Ivosidenib (Tibsovo®) monotherapy for the treatment of locally advanced or metastatic cholangiocarcinoma

General information [1]

Drug description	Indication
Ivosidenib (Tibsovo®, AG-120) is an antineoplastic agent. Ivosidenib inhibits the mutant IDH1 enzyme, which converts alpha-ketoglutarate to 2-hydroxyglutarate. This blocks cellular differentiation and promotes tumorigenesis in both hematologic and non-hematologic malignancies. The mechanism of action of ivosidenib is not fully understood beyond its ability to reduce 2-HG and restore cellular differentiation across indications.	Ivosidenib (Tibsovo®) monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who were previously treated by at least one prior line of systemic therapy.

Incidence [2, 3]

- The incidence of cholangiocarcinoma is relatively low in most high-income countries (0.3-2 cases per 100,000 people) but much higher (even 40-fold greater) in some regions of Thailand and China (where infection with liver flukes - a key determinant of cholangiocarcinoma - is endemic).
- While surgery and liver transplantation are therapeutic options for a small fraction of patients, the prognosis of cholangiocarcinoma is dramatically poor, with 95% of patients dying within 5 years.
- In Austria, the age-standardised mortality rate in men was 1.73/100,000 (ICC) and 0.76/100,000 (ECC); the rate in women was 0.98/100,000 (ICC) and 0.54/100,000 (ECC) in 2016.
- The average age at diagnosis for people with intrahepatic bile duct cancer is 70; for extrahepatic bile duct cancer, the average age at diagnosis is 72.

Current treatment [4]

- **For the treatment of advanced or metastatic disease, the current ESMO guideline (2023)[1] recommends the following:**
  - **First-line treatment**
    - Cisplatine-gemcitabine is recommended as SoC in the first-line setting for patients with a PS of 0-1 (I, A).
    - The combination of cisplatine-gemcitabine with durvalumab should be considered in first-line BTC (I, A; ESMO-MCBS v1.1 score: 4).
    - Oxaliplatin may be substituted for cisplatin when renal function is of concern (II, B).
    - Gemcitabine monotherapy may be used in patients with a PS of 2 (IV, B).
  - **Second- and later-line treatment**
    - FOLFOX is the SoC in the second-line setting after cisplatine-gemcitabine (I, A; ESMO-MCBS v1.1 score: 1; no specific licensed indication in BTC).
    - Ivosidenib is recommended for the treatment of patients with CCA and IDH1 mutations who have progressed after ≥1 prior line of systemic therapy (I, A; ESMO-MCBS v1.1 score: 2; ESCAT score: I-A; FDA approved, not EMA approved).
    - FGFR inhibitors are recommended for the treatment of patients with FGFR2 fusions who have progressed after ≥1 prior line of systemic therapy (III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-B).
    - Pembrolizumab is recommended in patients with MSI-H/dMMR who have progressed on or are intolerant to prior treatment (III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C).
    - Dabrafenibe-trametinib is recommended for the treatment of patients with BRAFV600E mutations who have progressed after ≥1 prior line of systemic therapy (III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-B; FDA approved, not EMA approved).
    - Patients with BRCA1/2 or PALB2 mutations responding to platinum-based therapy can be considered for treatment with PARP inhibitors (V, B; ESCAT score: III-A).
    - NTRK inhibitors are recommended in patients with NTRK fusions who have progressed on or are intolerant to prior treatment (III, A; ESCAT score: I-C). HER2-directed therapies can be considered in patients with the respective genetic alterations who have progressed on or are intolerant to prior treatment (III, A; ESCAT score: I-C).
    - During systemic and locoregional therapy for advanced disease, follow-up should be conducted at a frequency of 8-12 weeks. In addition to imaging with CT or MRI, CA 19-9 or CEA levels may be used to monitor the course of the disease if one or both are known to be secreted (IV, A).
  - **Supportive care**
    - In patients with biliary obstruction, biliary drainage and subsequent treatment should be carried out; when endoscopic access is impossible, percutaneous transhepatic drainage is recommended (IV, A). A metal stent is preferred in patients with a life expectancy of >3 months (IV, B).
    - Sepsis secondary to biliary obstruction is common and should be treated promptly (IV, A).
    - Patients should be advised of the likely duration of stent patency and symptoms and signs indicative of biliary obstruction or infection (V, A).

