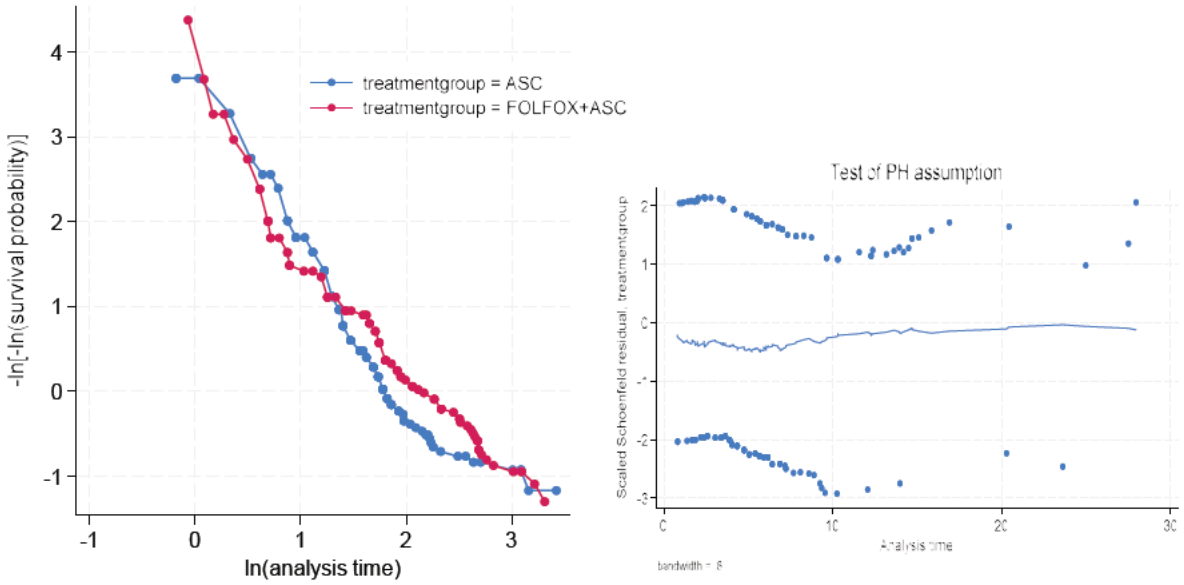


Figure 5 Log cumulative hazard plot (left) and Shoenfeld residual plot (right) for FOLFOX + ASC vs ASC (based on ABC-06 published OS KM curves (10)). Analysis performed by JNHB using Stata 18.0.

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.

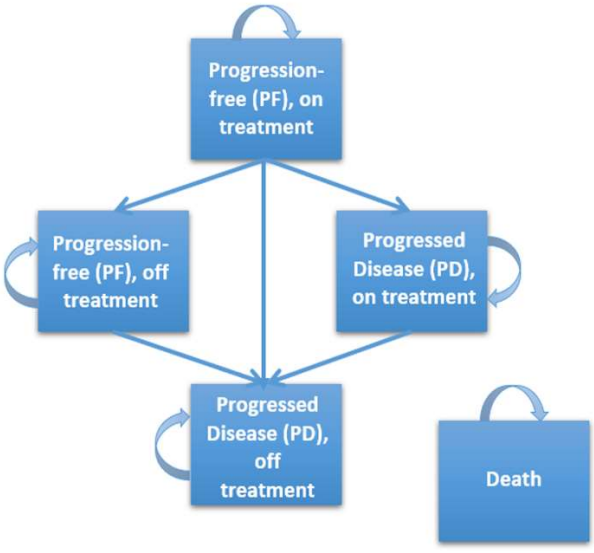


Figure 6 Servier's health economic model

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.

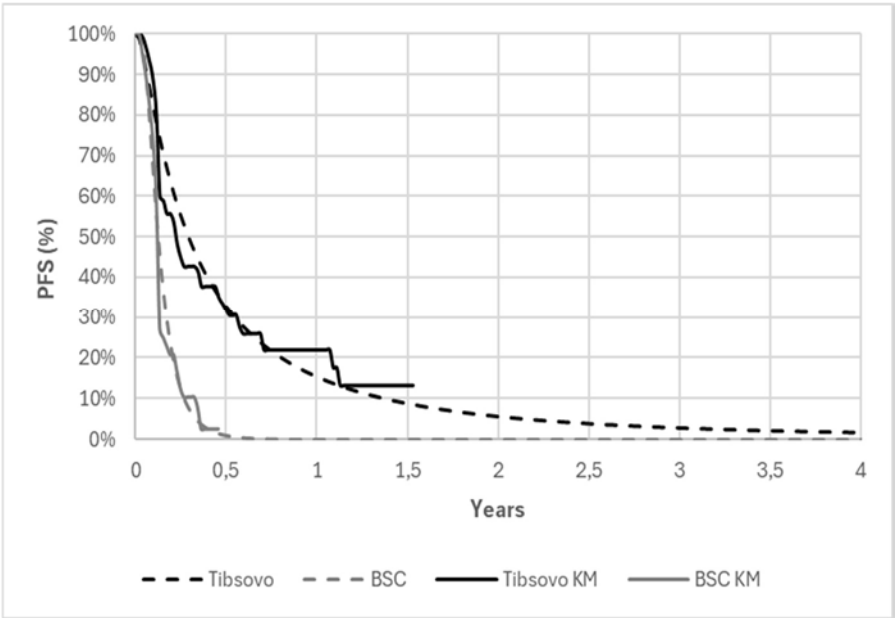


Figure 7 KM estimates from ClarIDHy and extrapolation of PFS in Servier's base case (versus BSC); jointly fitted log-normal curves

