Futibatinib (Lytgobi®) for the treatment of locally advanced or metastatic cholangiocarcinoma

General information [1]

Drug description	Indication
The active substance of Lytgobi® is futibatinib (TAS-120), a protein kinase inhibitor, which is an irreversible kinase inhibitor of FGFR 1, 2, 3 and 4.	Futibatinib (Lytgobi®) monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after 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

EMA [1]	FDA [5]

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

Approval status for this indication: On 26 April 2023, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Lytgobi®. **UPDATE:** Date of issue of marketing authorisation valid throughout the European Union: 04/07/2023 <u>The full indication is:</u> ❖ Lytgobi® monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy. **Other indications**: none ✓ **Medicine received a conditional marketing authorisation**[2] ✓ **Medicine is under additional monitoring**	**Approval status for this indication**: On 30 September 2022, the FDA granted accelerated approval to futibatinib (Lytgobi®) for adult patients with previously treated, unresectable, locally advanced, or metastatic intrahepatic cholangiocarcinoma harboring FGFR2 gene fusions or other rearrangements. ✓ Priority review ✓ Breakthrough designation ✓ Orphan drug designation **Other indications**: none

Manufacturer

The manufacturer of Lytgobi® is **Taiho Pharma** Netherlands B.V.

Costs

Currently, there is **no cost information** available.

Posology [6]

- Presence of FGFR2 gene fusions or rearrangements should be confirmed by an appropriate diagnostic test prior to initiation of Lytgobi® therapy.
- In all patients, dietary restrictions that limit phosphate intake are recommended as part of hyperphosphatemia management. A phosphate-lowering therapy should be initiated when serum phosphate level is ≥ 5.5 mg/dL. If the serum phosphate level is > 7 mg/dL, the dose of futibatinib should be modified based on the duration and severity of hyperphosphatemia.
- Prolonged hyperphosphatemia can cause soft tissue mineralisation, including cutaneous calcification, vascular calcification, and myocardial calcification.
- If Lytgobi® treatment is stopped or serum phosphate level falls below normal range, phosphate-lowering therapy and diet should be discontinued.
- Severe hypophosphatemia may present with confusion, seizures, focal neurologic findings, heart failure, respiratory failure, muscle weakness, rhabdomyolysis, and haemolytic anaemia.

Warnings and precautions [6]

- **Hyperphosphatemia**
  - Hyperphosphatemia is a pharmacodynamic effect expected with futibatinib administration.
  - Prolonged hyperphosphatemia may cause soft tissue mineralisation, including cutaneous calcification, vascular calcification, and myocardial calcification, anaemia, hyperparathyroidism, and hypocalcaemia that may cause muscle cramps, QT interval prolongation, and arrythmias.
  - Recommendations for management of hyperphosphatemia include dietary phosphate restriction, administration of phosphate-lowering therapy, and dose modification when required.
  - Phosphate-lowering therapy was used by 83.4 % of patients during treatment with futibatinib.
- **Serous retinal detachment**
  - Futibatinib can cause serous retinal detachment, which may present with symptoms such as blurred vision, visual floaters, or photopsia. This can moderately influence the ability to drive and use machines.
  - Ophthalmological examination should be performed prior to initiation of therapy, 6 weeks thereafter, and urgently at any time for visual symptoms. For serous retinal detachment reactions, the dose modification guidelines should be followed.

[2] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

- During the conduct of the clinical study, there was no routine monitoring, including optical coherence tomography (OCT), to detect asymptomatic serous retinal detachment; therefore, the incidence of asymptomatic serous retinal detachment with futibatinib is unknown.
- Careful consideration should be taken with patients that have clinically significant medical eye disorders, such as retinal disorders, including but not limited to, central serous retinopathy macular/retinal degeneration, diabetic retinopathy, and previous retinal detachment.

❖ **Dry eye**
- Futibatinib can cause dry eye. Patients should use ocular demulcents, in order to prevent or treat dry eye, as needed.

❖ **Embryo-foetal toxicity**
- Based on the mechanism of action and findings in an animal study, futibatinib can cause foetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to the foetus. An effective method of contraception should be used in women of childbearing potential and in men with women partners of childbearing potential during treatment with Lytgobi® and for 1 week following completion of therapy, barrier methods should be applied as a second form of contraception to avoid pregnancy. A pregnancy test should be performed before treatment initiation to exclude pregnancy.