Regulatory status

[1] The current ESMO guidelines (2023) are in line with the latest version of the Onkopedia guideline (2021, Sinn M et al., Biliäre Karzinome)

EMA [1]	FDA [5, 6]
Approval status for this indication: On 23 February 2023, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Tibsovo® for the following indication: ❖ Tibsovo® monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy. **UPDATE:** Date of issue of marketing authorisation valid throughout the European Union: 04/05/2023 **Other indications**: ❖ Tibsovo®, in combination with azacitidine, is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with a IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy. ✓ **Orphan status** ✓ **Medicine is under additional monitoring**	**Approval status for this indication**: On 25 August 2021, the FDA approved ivosidenib (Tibsovo®) for adult patients with previously treated, locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation as detected by an FDA-approved test. ✓ Priority review ✓ Fast track designation ✓ Orphan product designation The FDA also approved the Oncomine Dx Target Test (Life Technologies Corporation) as a companion diagnostic device to aid in selecting patients with cholangiocarcinoma for treatment with ivosidenib. **Other indications**: Tibsovo® is indicated for patients with a susceptible IDH1 mutation as detected by an FDA-approved test with: ❖ newly diagnosed AML in combination with azacitidine or as monotherapy for treating newly diagnosed AML in adults 75 years or older or with comorbidities that preclude the use of intensive induction chemotherapy. ❖ relapsed or refractory AML. ❖ For the treatment of adult patients with relapsed or refractory myelodysplastic syndromes.

Manufacturer

The manufacturer of Tibsovo® is Servier Pharmaceuticals LLC.

Costs

60 Tibsovo® film-coated tablets 250 mg = € 14,700.00 (ex-factory price) [7]

Posology [8]

- ❖ Treatment should be initiated under the supervision of physicians experienced in the use of anti-cancer medicinal products.
- ❖ Before taking Tibsovo®, patients must have confirmation of an IDH1 R132 mutation using an appropriate diagnostic test.
- ❖ Cholangiocarcinoma
  - 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.
- ❖ Precautions to be taken prior to administration and monitoring
  - An electrocardiogram (ECG) must be performed prior to treatment initiation. Heart rate corrected QT (QTc) should be less than 450 msec prior to treatment initiation and, in the presence of an abnormal QT, practitioners should thoroughly reassess the benefit/risk of initiating ivosidenib. In case QTc interval prolongation is between 480 msec and 500 msec, initiation of treatment with ivosidenib should remain exceptional and be accompanied by close monitoring.
  - An ECG must be performed prior to treatment initiation, at least weekly during the first 3 weeks of therapy and then monthly thereafter if the QTc interval remains ≤ 480 msec. QTc interval abnormalities should be managed promptly. In case of suggestive symptomatology, an ECG should be performed as clinically indicated.
  - Concomitant administration of medicinal products known to prolong the QTc interval, or moderate or strong CYP3A4 inhibitors may increase the risk of QTc interval prolongation and should be avoided whenever possible during treatment with Tibsovo®. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible. An ECG should be performed prior to co-administration, weekly monitoring for at least 3 weeks and then as clinically indicated.
    Complete blood count and blood chemistries should be assessed prior to the initiation of Tibsovo®, at least once weekly for the first month of treatment, once every other week for the second month, and at each medical visit for the duration of therapy as clinically indicated.

Warnings and precautions [5, 8]

- ❖ **Differentiation syndrome in AML**
  - Patients treated with Tibsovo® have experienced symptoms of differentiation syndrome, which can be fatal.

- Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripher edema, hypotension, and hepatic, renal, or multi-organ dysfunction.
- If differentiation syndrome is suspected, initiate corticosteroid therapy an hemodynamic monitoring until symptom resolution.