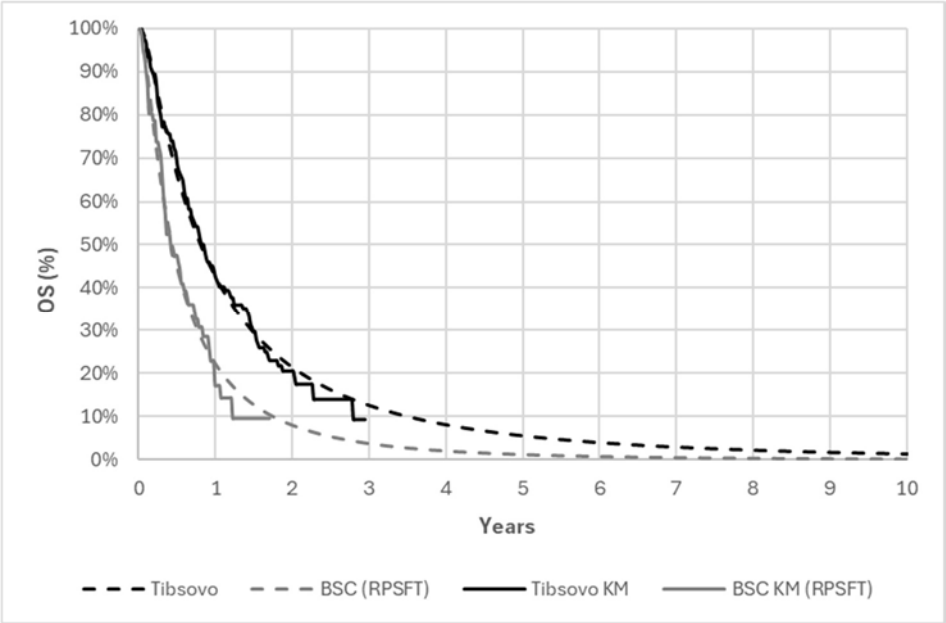


Figure 8 KM estimates from ClarIDHy and extrapolation of OS in Servier's base case (versus BSC); jointly fitted log-normal curves

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).

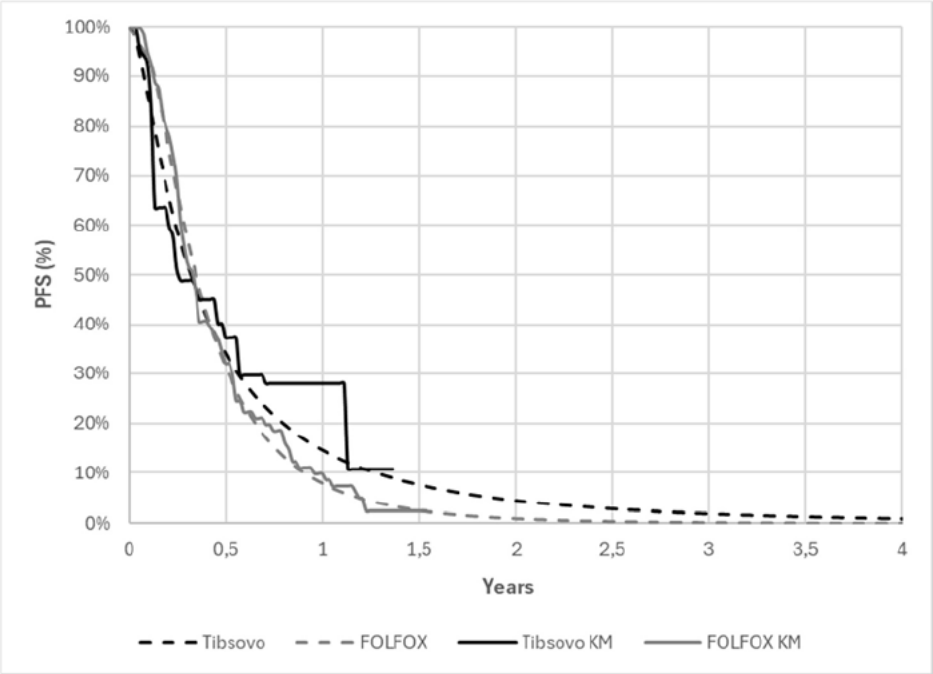


Figure 9 KM estimates from ClarIDHy and ABC-06 and extrapolation of PFS in Servier's case (versus FOLFOX); independently fitted log-normal curves

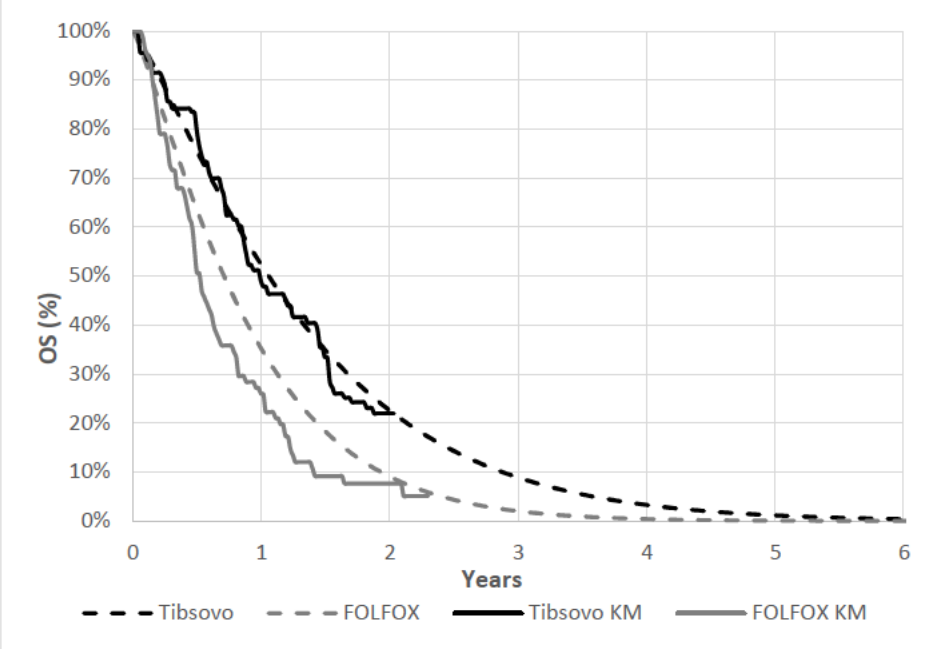


Figure 10 KM estimates from ClarIDHy and ABC-06 and extrapolation of OS in Servier's base case (versus FOLFOX); jointly fitted Weibull curves

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).

