Drugs (2022) 82:1737–1743
https://doi.org/10.1007/s40265-022-01806-z

ADISINSIGHT REPORT

Futibatinib: First Approval

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Published online: 28 November 2022

Abstract
Futibatinib (Lytgobi®) is an oral, covalently binding, irreversible inhibitor of fibroblast growth factor receptor (FGFR)1–4 that is being developed by Taiho Oncology and Taiho Pharmaceutical for the treatment of cancers, including cholangiocarcinoma, breast cancer, gastric cancer, urothelial cancer, oesophageal cancer and non-small cell lung cancer. Futibatinib was approved in the USA on 30 September 2022 for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harbouring FGFR2 gene fusions or other rearrangements. This article summarizes the milestones in the development of futibatinib leading to this first approval.

Digital Features for this AdisInsight Report can be found at https://doi.org/10.6084/m9.figshare.21508350.

Futibatinib (Lytgobi®): Key points

An oral, covalently binding irreversible FGFR1–4 inhibitor is being developed by Taiho Oncology and Taiho Pharmaceutical for the treatment of cancers

Received its first approval on 30 September 2022 in the USA

Approved for use in adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harbouring FGFR2 gene fusions or other rearrangements

1 Introduction

Fibroblast growth factor receptor (FGFR) signalling plays an important role in cell proliferation, differentiation, migration and survival. Deregulated FGFR signalling (resulting from upregulation, mutation, amplification and chromosomal rearrangements of FGFR) often leads to oncogenesis [1]. Thus, FGFR inhibition is a viable therapeutic approach for cancers that involve these abnormalities [2]. A number of small-molecule tyrosine kinase inhibitors (TKIs) that competitively bind to the adenosine triphosphate (ATP) pocket of FGFR1–4 are under clinical development [3]. Toxicities associated with non-selective TKIs led to the development of FGFR-specific reversible TKIs [3]. However, most selective TKIs do not competitively bind to FGFR4 and drug resistance remains a challenge even with selective TKIs. Thus, irreversible FGFR inhibitors are being developed [3, 4].

Futibatinib (Lytgobi®) is an oral, small-molecule, covalently binding, irreversible TKI of FGFR1-4 that is being developed by Taiho Oncology and Taiho Pharmaceutical for the treatment of cancers, including cholangiocarcinoma (bile duct cancer). In September 2022, futibatinib received its first approval in the USA for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harbouring FGFR2 gene fusions or other rearrangements [5]. The accelerated approval was based on results from a phase II trial (FOENIX-CCA2). Futibatinib is available as 4 mg oral tablets and the recommended dosage is 20 mg once daily taken with or without

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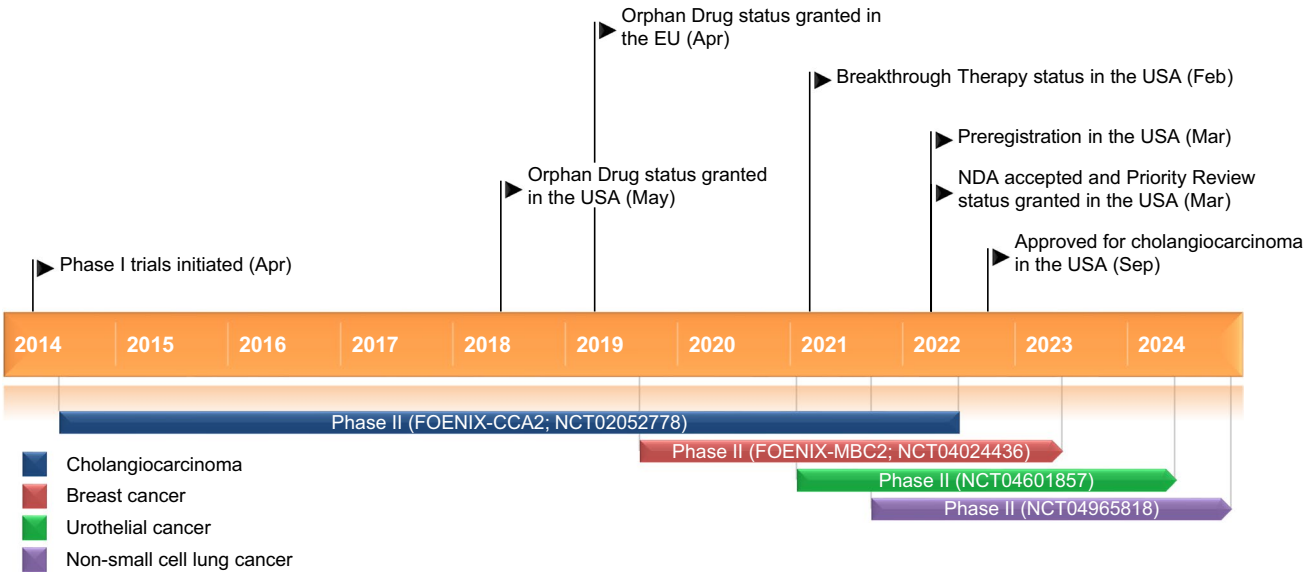