❖ **QTc interval prolongation**
- Monitor electrocardiograms and electrolytes. If QTc interval prolongation occurs, the dose reduces or withheld, then resume dose or permanently discontinue Tibsovo®.

❖ **Guillain-Barré syndrome**
- Monitor patients for signs and symptoms of new motor and/or sensory findings. Permanently discontinue Tibsovo® in patients who are diagnosed with Guillain-Barré syndrome.

❖ **Severe renal impairment**
- The safety and efficacy of ivosidenib have not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²).
- Tibsovo should be used with caution in patients with severe renal impairment and this patient population should be closely monitored.

❖ **Hepatic impairment**
- The safety and efficacy of ivosidenib have not been established in patients with moderate and severe hepatic impairment (Child-Pugh classes B and C).
- Tibsovo® should be used with caution in patients with moderate and severe hepatic impairment and this patient population should be closely monitored.
- Tibsovo® should be used with caution in patients with mild hepatic impairment (Child-Pugh class A).

❖ **CYP3A4 substrates**
- Ivosidenib induces CYP3A4 and it may, therefore, decrease systemic exposure to CYP3A4 substrates.
- Patients should be monitored for loss of antifungal efficacy if use of itraconazole or ketoconazole cannot be avoided.

❖ **Women of childbearing potential / contraception**
- Women of childbearing potential should have a pregnancy test prior to starting treatment with Tibsovo® and should avoid becoming pregnant during therapy.
- Women of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment with Tibsovo® and for at least 1 month after the last dose. Ivosidenib may decrease the systemic concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended.

❖ **Lactose intolerance**
- Tibsovo® contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should avoid this medicinal product.

❖ **Sodium content**
- This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Study characteristics [9-13]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up for PE	Characteristics	Biomarker	Funding	Publication(s)
ClarIDHyNCT, Study AG120-C-005 NCT02989857	187 (2:1)	oral ivosidenib 500 mg or once daily in continuous 28-day cycles	placebo	PFS by ICR	6.9 months (IQR 2.8–10.9)	multi-centre, randomised, double-blind, placebo-controlled, phase 3 study	IDH1	Agios Pharmaceuticals	ClarIDHy Trial [11]

Inclusion criteria[2]	Exclusion criteria	Patient characteristics at baseline (I vs. C)
❖ Patients ≥18 years of age with histopathological diagnosis consistent with nonresectable or metastatic cholangiocarcinoma who are not eligible for curative resection, transplantation, or ablative therapies. ❖ Documented IDH1 gene-mutated disease based on central laboratory testing. ❖ ECOG PS score of 0 or 1 and expected survival of ≥3 months.	❖ Prior IDH inhibitor. ❖ Systemic anticancer therapy or an investigational agent <2 weeks prior to day 1. ❖ Radiotherapy to metastatic sites of disease <2 weeks prior to day 1. ❖ Hepatic radiation, chemoembolisation, and radiofrequency ablation <4 weeks prior to day 1. ❖ Symptomatic brain metastases requiring steroids. ❖ History of another primary cancer (for exceptions, please see study protocol). ❖ Major surgery within 4 weeks of day 1 or have not recovered from post-surgery toxicities. ❖ Pregnant or breastfeeding women.	❖ Male: 35% vs. 39% ❖ Age: 61 vs. 63 years ❖ EGOG PS 0 or 1: 100% vs. 98% ❖ R132C mutation: 68% vs. 74% ❖ Metastatic disease: 93% vs. 92% ❖ 2 previous lines of therapy: 47% vs. 46%

[2] For complete in- and exclusion criteria, please see trial protocol.