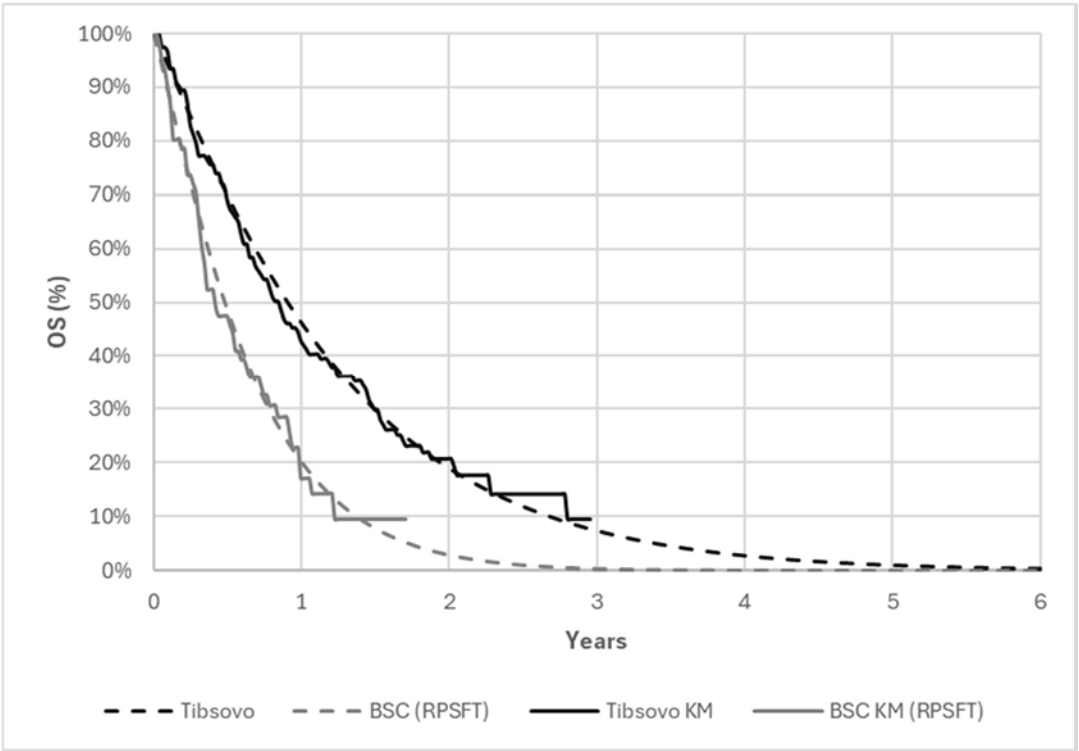


Figure 11 KM estimates from ClarIDHy and extrapolation of OS in JNHB base case (versus BSC); jointly fitted Weibull curves

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.

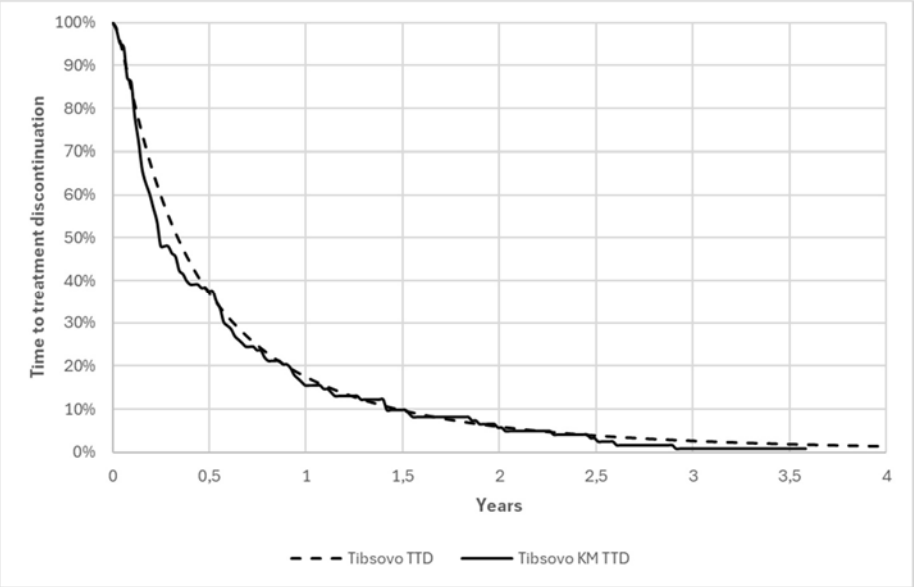


Figure 12 KM from ClarIDHy and extrapolation of TTD for Tibsovo (vs BSC) in Servier's base case

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 [redacted] in Finland and Norway respectively, [redacted] in Denmark and [redacted] in Sweden. This equals a total of [redacted] 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

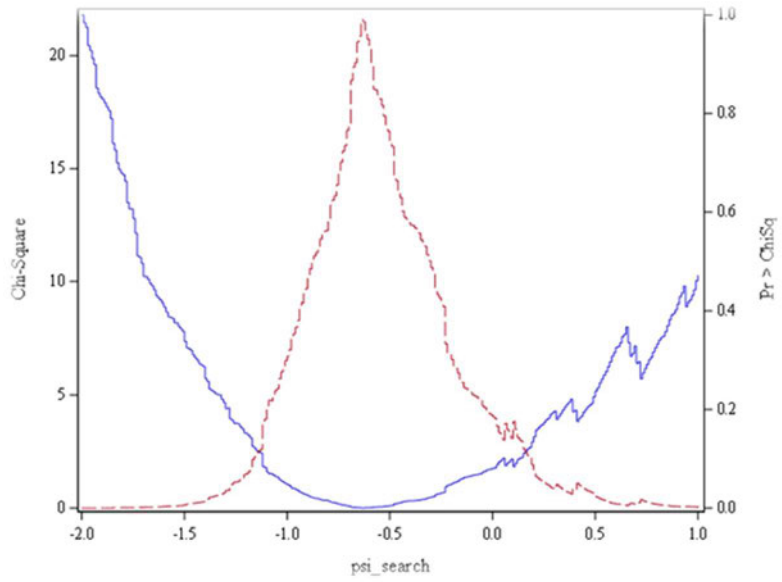
	N	Median OS (95% CI)
Tibsovo	126	10.3 (7.8, 12.4)
Placebo switchers	43	9.1 (5.4, 13.5)

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.

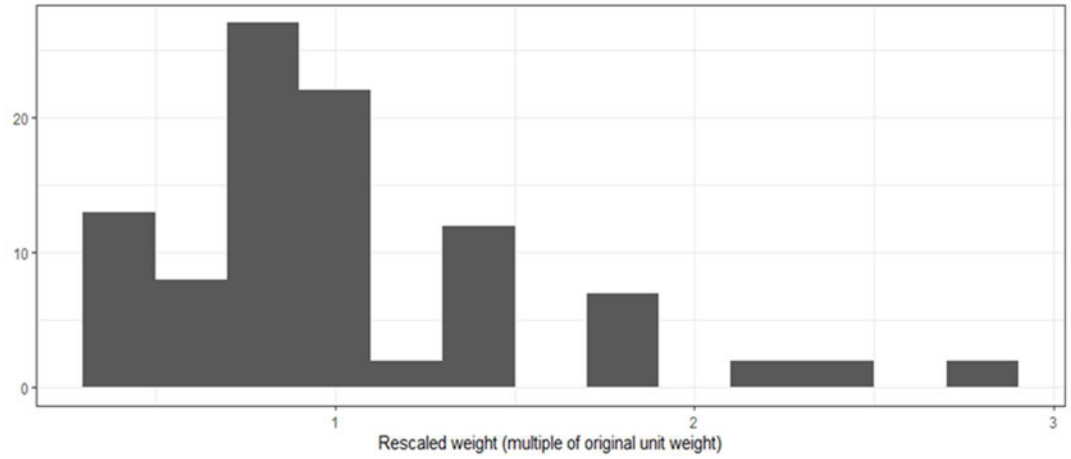


Figure 13 Distribution of rescaled weights after matching the ClarIDHy trial to ABC-06 population for OS: Base case