Key milestones in the development of futibatinib for cholangiocarcinoma. *Est.* estimated, *NDA* new drug application

food at approximately the same time each day, until disease progression or unacceptable toxicity occurs [5].

Futibatinib as second- or later-line therapy for cholangiocarcinoma is filed for approval in the EU [6] and Japan [7]. Phase I or II trials of futibatinib are underway for breast cancer with FGFR1 and FGFR2 amplification, urothelial and oesophageal cancers (in combination with pembrolizumab) and non-small cell lung cancer (NSCLC) with KRAS mutations (in combination with binimetinib).

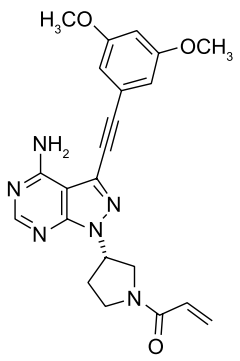
1.1 Company Agreements

In January 2020, the National Comprehensive Cancer Network entered into a collaboration with Taiho Oncology to conduct preclinical, translational and clinical trials of futibatinib as monotherapy and in combination with other drugs for malignancies with FGFR1–4 aberrations, supported by a $US2 million grant from Taiho Oncology [8]. In July 2022, the following projects were selected for the funding: a phase Ib trial of olaparib plus futibatinib in all solid tumours with BRCA1/2 alterations; a phase II trial of futibatinib plus pembrolizumab in metastatic microsatellite stable endometrial carcinoma; a phase II trial of futibatinib plus pembrolizumab in advanced or metastatic hepatocellular carcinoma with *FGF19* expression after first line therapy; and, developing futibatinib for use on novel FGFR genomic alterations and in therapy combinations [9].

2 Scientific Summary

2.1 Pharmacodynamics

Futibatinib inhibits all four FGFR subtypes with IC_{50} values < 4 nM [10]. Unlike reversible ATP-competitive inhibitors, futibatinib rapidly forms a covalent adduct with a cysteine side chain in the P-loop of the FGFR tyrosine kinase domain, with an inherent ability to capture multiple FGFR P-loop conformations [11]. Through FGFR inhibition, futibatinib inhibits FGFR phosphorylation and downstream signalling, resulting in decreased cell viability in cancer cell lines harbouring FGFR alterations (fusions, rearrangements, amplifications and mutations) [10]. Futibatinib exhibited potent antitumour activity in FGFR-deregulated cancer cell lines and xenograft models [10]. In animal models, futibatinib



Chemical structure of futibatinib

showed synergistic antitumour effects with cytotoxic agents [12], PI3K pathway inhibitors [13] and a selective AKT inhibitor [14].

Futibatinib provided clinical benefits in patients with cholangiocarcinoma harbouring FGFR2 fusion and other rearrangements (Sect. 2.3.1). It demonstrated antitumour activity in patients with FGFR2 fusion-positive intrahepatic cholangiocarcinoma who developed resistance to ATP-competitive FGFR inhibitors due to multiple FGFR2 mutations in the kinase domain [15]. Futibatinib also showed clinical activity in patients with intrahepatic cholangiocarcinoma harbouring FGFR2 extracellular domain in-frame deletions [16].

Since FGFRs play a crucial role in phosphorus homeostasis, FGFR inhibition by futibatinib dose-dependently increases serum phosphate levels, with increased risk of hyperphosphatemia at higher futibatinib exposure [4, 5].