❖ At least one evaluable and measurable lesion as defined by RECIST v1.1. ❖ Documented disease progression following at least 1 and no more than 2 prior systemic regimens for advanced disease. ❖ Patients have recovered from toxicities associated with prior anticancer therapy to baseline unless stabilised under medical management. ❖ Adequate bone marrow function and adequate hepatic function. ❖ Negative serum pregnancy test and effective forms of contraception.	❖ Patients taking known strong cytochrome P450 (CYP) 3A4 inducers or sensitive CYP3A4. ❖ Active infection requiring systemic anti-infective therapy or with an unexplained fever >38.5°C within 7 days of Day 1. ❖ Hypersensitivity to any of the components of AG-120 or the matched placebo. ❖ Significant active cardiac disease within 6 months prior to the start of study treatment. ❖ LVEF <40% by ECHO scan. ❖ Heart-rate corrected QT interval. ❖ Medications that are known to prolong the QT interval. ❖ Active hepatitis B or hepatitis C infections, known positive human immunodeficiency virus antibody results, or acquired immunodeficiency syndrome-related illness. ❖ Active inflammatory gastrointestinal disease, chronic diarrhoea, previous gastric resection or lap band dysphagia, short-gut syndrome, gastroparesis, or other conditions limiting ingestion or gastrointestinal absorption of drugs administered orally.	

Efficacy (I vs. C)	**Safety** (I vs. C)
Analysis cutoff date, 31 January 2019 (n=185)[3]: ❖ At the data cutoff, 57% of patients in the placebo group had **crossed over**[4] to receive open-label ivosidenib. ❖ Lost to follow-up: n=1 vs. n=0 ❖ ITT analysis set: n=124 vs. n=61 **PFS events by IRC assessment**. 61% vs. 82% **Median PFS by IRC assessment**: 2.7 months (95% CI, 1.6–4.2) vs. 1.4 months (1.4–1.6); HR 0.37; 95% CI, 0.25–0.54; one-sided p<0.0001 **PFS at 6 months:** 32% (95% CI, 23–42) vs. 0 **PFS at 12 months**: 22% (95% CI, 13–32) vs. 0 **Median PFS by investigator review:** 2.7 months (95% CI, 1.6–3.6) vs. 1.4 months (1.4–2.5); HR 0.47; 95% CI, 0.33–0.68; p<0.0001; with an overall concordance of 77% for PFS status between investigator and IRC assessment. **Median OS (ITT population):** 10.8 months (95% CI, 7.7–17.6) vs. 9.7 months (4.8–12.1); HR 0.69; 95% CI, 0.44–1.10; p=0.060 **6-month OS rate**: 67% (95% CI, 56–75) vs. 59% (44–71) **12-month OS rate**: 48% (36–59) vs. 38% (22–54) **RPSFT-adjusted median OS**: 6.0 months (95% CI, 3.6–6.3); HR 0.46; 95% CI, 0.28–0.75; p=0.0008 **ORR per IRC assessment**: 2% vs. 0 **Stable disease**: 51% vs. 28%	**Analysis cutoff date, 31 January 2019 (n=185):** **Serious AEs**: n=36/121 (30%) vs. 13/59 (22%) **Treatment-related SAEs**: n=3/121 (2%)[6] vs. 0 **Deaths within 30 days of receiving the last dose:** n=14/121 (12%) vs. n=10/59 (17%) **TEAEs leading to death**: n=4/121 (3%)[7] vs. 0 **Death due to progressive disease**: n=10/121 (8%) vs. n=10/59 (17%) **TEAEs requiring a dose reduction:** n=4/121 (3%) vs. 0 **TEAEs leading to treatment discontinuation**: n=7/121 (6%) vs. n=5/59 (8%) **TRAEs leading to treatment discontinuation**: n=2/121 (2%)[8] **Data cutoff date, 31 May 2020 (n=187):** **TEAEs leading to death:** n=6/123 (5%)[9] **Serious TEAEs:** n=42/123 (34%)[10] vs. n=14/ 59 (24%)[11] **Prolonged QT interval on electrocardiogram**: n=12/123 (10%) vs. n=2/59 (3%) **TEAEs requiring a dose reduction and interruption**: n=5/123 (4%) vs. 0 **TEAEs leading to study drug discontinuation:** n=9/123 (7%) vs. n=5/59 (8%) **Dosimetry of 177Lu-PSMA-617 for the treatment of mCRPC (results from the VISION trial sub-study) [14]:**