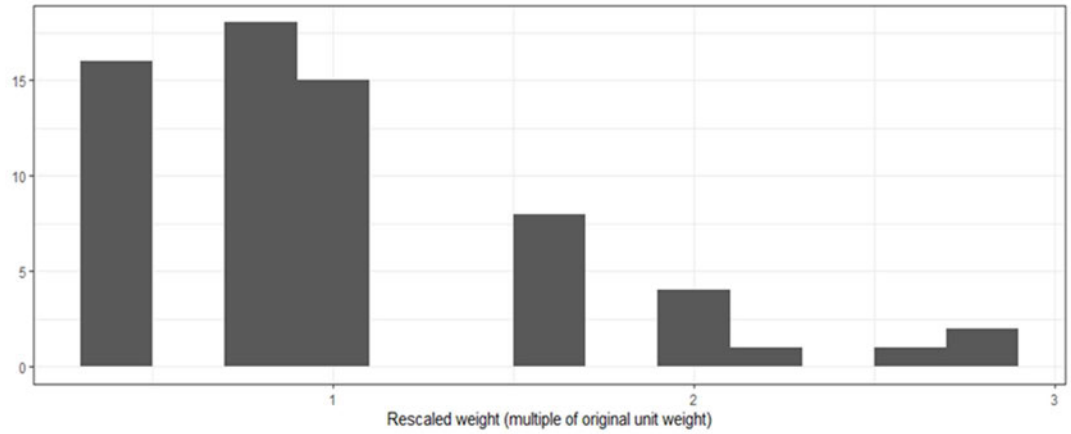


Figure 14 Distribution of rescaled weights after matching the ClarIDHy trial to ABC-06 population for PFS: Base case

Proportional hazard diagnostics

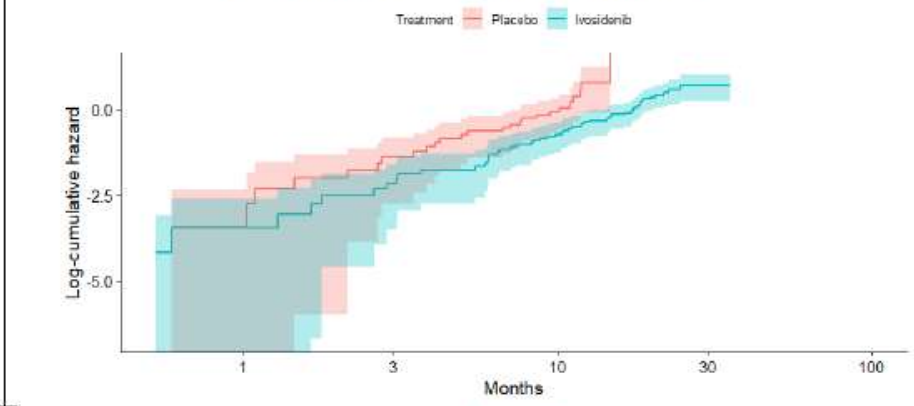
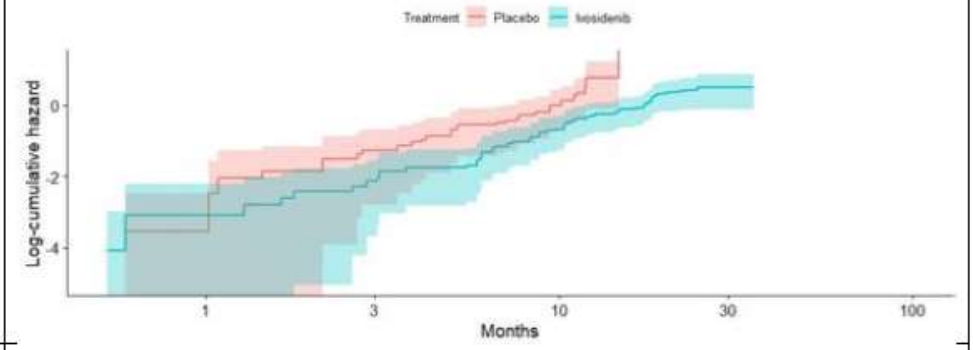
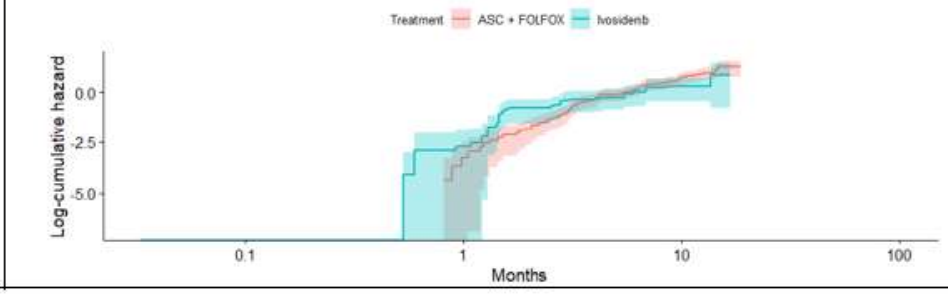
Comparison	Log-cumulative hazard vs log-time plot
OS – Tibsovo vs Placebo within ClarIDHy – Unadjusted	
OS – Tibsovo vs Placebo within ClarIDHy – Anchored MAIC adjusted – Base case analysis	
PFS – Tibsovo vs FOLFOX (ClarIDHy vs ABC-06) – Unanchored MAIC adjusted – Base case analysis	