❖ **Combination with strong CYP3A/P-gp inhibitors**
- Concomitant use of strong CYP3A/P-gp inhibitors should be avoided because it may increase futibatinib plasma concentration.

❖ **Combination with strong or moderate CYP3A/P-gp inducers**
- Concomitant use of strong or moderate CYP3A/P-gp inducers should be avoided because it may decrease futibatinib plasma concentration.

❖ **Lactose**
- Lytgobi® contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

❖ **Sodium**
- Lytgobi® contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

Study characteristics [8-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
FOENIX-CCA2, TAS-120-101 NCT02052778	103	oral futibatinib 20 mg once daily (five 4-mg tablets) in a continuous regimen over a 21-day cycle[3]	-	objective response (partial or complete response), as assessed by ICR	17.1 months (range, 10.1-29.6)	multinational, open-label, single-group, phase 2 study	FGFR	Taiho Oncology and Taiho Pharmaceutical	FOENIX-CCA2 [10]

Inclusion criteria[4]	Exclusion criteria	Patient characteristics at baseline
❖ Patients ≥18 years with unresectable or metastatic intrahepatic cholangiocarcinoma harbouring an FGFR2 fusion or rearrangement that had been prospectively identified by local testing of tumour tissue or ctDNA or by testing of tumour tissue at a central or local laboratory with the use of a 324-gene-panel assay (Foundation One CDx assay, Foundation Medicine)	❖ History or current evidence of nontumor-related, altered calcium-phosphorus homeostasis ❖ Ectopic mineralisation/calcification ❖ Retinal disorder ❖ Uncontrolled ventricular arrhythmia ❖ Current clinically significant primary malignancy other than ICC	❖ **Median age**: 58 years (range, 22–79) ❖ **Male sex**: 44% ❖ **ECOG PS 0**: 47% ❖ **ECOG PS 1**: 53% ❖ **Race or ethnic group** • White: 50% • Asian: 29%

[3] Treatment continued until the occurrence of imaging-based or clinical disease progression or unacceptable toxic effects or until any other discontinuation criterion was met. For patients with continued clinical benefit, treatment after disease progression was permitted after discussion between the investigators and one of the sponsors (Taiho Oncology). Thirteen patients (13%) received futibatinib after imaging-based disease progression because of continued clinical benefit.
[4] For full in- and exclusion criteria, please see study protocol.

❖ Radiologically measurable disease, according to RECIST, version 1.1 ❖ Disease progression after systemic therapy (including ≥1 previous regimen of gemcitabine plus platinum-based chemotherapy and no previous treatment with an FGFR inhibitor) ❖ Adequate organ function ❖ ECOG PS of 0 or 1		• Black: 8% • Native Hawaiian or Pacific Islander: 1% • Unknown: 13% ❖ **Geographic region** • North America: 46% • Europe: 27% • Japan: 14% • Asia Pacific, excluding Japan: 14% ❖ **FGFR2 alteration** • Fusion: 78% • Rearrangement: 22% ❖ **Previous therapy** • Anticancer therapy: 100% • Radiotherapy: 27% • Anticancer surgery: 40% ❖ **Number of previous lines of systemic therapy** • 1: 47% • 2: 30% • ≥3: 23% ❖ **Median time from previous anticancer therapy to first dose of futibatinib**: 1.5 months (IQR, 1.0–3.4)

Efficacy (I vs. C)	**Safety** (I vs. C)
<u>**Data-cut-off date for the primary analysis (1 October 2020; median follow-up 17.1; median duration of treatment 9.1 months)**</u> **Objective response (assessed by ICR)**: 42% (95% CI, 32-52); including 1 patient who had a CR **Disease control**: 83% (95% CI, 74-89) **Median duration of response**: 9.7 months (95% CI, 7.6-17.0) **Responses lasting at least 6 months** (among patients with a response): 72% **Responses lasting at least 12 months** (among patients with a response): 14% **Median time to response**: NR **Kaplan–Meier cumulative response after the start of treatment**: 34% (at 4 months) and 42% (at 8 months) **Median time to response** (among patients with a response): 2.5 months (range, 0.7-7.4) **Ongoing response at the time of data cut-off**: 21 of 43 patients who had a response **Median PFS**: 9.0 months (95% CI, 6.9-13.1) **6-month PFS**: 66% (95% CI, 56-75) **12-month PFS**: 40% (95% CI, 29-51) **Median OS:** 21.7 months (95% CI, 14.5-NR) **12-month OS rate**: 72% (95% CI, 62-80) <u>Genomic profiling analysis</u> ❖ Analysis of the molecular profile of the tumours in the 103 patients in the efficacy population indicated that responses did not correlate with FGFR2 fusion-partner status or co-occurring alterations in tumour-suppressor genes or oncogenes. ❖ Overall, 46 unique FGFR2 fusion partners were identified in this patient population. ❖ BICC1 was the most common (n=24), followed by KIAA1217 and WAC (n=3 each).	**Any TRAE grade 3:** n=58/103 (56%) **Any TRAE grade 4**: n=1/103 (1%) **Patients with at least one grade 3 TEAE of any cause**: n=68/103 (66%) **Patients with at least one grade 4 TEAE of any cause**: n=6/103 (6%) **Patients with at least one grade 5 TEAE of any cause**: n=5/103 (5%) **Serious TRAEs of any grade**: n=10/103 (10%) **Serious TRAEs of grade 3**: n=7/103 (7%) **TRAEs leading to permanent discontinuation of futibatinib:** n=2/103 (2%) **Treatment-related deaths**: 0