[3] Of the remaining patients, 50% had died, 31% were still receiving placebo, 2 never received study drug, 2 withdrew consent, and 1 received another treatment. Among the 121 patients who received ivosidenib, 12% were permitted to continue treatment beyond radiographic progression, as determined by the local investigator. Median duration of treatment: 2.6 months (IQR 1.4–6.0) vs. 1.6 months (1.1–2.7).
[4] Placebo to ivosidenib crossover was permitted on radiological progression per investigator assessment.
[6] Grade 4 hyper bilirubinaemia, grade 3 jaundice cholestatic, grade 2 electrocardiogram QT prolonged, and grade 3 pleural effusion; hyperbilirubinaemia and jaundice cholestatic were recorded for the same patient.
[7] Pneumonia, sepsis, intestinal obstruction, and pulmonary embolism (n=1 each).
[8] Grade 2 generalised oedema and grade 4 hyperbilirubinaemia.
[9] None of which were assessed by the investigator as being associated with treatment, and were considered to be complications associated with the underlying disease or comorbid conditions.
[10] Considered associated with treatment for 3 patients (2%) (grade 4 hyperbilirubinemia, grade 3 cholestatic jaundice, grade 2 prolonged QT interval on electrocardiogram, and grade 3 pleural effusion; hyperbilirubinemia and cholestatic jaundice were observed in the same patient). These patients were the same 3 reported previously.
[11] None were associated with treatment.

Data cutoff date, 31 May 2020, for the final OS analysis (n=187)[5]:

- As of the data cutoff date, 43 patients (70%) initially randomly assigned to receive placebo had crossed over to receive open-label ivosidenib.
- Lost to follow-up: n=1 vs. n=1

Median OS: 10.3 months (95%CI, 7.8-12.4) vs. 7.5 months (95% CI, 4.8-11.1); HR 0.79; 95%CI, 0.56-1.12; 1-sided p= 0.09

RPSFT-adjusted median OS: 5.1 months (95% CI, 3.8-7.6); HR 0.49; 95%CI, 0.34-0.70; 1-sided p< .001

12-month survival rate: 43% (95% CI, 34-51) vs. 36% (95% CI, 24-48)

Baseline covariant analyses:

- All screened patients underwent a determination of variant IDH1 status and identification of covariants in archival formalin-fixed paraffin-embedded samples using a 52-gene next-generation sequencing panel (Oncomine Focus Assay).
- Tumour tissue specimens were collected from 0.3 months up to 7.5 years before randomisation (median, 3.7 months). The most frequent oncogenic covariants found in this data set were PI3KCA (n=20; 11%), KRAS (n=14; 8%), BRAF (n=8; 4%), and FGFR2 (n=8; 4%).
- These findings are consistent with covariant analyses reported previously in a phase 1 study of ivosidenib.
- No significant association between baseline covariants in any single gene and OS, PFS, or treatment duration was observed.

- This dosimetry sub-study aimed to quantify the absorbed dose of 177Lu-PSMA-617 in organs at risk of radiotoxicity due to exposure levels or radiosensitivity.
- Study was performed in a separate cohort of 29 non-randomised participants at four German sites.
- Eligible patients received 177Lu-PSMA-617 (7.4 GBq per cycle) plus SOC every 6 weeks for a maximum of 6 cycles.
- Results:
  - Radiation-absorbed doses per unit activity were highest in the lacrimal glands, followed by the salivary glands, with mean values of 2.1 Gy/GBq (SD 0.47) and 0.63 Gy/GBq (0.36), respectively.
  - The kidneys received 0.43 Gy/GBq (SD, 0.16) and the blood-based red marrow dose was 0.035 Gy/GBq (0.02). The 6-cycle cumulative estimated absorbed dose was 92 Gy (SD, 21) in the lacrimal glands, 28 Gy (16) in the salivary glands, 19 Gy (7.3) in the kidneys and 1.5 Gy (0.90) in the red marrow.
  - In cycle 1, 20% of patients had at least one haematological AE of CTCAE grade ≥ 2; no patient experienced any renal AE of CTCAE grade ≥ 2 or any lacrimal gland toxicity, and 2 patients had a grade 1 salivary gland AE.

