NEW DRUG APPROVAL

Brand Name	Lytgobi®
Generic Name	futibatinib
Drug Manufacturer	Taiho Oncology Inc.

New Drug Approval

FDA Approval Date: September 30, 2022

Review designation: Priority; Orphan

Type of review: Type 1 - New Molecular Entity; New Drug Application (NDA): 214801

Dispensing restriction: Specialty Pharmacy Required, Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Advanced, unresectable cholangiocarcinoma (CCA; also known as bile duct cancer) is a rare, aggressive malignancy with a poor prognosis.

Bile duct cancer may occur more frequently in patients with a history of primary sclerosing cholangitis, chronic ulcerative colitis, choledochal cysts, or infections with the liver fluke Clonorchis sinensis.

Bile duct cancer is mainly seen in older people (the average age at diagnosis in the United States is 70 years for those with cancer of the intrahepatic bile ducts and 72 years for cancer of the extrahepatic bile ducts). *FGFR2* genetic aberrations are present in approximately 10%–16% of people who have intrahepatic CCA.

The incidence of cholangiocarcinoma ranges between 0.3 and 6.0 per 100,000 people in North America. It is estimated that approximately 8000 people in the United States are diagnosed annually; however, the actual number of CCA cases is likely to be higher because establishing an accurate diagnosis can be difficult.

Efficacy

Table 1. FOENIX-CCA2 (NCT02052778): Study Design Summary	
Study Design	Phase 1/2, open-label, nonrandomized, three-part trial of the safety, tolerability, pharmacokinetics, pharmacodynamics, and antitumor activity of Lytgobi®

Study Population	• 103 patients with previously treated, unresectable, locally advanced or metastatic intrahepatic CCA.
	  ○ The presence of *FGFR2* fusions or other rearrangements was confirmed in 102 enrolled patients (99%) using NGS testing.
	• Median age: 58 years (range: 22–79 years)
	  ○ 22% of patients ≥65 years
	  ○ 56% female
	  ○ 50% White
	  ○ 29% Asian
	  ○ 8% Black or African American
	  ○ 1% Native Hawaiian or Other Pacific Islander
	  ○ 13% with unknown race/ethnicity
	• 100% had baseline ECOG PS of 0 (47%) or 1 (53%)
	• All patients had received at least one prior systemic therapy
	  ○ 30% had received two prior lines of therapy
	  ○ 23% had received three or more prior lines of therapy
	• All patients received a prior platinum-based therapy, with 91% receiving prior gemcitabine/cisplatin.

Key Exclusion Criterion	Patients must not have previously received an FGFR inhibitor.
Interventions	Patients received Lytgobi® at a dosage of 20 mg orally once daily until disease progression or unacceptable toxicity.
Endpoints	**Primary:** ORR according to RECIST v1.1 • **Secondary:** DOR, DCR, PFS, OS, safety, and patient-reported outcomes
Safety Results	• SARs occurred in 39% of patients receiving Lytgobi®. SARs in ≥2% of patients who received Lytgobi® included pyrexia (3.9%), gastrointestinal hemorrhage (3.9%), ascites (2.9%), musculoskeletal pain (2.9%), and bile duct obstruction (2.9%). • Permanent discontinuation due to an AR occurred in 4.9% of patients who received Lytgobi®. ARs requiring permanent discontinuation of Lytgobi® in one patient each were esophagitis, oral dysesthesia, bile duct obstruction, dizziness, and anemia. • Dosage interruptions due to an AR occurred in 66% of patients who received Lytgobi®. ARs requiring dosage interruption in ≥5% of patients included hyperphosphatemia, palmar-plantar erythrodysesthesia syndrome, increased alanine aminotransferase, increased aspartate aminotransferase, and fatigue. • Dose reductions due to an AR occurred in 58% of patients who received Lytgobi®. ARs requiring dosage reductions in ≥2% of patients who received Lytgobi® included hyperphosphatemia, palmar-plantar erythrodysesthesia syndrome, fatigue, increased alanine aminotransferase, increased aspartate aminotransferase, nail toxicity, and stomatitis.

Abbreviations: AR, adverse reaction; CCA, cholangiocarcinoma; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *FGFR2*, fibroblast growth factor receptor 2; NGS,

next-generation sequencing; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SAR, serious adverse reaction.

Table 2. Efficacy Results from FOENIX-CCA2 Trial

Efficacy Parameter	Lytgobi®(N =103)
ORR (95% CI)[a]	42% (32, 52)
Partial Response, n (%)	43 (42%)
Median DOR (Months) (95% CI)[b]	9.7 (7.6, 17.1)
Patients with DOR ≥6 Months, n (%)	31 (72%)
Patients with DOR ≥12 Months, n (%)	6 (14%)

Safety

ADVERSE EVENTS

Most common (≥20%) adverse reactions were nail toxicity, musculoskeletal pain, constipation, diarrhea, fatigue, dry mouth, alopecia, stomatitis, abdominal pain, dry skin, arthralgia, dysgeusia, dry eye, nausea, decreased appetite, urinary tract infection, palmar-plantar.

Most common laboratory abnormalities (≥20%) were increased phosphate, increased creatinine, decreased hemoglobin, increased glucose, increased calcium, decreased sodium, decreased phosphate, increased alanine aminotransferase, increased alkaline phosphatase, decreased lymphocytes, increased aspartate aminotransferase, decreased platelets, increased activated partial thromboplastin time, decreased leukocytes, decreased albumin, decreased neutrophils, increased creatine kinase, increased bilirubin, decreased glucose, increased prothrombin international normalized ratio, and decreased potassium.

WARNINGS & PRECAUTIONS

Ocular Toxicity: LYTGOBI can cause retinal pigment epithelial detachment (RPED). Perform a comprehensive ophthalmological examination including optical coherence tomography (OCT) prior to initiation of therapy, every 2 months for the first 6 months, and every 3 months thereafter and urgently at any time for visual symptoms.

Hyperphosphatemia and Soft Tissue Mineralization: Increases in phosphate levels can cause hyperphosphatemia leading to soft tissue mineralization, calcinosis, nonuremic calciphylaxis and vascular calcification. Monitor for hyperphosphatemia and withhold, reduce the dose, or permanently discontinue based on duration and severity of hyperphosphatemia.

Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of reproductive potential of the potential risk to the fetus and to use effective contraception.

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS OF ACTION

NEW DRUG APPROVAL

Futibatinib is a small molecule kinase inhibitor of FGFR 1, 2, 3, and 4 with IC50 values of less than 4 nM. Futibatinib covalently binds FGFR. Constitutive FGFR signaling can support the proliferation and survival of malignant cells. Futibatinib inhibited FGFR phosphorylation and downstream signaling and decreased cell viability in cancer cell lines with FGFR alterations including FGFR fusions/rearrangements, amplifications, and mutations. Futibatinib demonstrated anti-tumor activity in mouse and rat xenograft models of human tumors with activating FGFR genetic alterations.

Dose & Administration

ADULTS

20 mg orally (five 4-mg tablets) once daily until disease progression or unacceptable toxicity occurs.

PEDIATRICS

None

GERIATRICS

Refer to adult dosing

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 4 mg