Figure 15 Proportional hazard diagnostic plots

Results

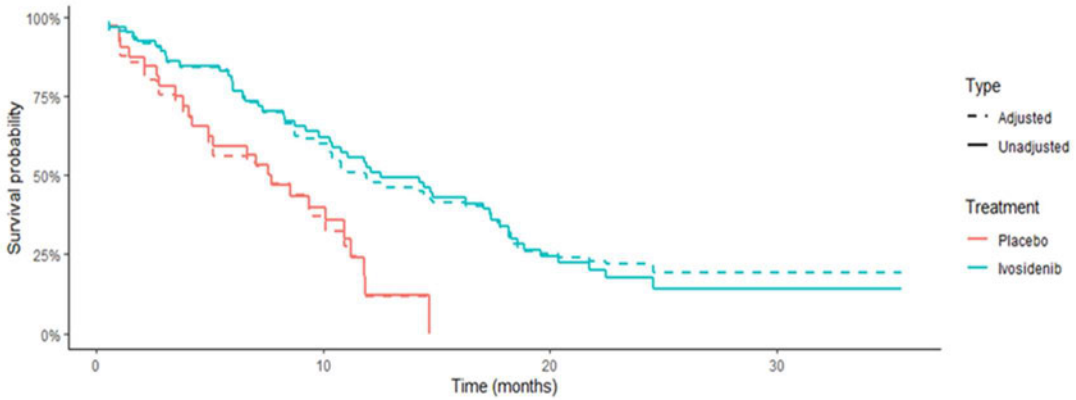
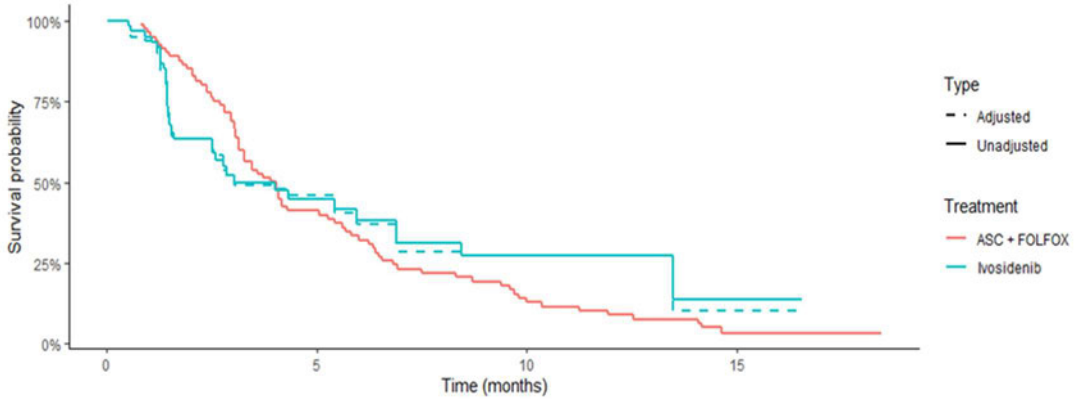