2.2 Pharmacokinetics

The pharmacokinetic properties of oral futibatinib 20 mg once daily have been evaluated in patients with advanced solid tumours [4, 5]. Futibatinib exposure increased in a dose-proportional manner over a dose range of 4–24 mg [5]. Following a 20 mg dose, the median time to maximum futibatinib plasma concentration was 2 h. The geometric mean apparent volume of distribution of futibatinib was 66 L. Futibatinib is 95% bound to human plasma protein, primarily to albumin and α1-acid glycoprotein. The drug is metabolized mainly by CYP3A, and to a lesser extent by CYP2C9 and CYP2D6, with unchanged drug being the main active moiety. Following a single 20 mg oral dose of radiolabelled futibatinib, ≈ 91% of the total radioactivity was recovered in faeces and 9% in urine, with an insignificant proportion of unchanged drug in urine or faeces. The mean elimination half-life of futibatinib is 2.9 h and the geometric mean apparent clearance is 20 L/h [5].

There were no clinically meaningful differences in futibatinib exposure based on age (18–82 years), sex, race (White, Asian, and African American), body weight (36–152 kg), mild to moderate kidney function impairment or mild liver function impairment [5]. The effects of severe kidney function impairment, kidney failure and moderate or severe liver function impairment on futibatinib pharmacokinetics have not been studied [5].

Concomitant use of futibatinib with dual P-glycoprotein (P-gp) and strong CYP3A inhibitors (which may increase futibatinib exposure) or with dual P-gp and strong CYP3A inhibitors (which may decrease futibatinib exposure) should be avoided [5]. As futibatinib is an inhibitor of P-gp and BCRP, it may increase the exposure of drugs that are substrates of these proteins [5].

Features and properties of futibatinib

Alternative names	LYTGOBI; TAS-120
Class	Amines; antineoplastics; ketones; phenyl ethers; pyrazoles; pyrimidines; pyrrolidines; small molecules
Mechanism of action	Fibroblast growth factor receptor (FGFR) antagonist
Route of administration	Oral
Pharmacodynamics	Inhibits FGFR phosphorylation and downstream signalling; exhibits antitumour activity in FGFR-deregulated cancer cell lines and xenograft models; increases serum phosphate levels, with increased risk of hyperphosphatemia at higher drug exposure
Pharmacokinetics	T_{max} 2 h, V_d/F 66 L, plasma protein binding 95%, primarily metabolised by CYP3A, $t_{1/2}$ 2.9 h, CL/F 20 L/h, faecal excretion is the major route of elimination
Adverse events	
Most frequent grade ≥ 3 treatment-related	Hyperphosphatemia, increased ALT, increased AST, fatigue, stomatitis and palmar-plantar erythrodysesthesia syndrome
ATC codes	
WHO ATC code	L01-EN04 (Futibatinib)
EphMRA ATC code	L1 (Antineoplastics)
Chemical name	1-[(3S)-3-[4-amino-3-[2-(3,5-dimethoxyphenyl)ethynyl]pyrazolo[3,4-d]pyrimidin-1-yl] pyrrolidin-1-yl]prop-2-en-1-one

2.3 Therapeutic Trials

Phase I pharmacological and safety data supported futibatinib 20 mg once daily as the recommended phase II dose [4, 17, 18].

2.3.1 Intrahepatic Cholangiocarcinoma

Futibatinib demonstrated efficacy in patients with advanced/metastatic, unresectable, intrahepatic cholangiocarcinoma harbouring FGFR2 fusion/rearrangements in the pivotal, single-arm, phase II part (FOENIX-CCA2) of an open-label, multicentre phase I/II trial (NCT02052778) [5, 19]. Eligible patients had disease progression after one or more lines of systemic therapy (including gemcitabine plus platinum-based chemotherapy), no prior FGFR inhibitor treatment and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients received futibatinib 20 mg once daily until disease progression or unacceptable toxicity. The primary endpoint of objective response rate (ORR; per RECIST 1.1 criteria, assessed by an independent central review, with a target ORR of 20% for futibatinib) was 42% (95% CI 32–52) in 103 evaluable patients. ORRs were consistent in patients with FGFR2 fusions, FGFR2 rearrangements, BICC1 and non-BICC1 fusion partners, and co-occurring mutations. In the overall population, the median duration of response (DoR) was 9.7 months (95% CI 7.6–17.1); DoR was ≥ 6 and ≥ 12 months in 72% and 14% of responders, respectively. Disease control rate was 82.5%, median progression-free survival (PFS) was 9.0 months and median overall survival (OS) was 21.7 months (12-month OS rate 72%) [5, 19]. The primary analysis findings were confirmed by a final analysis, which included an additional 8 months' follow-up [20].