177Lu-PSMA-617 dosimetry results in this sub-study were consistent with the published ranges, and cycle 1 AEs affecting at-risk organs were infrequent and of low-to-moderate severity. The findings indicate that patients with mCRPC receiving 177Lu-PSMA-617 should be at low risk of radiation-induced AEs.

Patient-reported outcomes [9-13]

Analysis cutoff date, 31 January 2019 (n=185):

- At baseline, 91% vs. 85% completed the EORTC QLQ-C30 assessment, and 86% vs. 84% completed the QLQ-BIL21 assessment.
- The decline from baseline at cycle 2 day 1 on the EORTC QLQ-C30 physical functioning subscale (higher score denoting better functioning) was significantly less for patients in the ivosidenib group (n=62; least squares mean −3.4; SE 1.81) than for patients in the placebo group (n=20; −13.1; 3.04; difference 9.8; 95% CI, 2.8–16.7; p=0.0059). The decline was clinically meaningful in the placebo arm only.
- Differences in change from baseline for pain and appetite loss subscales were insignificant between groups, and clinically meaningful changes could not be established due to data availability.

Data cutoff date: 31 May 2020 (n=187):

- Ivosidenib preserved QLQ-C30 physical functioning (where a higher score denotes better functioning), whereas patients receiving placebo experienced declines from baseline on day 1 of cycle 2 and day 1 of cycle 3.
- At day 1 of cycle 2, the SE change from baseline was –2.4 (1.8) for ivosidenib vs. –13.3 (3.0) for placebo, with a least-squares mean difference in change from baseline for ivosidenib vs. placebo of 11.0 (95%CI, 4.2-17.7; 2-sided p= .002).
- The decline in physical functioning on day 1 of cycle 2 was clinically meaningful only in the placebo group[12].
- At day 1 of cycle 3, the SE change from baseline was –0.2 (1.9) for ivosidenib vs. –12.6 (3.9) for placebo, with a least squares mean difference in change from baseline for ivosidenib vs. placebo of 12.3 (95%CI, 3.9-20.8; 2-sided P = .004).
- Ivosidenib was favoured on the QLQC30 pain subscale (where a higher score denotes worse symptoms) at day 1 of cycle 2 (least-squares mean difference in change from baseline for ivosidenib vs. placebo, –10.4; 95% CI, –20.2 to –0.5; 2-sided p=0.04). Neither group was favoured on other prespecified subscales (QLQ-C30 appetite loss and QLQ-BIL21 pain and eating).
- On day 1 of cycle 2, ivosidenib was favoured for all other subscales in which differences were observed, including QLQ-C30 emotional functioning, cognitive functioning, dyspnoea and QLQ-BIL21 anxiety and tiredness.

5 The OS data were mature; 37 patients were censored. The median treatment duration was 2.8 months vs. 1.6 months. Median treatment duration for the ivosidenib group after 43 patients crossed over from the placebo group was 2.7 months (range, 0.3-29.8 months). A total of 25 of 166 patients (15%), including 6 patients who crossed over from the placebo group, remained in the ivosidenib group for at least 1 year.

[12] Based on the threshold estimated using anchor-based methods described previously.

- On day 1 of cycle 3, the difference in the QLQC30 emotional functioning subscale persisted, favouring ivosidenib.