Figure 16 MAIC-adjusted vs unadjusted KM Curve for OS from ClarIDHy

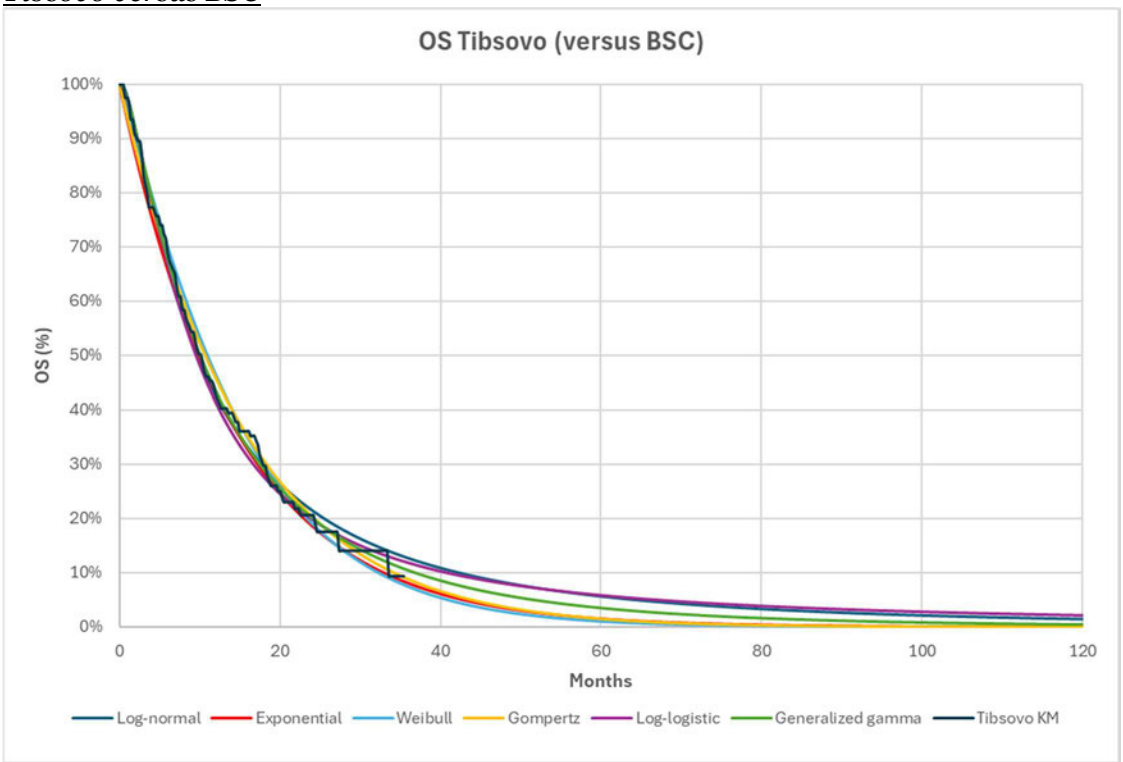


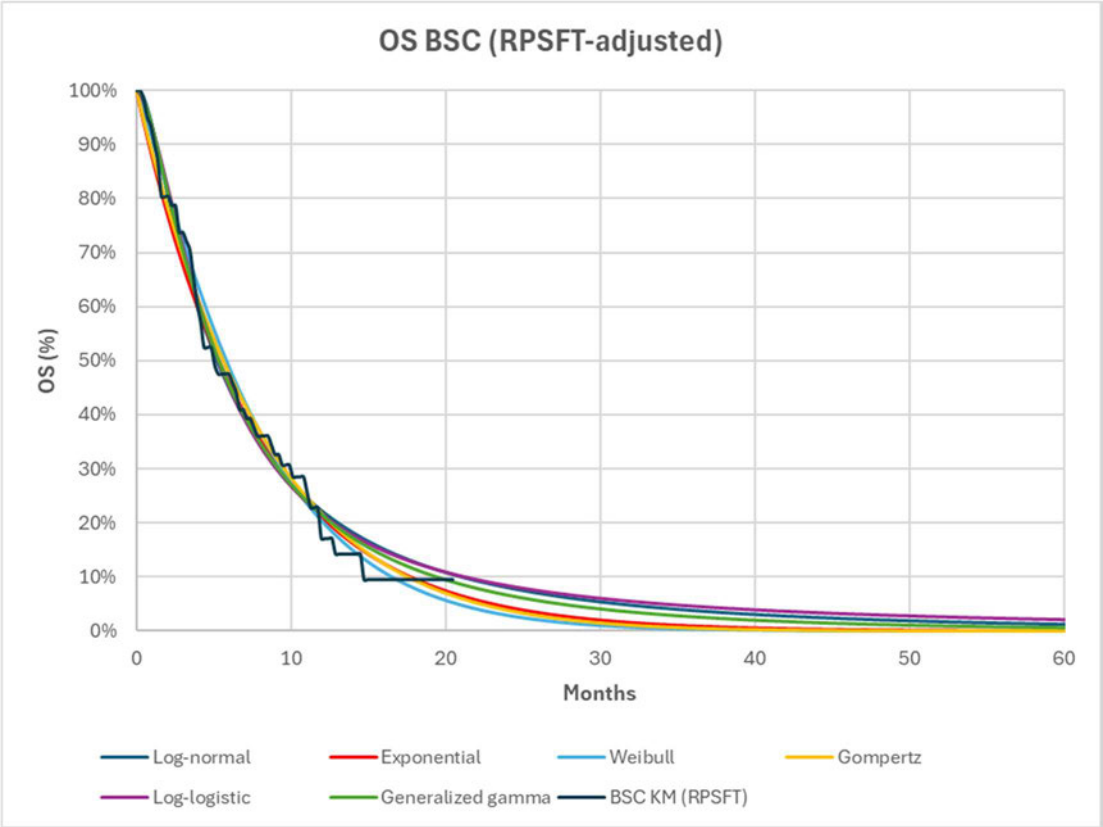
Abbreviations: ASC, Active symptom control; FOLFOX, Folinic acid, fluorouracil, and oxaliplatin; KM, Kaplan-Meier; PFS, Progression-free survival.

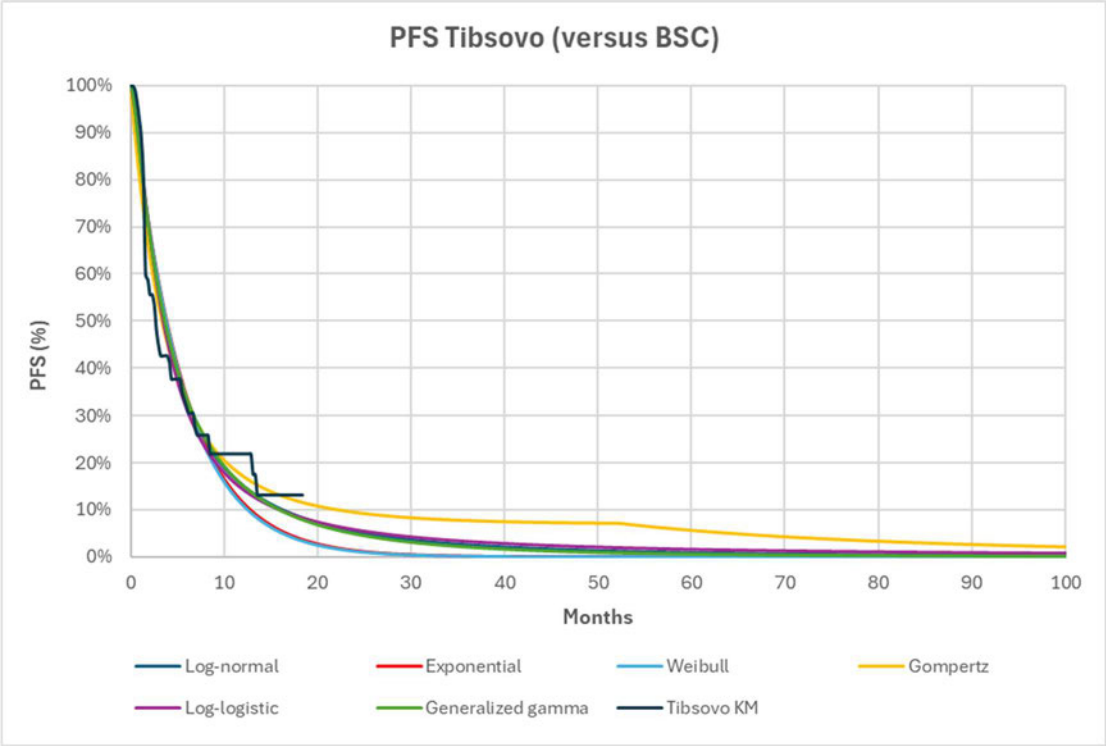
Figure 17 MAIC-adjusted vs unadjusted KM Curve for PFS: based on ClarIDHy and ABC-06

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

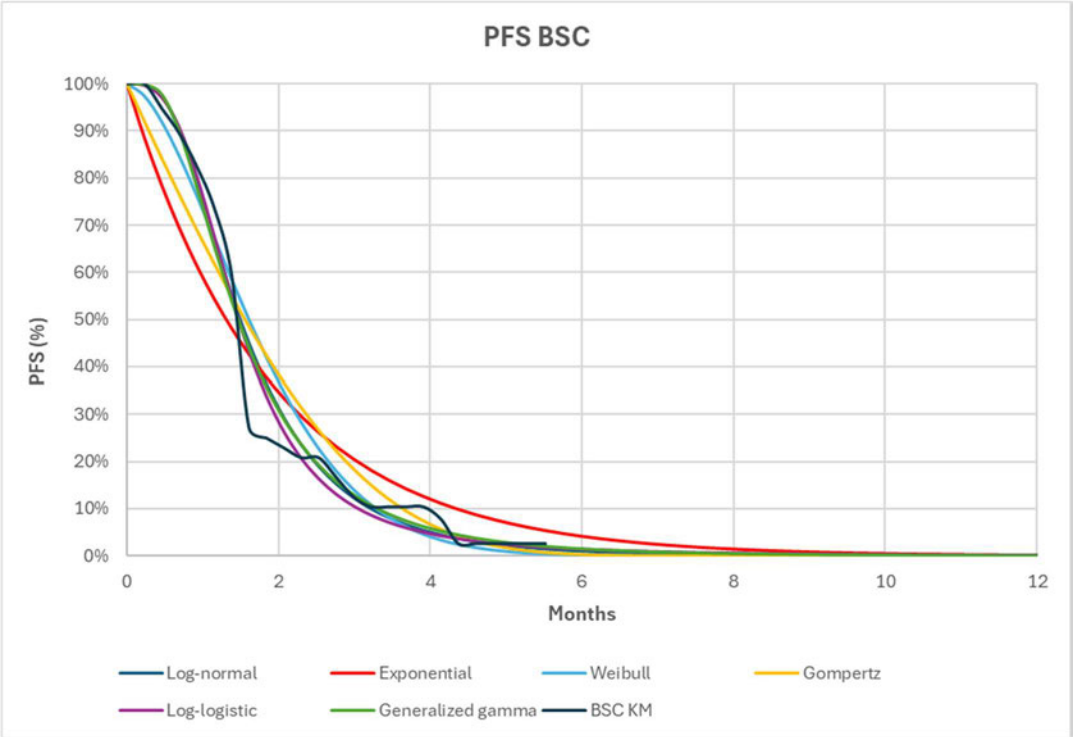


Table 4. AIC and BIC statistics for OS parametric fits (overall population)