In FOENIX-CCA2, physical, cognitive and emotional functioning, and overall health status were maintained during 9 months of futibatinib treatment, based on patient-reported outcomes assessed using the EORTC QLQ-C30, EQ-5D-3L and EQ visual analogue scale [21].

A simulated indirect treatment comparison using patient-level data from FOENIX-CCA2 and other published aggregated data suggests that futibatinib may be similar to pemigatinib and is better than chemotherapy in terms of PFS and OS benefits [22].

2.3.2 Advanced Solid Tumours

Futibatinib showed preliminary activity in patients with advanced solid tumours in the first-in-human, phase I dose-escalation part of the NCT02052778 trial [4]. In the dose-expansion part, 170 patients with advanced solid tumours (cholangiocarcinoma and gastric, urothelial, CNS, head and neck, and breast cancer) received futibatinib 20 mg [23]. The ORR was 13.7% in the overall cohort and 25.4% in patients with FGFR2 fusion/rearrangement-positive intrahepatic cholangiocarcinoma [23].

In a phase I trial (JapicCTI-142552), futibatinib showed antitumour activity in Japanese patients with advanced solid tumours, including gastric cancer [18, 24]. In a phase Ib trial (JapicCTI-195063), futibatinib in combination with pembrolizumab [an immune checkpoint inhibitor (ICI)] showed antitumour activity in patients advanced or metastatic solid tumours, including oesophageal cancer; the activity was seen in ICI-naïve as well as in ICI-refractory patients [25].

Key clinical trials of futibatinib sponsored by Taiho Oncology

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Futibatinib	Cholangiocarcinoma (2nd line)	I/II	Active, not recruiting	Global	NCT02052778, EudraCT2013-004810-16, FOENIX-101, FOENIX-CCA2
Futibatinib	Cholangiocarcinoma (1st line)	III	Active, not recruiting	Global	NCT04093362, EudraCT2019-004630-42, FOENIX-CCA3
Futibatinib, fulvestrant	Breast cancer with FGFR-1, -2 amplification	II	Recruiting	Global	NCT04024436, EudraCT2019-001164-30, FOENIX-MBC2
Futibatinib	Tumours with FGFR aberrations	II	Active, not recruiting	Global	NCT04189445, EudraCT2019-004084-49, JapicCTI205312
Futibatinib, pembrolizumab	Urothelial cancer	II	Recruiting	France, Spain, USA	NCT04601857
Futibatinib, binimetinib	Non-small cell lung cancer with KRAS mutations	I/II	Recruiting	USA	NCT04965818
Futibatinib, pembrolizumab	Solid tumours (including oesophageal cancer)	Ib	Recruiting	Japan	JapicCTI-195063

FGFR fibroblast growth factor receptor

2.4 Adverse Events

2.4.1 Intrahepatic Cholangiocarcinoma

In FOENIX-CCA2, two patients (1.9%) discontinued treatment because of treatment-related adverse events (TRAEs) [19]. Adverse reactions led to dose interruption in 66% of patients and dose reductions in 58% of patients [5]. The most common (incidence ≥ 20%) adverse reactions with futibatinib were nail toxicity, musculoskeletal pain, constipation, diarrhoea, fatigue, dry mouth, alopecia, stomatitis, abdominal pain, dry skin, arthralgia, dysgeusia, dry eye, nausea, decreased appetite, urinary tract infection, palmar-plantar erythrodysesthesia syndrome (PPES) and vomiting. The most common (incidence ≥ 2%) grade 3 adverse reactions were fatigue (8%), stomatitis (6%), PPES (4.9%), musculoskeletal pain (3.9%), weight loss (3.9%), abdominal pain (2.9%), decreased appetite (2.9%) and urinary tract infection (2.9%). The most common (incidence ≥ 5%) grade 3 or 4 laboratory abnormalities were decreased haemoglobin, decreased lymphocytes, decreased phosphate, increased phosphate, increased aspartate aminotransferase (AST), increased creatine kinase and increased activated partial thromboplastin time. Serious adverse reactions occurred in 39% of futibatinib recipients; the most common (incidence ≥ 2%) of these were pyrexia (3.9%), gastrointestinal haemorrhage (3.9%), ascites (2.9%), musculoskeletal pain (2.9%) and bile duct obstruction (2.9%) [5]. Results of the final analysis of FOENIX-CCA2 were consistent with that of the primary analysis, with no new safety signals [20].