- Responses occurred in (42%) with BICC1 fusions and in 45% with non-BICC1 fusions.
- In 93 patients with available results of the 324-gene-panel assay, BAP1 was identified as the most frequently co-altered gene (in 43% of the patients), followed by CDKN2A (in 22%), CDKN2B (in 17%), and TP53 (in 14%).
- Responses occurred in 35% to 49% of patients with or without BAP1, TP53, CDKN2A, or CDKN2B alterations.
- Median PFS was similar among patients with and those without BAP1 alterations (9.0 months and 8.0 months, respectively), as it was among patients with and those without TP53 alterations (7.0 months and 9.0 months).
- Numerical differences were noted with respect to median PFS between patients with and those without CDKN2A (4.9 months and 9.7 months, respectively) and those with and those without CDKN2B alterations (4.8 months and 11.0 months).
- Exploratory ctDNA analysis identified FGFR2 fusions or rearrangements in 83 of the 95 patients (87%) evaluated, including 78 of 90 with a baseline sample and 5 of 5 with an on-treatment sample.

Exploratory pharmacokinetic analyses

- Within the range of futibatinib exposures (area under the concentration-time curve at steady state) at a dose of 20 mg once daily (the recommended dose used in this study), no significant associations were observed between futibatinib exposure and any of the efficacy end points.
- The numerically lowest response duration and PFS values were observed at the lowest exposure quartile.

Response and survival data at extended follow-up (data cutoff, May 29, 2021)

- Median follow-up: 25.0 months
- ORR: 41.7% (95% CI, 32.1%-51.9%)
- Disease control rate: 82.5% (95% CI, 73.8%-89.3%)
- Median duration of response: 9.5 months (95% CI, 7.6-10.4)
- Median PFS: 8.9 months (95% CI, 6.7-11.0)
- Median OS: 20.0 months (95% CI, 16.4-24.6)

Patient-reported outcomes

- **89% of patients completed** at least one EORTC QLQ-C30 or EQ-5D at baseline and at one or more follow-up assessments.
- Patient-reported outcome data were evaluated through the cycle 13 visit (in 48 patients) because this was the last visit before data were missing for more than 50% of the patients in the patient-reported outcome population. During these 9.0 months of treatment, **EORTC QLQ-C30 scores were stable and global health status was well maintained,** except for constipation, which **worsened** by the minimal threshold of 10.0 points only at cycle 4.
- The status across all **EQ-5D-3L dimensions remained the same or improved** in most patients.
- Mean (±SD) **EQ VAS** scores were **sustained** from baseline (71.7±20.3) to cycle 13 (75.6±21.6).
- **ECOG PS** was also **maintained or improved** relative to baseline in most patients with available data (in 95% of the patients at cycle 2 and in 81% of those at cycle 13).

ESMO-MCBS version 1.1 [12]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	ORR:42%	-	ORR ≥20-≤60% AND DoR ≥9 months	3	-	No benefit, QoL was maintained	-	3
Adapted	The adapted ESMO-MCBS version is not applied for single-arm studies.										