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

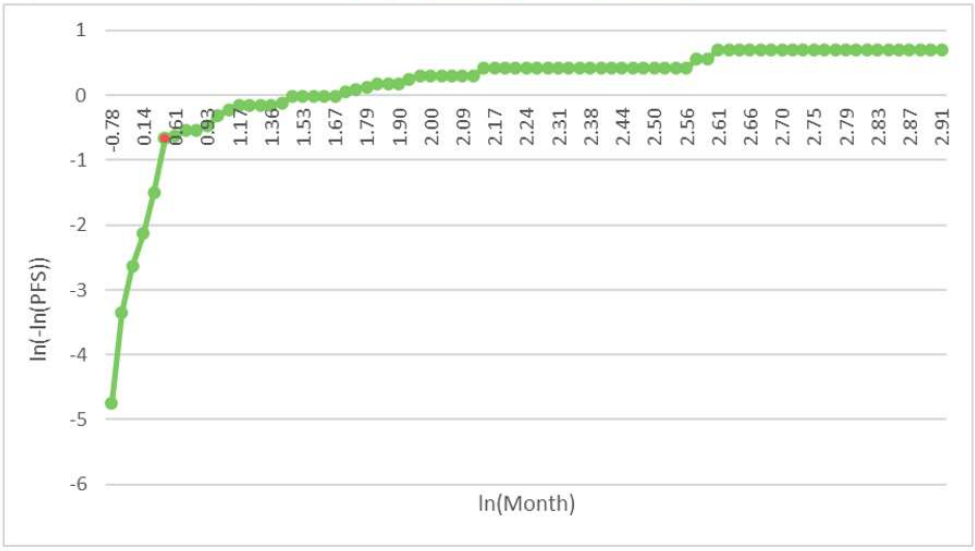
Abbreviations: AIC, Akaike information criterion, BIC, Bayesian information criterion; BSC, best supportive care; OS, overall survival, RPSFT, rank-preserved structural failure time