2.4.2 Breast Cancer

In an ongoing phase II trial (NCT04024436), eight patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative, metastatic breast cancer harbouring high-level FGFR1 amplification were treated with futibatinib 20 mg once daily in combination with intramuscular fulvestrant 500 mg on days 1 and 15 of cycle 1, and on day 1 of every subsequent 28-day cycle (median treatment duration 8 weeks) [26]. All patients experienced TRAEs, with 25% experiencing grade ≥ 3 TRAEs. The most common TRAEs were hyperphosphatemia (88%; grade ≥ 3: 12%), constipation (62%), transaminase elevation (50%), dry mouth (38%) and alopecia (38%). TRAEs led to treatment discontinuation in one patient, dose reductions in four patients and dosing interruptions in three patients. There were no dose-limiting toxicities (in five evaluable patients), serious adverse events (AEs) or fatal AEs [26].

2.4.3 Urothelial Carcinoma

In an ongoing phase II trial (NCT04601857), six patients with advanced or metastatic urothelial carcinoma were treated with futibatinib 20 mg once daily in combination with intravenous pembrolizumab 200 mg every 21 days (median treatment duration 48 days for futibatinib and 35 days pembrolizumab) [27]. AEs occurred in all patients and they led to any study drug discontinuation, dose interruption and dose modification in three patients each. AEs occurring in more than two patients included diarrhoea, hyperphosphatemia, increased AST and pruritis. Grade 3 AEs (increased AST, maculopapular rash, myositis) occurred in two patients. There were no dose-limiting toxicities or grade 4–5 AEs [27].

2.4.4 Pooled Analysis

An integrated safety analysis showed that futibatinib 20 mg once daily (median treatment duration 111 days) had a manageable tolerability profile and an acceptable safety profile in 318 patients with advanced solid tumours harbouring FGFR aberrations [28]. There was no grade 5 TRAE; grade 3 and 4 TRAEs (incidence 45% and 1%) were manageable with dosage reduction (36%) and/or interruptions (42%). TRAEs led to treatment discontinuation in 3% of patients. The most frequent grade ≥ 3 TRAEs were hyperphosphatemia (23%), increased alanine transaminase (ALT; 6%), increased AST (5%), fatigue (3%), stomatitis (3%) and PPES (≈ 3%). AEs of special interest with futibatinib were hyperphosphatemia, hepatotoxicity, nail toxicities, PPES, retinal disorders and rash. There were no grade 4 hyperphosphatemia and no patient discontinued treatment because of hyperphosphatemia. Grade 3–4 nail toxicity occurred in 1% of patients and there were no grade 3–4 retinal disorders or rash. Most grade ≥ 3 AEs of special interest resolved to grade < 3 within 7–8 days [28].

2.5 Ongoing Clinical Trials

The FOENIX-CCA2 trial in patients with cholangiocarcinoma is still ongoing. A phase III trial (NCT04093362; FOENIX-CCA3) is evaluating futibatinib versus gemcitabine-cisplatin as first-line therapy in patients with advanced cholangiocarcinoma. A phase II trial (NCT04189445) is evaluating futibatinib in tumours with specific FGFR aberrations. The phase II trials in patients with breast cancer (NCT04024436; FOENIX-MBC2) and urothelial cancer (NCT04601857) are ongoing.

A phase Ib/II trial (NCT04965818) is evaluating futibatinib plus binimetinib (a MEK inhibitor) in patients with KRAS mutation-positive advanced NSCLC. The phase Ib

trial (JapicCTI-195063) of futibatinib plus pembrolizumab in patients advanced solid tumours, including oesophageal cancer, is ongoing.

3 Current Status

Futibatinib received its first approval on 30 September 2022 in the USA for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harbouring FGFR2 gene fusions or other rearrangements [29].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-022-01806-z.

Declarations

Funding The preparation of this review was not supported by any external funding.

Authorship and Conflict of interest During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the authors on the basis of scientific completeness and accuracy. Yahiya Y. Syed is a salaried employee of Adis International Ltd/Springer Nature, and declares no relevant conflicts of interest. All authors contributed to the review and are responsible for the article content.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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