ESMO-MCBS version 1.1 [15]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2b	<6 months	PFS: +1.3 months	0.37 (0.25-0.54)	HR≤0.65 BUT gain <1.5 months	2	-	-	+1[13]	3
Adapted	NC	2b	<6 months	PFS: +1.3 months	0.37 (0.25-0.54)	HR≤0.65 BUT gain <1.5 months	2	+10% serious TEAEs	-	-1/+1[14]	2

Risk of bias (RCT) [16]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	unclear	yes	yes	yes[15,16]	unclear

Ongoing trials [17]

NCT number/trial name	Description	Estimated study completion date
NCT04088188	A phase I, multi-centre, open-label, dose de-escalation and expansion study of gemcitabine and cisplatin with AG120 or pemigatinib for advanced cholangiocarcinoma.	01/2025
NCT02073994	A phase 1, multi-centre, open-label, dose-escalation and expansion, safety, pharmacokinetic, pharmacodynamic, and clinical activity study of orally administered AG-120 in subjects with advanced solid tumours, including glioma, with an IDH1 mutation.	06/2023

Available assessments

- A Health Technology Briefing "Ivosidenib for previously treated advanced cholangiocarcinoma", published by NIHR in July 2022, was identified [18].
- No assessments were available from CADTH, NICE, ICER or G-BA.

Other aspects and conclusions

- In February 2023, the **CHMP** adopted a **positive opinion**, recommending granting marketing authorisation for Tibsovo® as monotherapy for treating 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. Marketing authorisation throughout the European Union was granted May 2023.The **FDA approved** this indication in August 2021.
- The phase 3 **ClarIDHy trial (NCT02989857)** evaluated ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma. Patients ≥18 years of age with histopathological diagnosis consistent with nonresectable or metastatic cholangiocarcinoma who are not eligible for curative resection, transplantation, or ablative therapies, documented IDH1 gene-mutated disease and an ECOG PS score of 0 or 1 were included. There was a wide range of exclusion criteria, including prior IDH inhibitor, systemic anticancer therapy (or an investigational agent <2 weeks prior to Day 1), radiotherapy to metastatic sites of disease <2 weeks prior to Day 1, hepatic radiation, chemoembolisation, and radiofrequency ablation <4 weeks prior to Day 1.
- Crossover (placebo to ivosidenib) was permitted on radiological progression per investigator assessment.
- Median PFS (PFS was the primary endpoint) by IRC assessment was 2.7 months (95% CI, 1.6–4.2) vs. 1.4 months (1.4–1.6); HR 0.37; 95% CI, 0.25–0.54; one-sided p<0.000.
- Patients receiving ivosidenib reported no apparent decline in QoL compared with placebo.
- The original and adapted ESMO-MCBS were applied, resulting in a final adjusted magnitude of clinical benefit grade of 3 and 2, respectively.
- The risk of bias of ClarIDHy trial was considered unclear (insufficient information regarding method of concealment) and was increased mainly due to the high crossover rate.
- Of note, ClarIDHy trial patients had an average age of **62 years** (the average age at diagnosis for people with intrahepatic bile duct cancer is 70) and predominantly an **ECOG PS of 0 or 1, indicating that the trial population was younger and had a better performance status than the average cholangiocarcinoma patient**.
- 2 ongoing phase I trials (no RCTs) assessing the efficacy and safety of ivosidenib in cholangiocarcinoma patients were identified.

First published: 04/2023
Last updated: 01/2024

Abbreviations: AE=adverse event, AJ=adjustment, AML=acute myeloid leukaemia; BRCA=Breast cancer gene, BTC=biliary tract cancer, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, ECC=extrahepatic cholangiocarcinoma; ECG=electrocardiogram, ECOG-PS=Eastern Cooperative Oncology Group Performance Status,eGFR=estimated glomerular filtration rate, EMA=European Medicines Agency, EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, EORTC QL-BIL21=European Organisation for Research and Treatment of Cancer Quality of Life

[13] Upgrade: >10% improvement of PFS in 1 year.
[14] Upgrade: >10% improvement of PFS in 1 year.
[15] The funder had a role in study design, data collection, data analysis, and data interpretation. Medical writing support was provided by the funder.
[16] Deviation from intended intervention: high crossover rate.