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

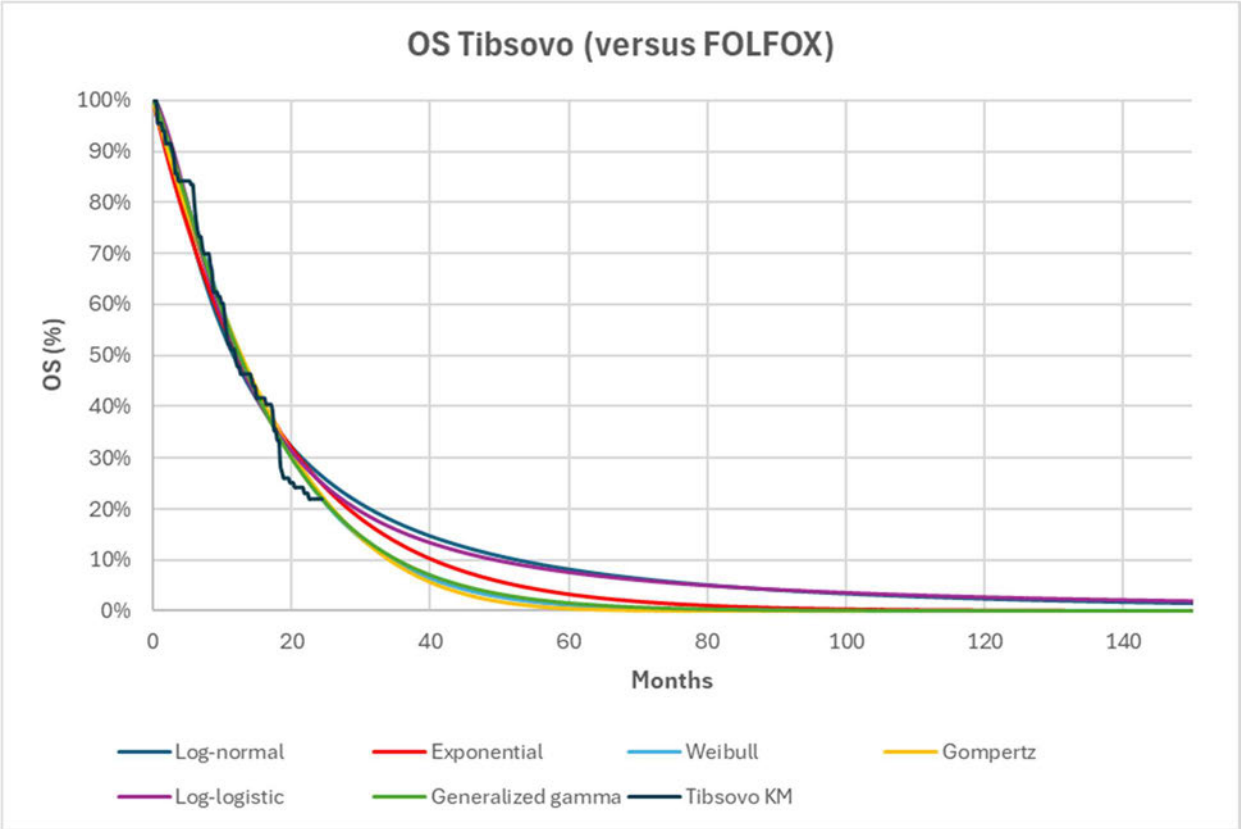


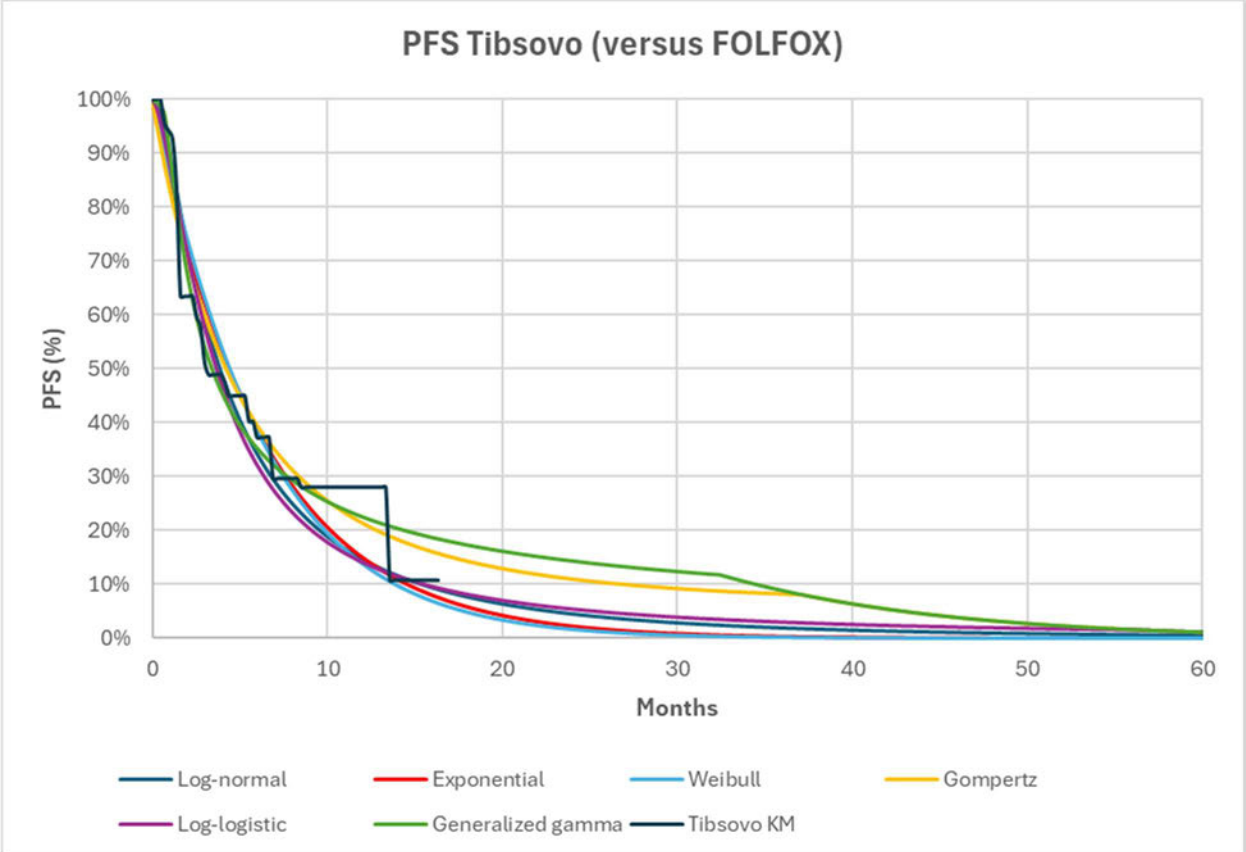
Abbreviations: PFS, progression-free survival

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

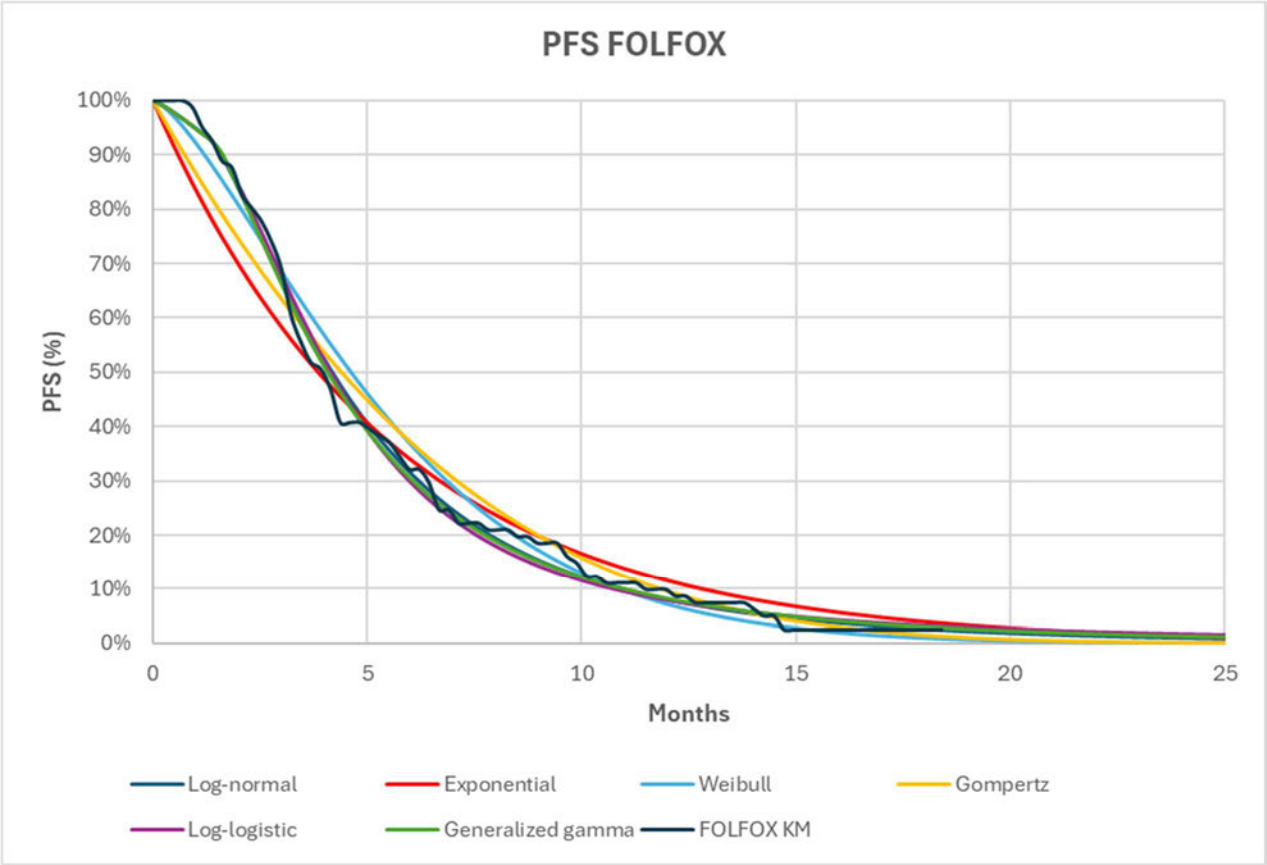


Table 30. AIC and BIC statistics for OS parametric fits (overall population)

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.