Trends in Pharmacological Sciences | Drug of the Month

Futibatinib (Lytgobi) for cholangiocarcinoma

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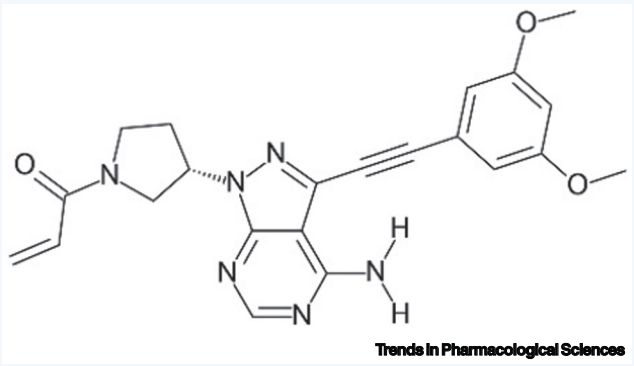
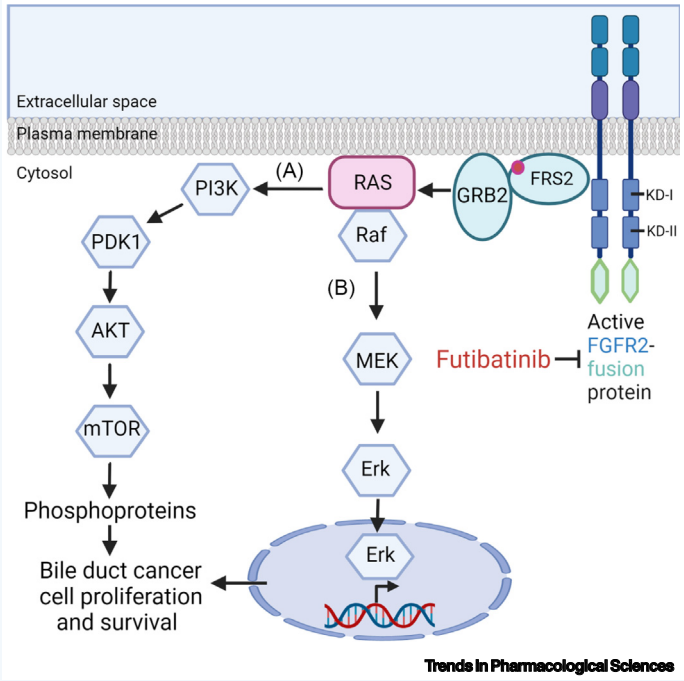


STRUCTURE: Futibatinib (brand name Lytgobi™) is a small molecule kinase inhibitor with the molecular formula $C_{22}H_{22}N_6O_3$ and a molecular mass of 418.45 g/mole. The drug is a pyrazolo[3,4-*d*]pyrimidine derivative with an attached α,β-unsaturated amide warhead, also called a Michael acceptor, that forms a covalent bond with a cysteine residue in the fibroblast growth factor receptor (FGFR) protein-tyrosine kinase glycine-rich loop.



MECHANISM OF ACTION: Futibatinib is an inhibitor of the FGFR family, which comprises a group of receptor tyrosine kinases that play a key role in cell growth, proliferation, and survival. FGFR was investigated in oncology as a therapeutic target, as FGFR genomic aberrations and dysregulated FGFR signaling pathways are observed in some cancers such as cholangiocarcinoma (bile duct cancer) and malignancies of the urinary tract. Futibatinib is a selective, irreversible inhibitor of FGFR 1–4 with IC_{50} values of less than 4 nM. It forms a covalent bond with a cysteine in the ATP-binding pocket glycine-rich loop that is found in kinase domain I (KD-I) of FGFR2. After binding to FGFR2, futibatinib blocks FGFR2 autophosphorylation and the phosphorylation of FRS2 (denoted by the red circle). The chief downstream signaling pathways of the FGFRs include the (A) PI3K/Akt/mTOR and (B) RAS-dependent Raf-MEK-Erk (MAP kinase) pathways. Erk and mTOR catalyze the phosphorylation of numerous cytosolic proteins. Moreover, Erk is translocated into the cell nucleus leading to the phosphorylation and activation of many transcription factors. Futibatinib decreases cell viability in cancer cell lines with FGFR alterations, including FGFR fusions or rearrangements, amplifications, and mutations.

NAME:
The drug name is futibatinib, the brand name is Lytgobi, and its code name is TAS-120.

DRUG CLASS:
Futibatinib is a small molecule targeted covalent inhibitor (TCI) of FGFR1–4 protein-tyrosine kinase activity.

CLINICAL USE:
Futibatinib is prescribed for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring FGFR2 gene fusions or other rearrangements. Selected FGFR-fusion proteins are active in the absence of FGF, leading to cancer cell proliferation and survival.

DEVELOPED BY:
Futibatinib was developed by Taiho Pharmaceutical Co. (located in Japan).

ADVERSE EFFECTS:
Hyperphosphatemia (80%), diarrhea (33%), constipation (32%), nausea (31%), fatigue (25%), vomiting (25%), abdominal pain (19%), dry mouth (17%), anemia (14%), dry skin (13%), arthralgia (11%).

TIMELINE:
February 3, 2014, ongoing, Phase 2, NCT02052778

September 18, 2019, ongoing, Phase 3, NCT04093362

December 6, 2019, ongoing, Phase 2, NCT04189445

August 11, 2020, ongoing, expanded access, NCT04507503

FDA approval September 30, 2022.

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Declaration of interests

No interests are declared.

Literature

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