Risk of bias - study level [13]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?

			entry into the study clearly stated?					
yes	yes	yes	yes	partial[5]	yes	unclear[6]	yes	no
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	no[7]	yes	yes	yes	yes
Overall risk of bias: moderate								

Ongoing trials [14]

NCT number/trial name	Description	Estimated study completion date
NCT04093362/ FOENIX-CCA3	A phase 3, open-label, randomised study of futibatinib vs. gemcitabine-cisplatin chemotherapy as first-line treatment of patients with advanced cholangiocarcinoma harboring FGFR2 gene rearrangements FOENIX-CCA3.	09/2023
NCT05727176/ FOENIX-CCA4	A phase 2 study of futibatinib 20 mg and 16 mg in patients with advanced cholangiocarcinoma with FGFR2 fusions or rearrangements.	06/2026

Available assessments

No assessments were identified.

Other aspects and conclusions

- In April 2023, the **CHMP adopted a positive opinion,** recommending the granting of a conditional marketing authorisation for futibatinib (Lytgobi®) for the treatment of locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement that has progressed after at least one prior line of systemic therapy. **The marketing authorisation for Lytgobi® became valid throughout the European Union on 4 July 2023**. In September 2022, the **FDA granted accelerated approval** to Lytgobi® for patients with previously treated, unresectable, locally advanced, or metastatic intrahepatic cholangiocarcinoma harbouring FGFR2 gene fusions or other rearrangements.
- The open-label, single-group, phase 2, **FOENIX-CCA2 trial** (NCT02052778) evaluated the efficacy and safety of futibatinib in patients with intrahepatic cholangiocarcinoma harbouring FGFR2 fusions or other rearrangements after one or more lines of systemic therapy. Eligible patients were ≥18 years, had unresectable or metastatic intrahepatic cholangiocarcinoma harbouring an FGFR2 fusion or rearrangement, radiologically measurable disease, disease progression after systemic therapy, adequate organ function, and an ECOG of 0 or 1. Patients with a history of or current clinically significant retinal disorder or altered non–tumour-related calcium–phosphorus homeostasis were excluded.
- The primary endpoint of FOENIX-CCA2 was ORR (PR or CR, by ICR). At a median follow-up of 17.1 months; 42 % of patients (95% CI, 32-52) had a response, including 1 patient who had a CR.
- Assessment of patient-reported outcomes (n=48) showed that the **QoL was maintained** throughout study treatment.
- The original **ESMO-MCBS** was applied, resulting in a final magnitude of clinical benefit score of 3.
- The **overall risk of bias** was considered as **moderate**; it is increased by the single-arm- and open-label design, heterogenous patient characteristics at baseline as well as by lacking data regarding co-interventions and loss to follow-up.
- Since the FOENIX-CCA2 trial population was young (median age was 58 years), the **transferability** of trial results to the average cholangiocarcinoma patient population (median age at diagnosis is 70-72 years) remains unclear.
- Hence, robust phase 3- and long-term data derived from a more appropriate patient population is required to determine the role of futibatinib in cholangiocarcinoma patients.

[5] Patient characteristics at baseline, regarding number and types of previous therapies, were heterogenous.
[6] No information was found regarding co-interventions.
[7] No information was found regarding loss to follow-up.

- ❖ One ongoing phase 3, open-label, randomised study of futibatinib vs. gemcitabine-cisplatin chemotherapy as first-line treatment of patients with advanced cholangiocarcinoma harbouring FGFR2 gene rearrangements (NCT04093362, FOENIX-CCA3) was identified.

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Abbreviations: AE=adverse event, AJ=adjustment, BRCA=breast cancer gene, BTC=biliary tract cancer, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CEA=carcinoembryonic antigen, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, CT=computed tomography, ctDNA=circulating tumor DNA, DoR=duration of response, ECC=extrahepatic cholangiocarcinoma, ECOG PS=Eastern Cooperative Oncology Group performance statis, EMA=European Medicines Agency, EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, EQ-5D= EuroQol Group 5-Dimension questionnaire, 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, FGFR2=fibroblast growth factor receptor 2, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HER2=human epidermal growth factor receptor 2, HR=hazard ratio, I=intervention, ICC=intrahepatic cholangiocarcinoma, ICER=Institute for Clinical and Economic Review, ICR=independent central review, Int.=intention, IQR=interquartile range, MG=median gain, MRI=magnetic resonance imaging, MSI-H=microsatellite instability-high, n=number of patients, NICE=National Institute for Health Care Excellence, NTRK=neurotrophic tyrosine receptor kinase, OS=overall survival, PALB2=partner and localiser of BRCA2, PARP=poly (ADP-ribose) polymerase, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, PS=performance status, QoL=quality of life, ORR=overall response rate, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, SOC=standard of care, ST=standard treatment, TEAE=treatment-emergent adverse events, TRAE=treatment-related adverse events

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