Questionnaire cholangio carcinoma and gallbladder cancer module, ESCAT= ESMO Scale for Clinical Actionability of Molecular Targets, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FGFR= fibroblast growth factor receptor, FM=final magnitude of clinical benefit grade, FOLFOX=5-fluorouracil-leucovorin-oxaliplatin, G-BA=Gemeinsamer Bundesausschuss, HR=hazard ratio, I=intervention, ICC=Intrahepatic cholangiocarcinoma, ICER=Institute for Clinical and Economic Review, IDH-1=isocitrate dehydrogenase-1, Int.=intention, IRC=independent radiology centre, IQR=interquartile range, ITT=intention-to-treat, LVEF=Left ventricular ejection fraction, MG=median gain, n=number of patients, NICE=National Institute for Health Care Excellence, NIHR=National Institute for Health Research, NTRK= neurotrophic tyrosine receptor kinase; NYHA=New York Heart Association, ORR=overall response rate, OS=overall survival, QTc=heart rate corrected QT, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RPSFT=rank-preserving structural failure time, SAE=serious adverse event, SE=least-squares mean, SoC=Standard of Care, ST=standard treatment, TEAE=treatment-emergent adverse event, TRAE=treatment-related adverse event

References:

1. European Medicines Agency (EMA). Medicines. Tibsovo. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/tibsovo].
2. Cancer.net. Bile Duct Cancer (Cholangiocarcinoma): Statistics. [Available from: https://www.cancer.net/cancer-types/bile-duct-cancer-cholangiocarcinoma/statistics#:~:text=Each%20year%2C%20an%20estimated%208%2C000,age%20at%20diagnosis%20is%2072].
3. Turati F, et al. Epidemiology of cholangiocarcinoma. Hepatoma Res 2022;8:19. DOI: 10.20517/2394-5079.2021.130
4. Vogel A, Bridgewater J, Edeline J, et al., on behalf of the ESMO Guidelines Committee. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol Volume 34, Issue 2, 2023.
5. U.S. Food and Drug Administration (FDA). Tibsovo. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/211192s009lbl.pdf].
6. U.S. Food and Drug Administration (FDA). FDA approves ivosidenib for advanced or metastatic cholangiocarcinoma. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ivosidenib-advanced-or-metastatic-cholangiocarcinoma].
7. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
8. European Medicines Agency (EMA). Tibsovo: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/tibsovo-epar-product-information_en.pdf].
9. Supplement to: Abou-Alfa GK, Macarulla T, M Javle MM, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2020; published online May 13. [Available from: https://linkinghub.elsevier.com/retrieve/pii/S1470204520301571].
10. Supplementary Online Content: Zhu AX, Macarulla T, Javle MM, et al. Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with IDH1 mutation: the phase 3 randomized clinical ClarIDHy trial. JAMA Oncol. Published online September 23, 2021. DOI: 10.1001/jamaoncol.2021.3836.
11. Abou-Alfa GK, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2020 June ; 21(6): 796–807.
12. U.S. Food and Drug Administration (FDA), ClinicalTrials.gov. Study of AG-120 in Previously Treated Advanced Cholangiocarcinoma With IDH1 Mutations (ClarIDHy) [Available from: https://clinicaltrials.gov/ct2/show/NCT02989857].
13. Zhu AX, Macarulla T, Javle MM, et al. Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With IDH1 Mutation The Phase 3 Randomized Clinical ClarIDHy Trial. JAMA Oncol 2021;7(11):1669-1677.
14. Herrmann K, et al. Dosimetry of 177Lu-PSMA-617 for the treatment of metastatic castration-resistant prostate cancer: results from the VISION trial sub-study. Journal of Clinical Oncology 40, no 6_suppl (February 20, 2022) 97-97.
15. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28: 2340–2366, 2017.

16. European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].
17. U.S. National Library of Medicine, ClinicalTrials.gov. [Available from: https://clinicaltrials.gov/ct2/home].
18. National Institute for Health Research (NIHR). Ivosidenib for previously treated advanced cholangiocarcinoma. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/07/19362-TSID_10360-Ivosidenib-for-Cholangiocarcinoma-V1.0-JUL2022-NONCONF.pdf].