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FDA Approval Summary: Futibatinib for Unresectable Advanced or Metastatic, Chemotherapy Refractory Intrahepatic Cholangiocarcinoma with FGFR2 Fusions or Other Rearrangements

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Abstract

On September 30, 2022, the Food and Drug Administration (FDA) granted accelerated approval to futibatinib for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma (iCCA) with fibroblast growth factor receptor 2 (FGFR2) fusions or other rearrangements. Approval was based on Study TAS-120–101, a multicenter, open-label, single-arm trial. Patients received futibatinib 20 mg orally once daily. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DoR) as determined by an independent review committee (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. ORR was 42% (95% [Confidence Interval] CI: 32%, 52%). Median DoR was 9.7 months. Adverse reactions occurring in ≥ 30% patients were nail toxicity, musculoskeletal pain, constipation, diarrhea, fatigue, dry mouth, alopecia, stomatitis, and abdominal pain. The most common laboratory abnormalities (≥ 50%) were increased phosphate, increased creatinine, decreased hemoglobin, and increased glucose. Ocular toxicity (including dry eye, keratitis, and retinal epithelial detachment) and hyperphosphatemia are important risks of futibatinib, which are listed under Warnings and Precautions. This article summarizes the FDA's thought process and data supporting the approval of futibatinib.

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Introduction

Cholangiocarcinoma (CCA) is a rare cancer that arises from epithelial cells of the intrahepatic and extrahepatic bile ducts. Approximately 8,000 to 10,000 patients are diagnosed with CCA each year in the United States [1]. Approximately 65% of tumors originate in the biliary tract within the liver (intrahepatic CCA [iCCA]) and are considered anatomically distinct from tumors that arise extrahepatically (eCCA). Data also suggests that there is variable prevalence of molecular tumor drivers across each subtype [2]. CCA is often advanced and incurable at the time of diagnosis, with a 5-year survival of less than 10%. At the time of NDA submission and approval, for patients with unresectable or metastatic CCA, treatment with gemcitabine and cisplatin was the standard-of-care [3]. In 2022, FDA approved durvalumab in combination with gemcitabine and cisplatin for adult patients with locally advanced or metastatic biliary tract cancer. In patients with advanced disease and disease progression after prior treatment, median overall survival (OS) is approximately 6 months [4].

Fibroblast growth factor receptor 2 (FGFR2) fusions have been detected in approximately 10-20% of CCA with most (87%) of these FGFR2 fusion-positive cases being iCCA [5, 6]. FGFR2 fusions appear to be associated with longer survival compared to patients without fusions [5, 7]. Pemigatinib and infigratinib are orally administered small molecule kinase inhibitors of fibroblast growth factor receptors (FGFR) 1–4. FDA granted accelerated approval to pemigatinib and infigratinib in 2020 and 2021, respectively, for treatment of patients with unresectable advanced or metastatic CCA with FGFR2 fusions or other rearrangements with disease progression after prior therapy [8, 9]. Approval in both cases was based on a demonstration of a durable response rate. Herein, the authors summarize the FDA's review of data supporting the approval of futibatinib for the treatment of previously treated, unresectable advanced or metastatic iCCA with an FGFR2 gene alteration. The investigators' analyses and interpretation of the data have been previously published [10].

Nonclinical Pharmacology and Toxicology

Futibatinib is a small molecule kinase inhibitor of FGFR 1, 2, 3, and 4 that covalently binds FGFR, inhibiting FGFR2 phosphorylation and downstream signaling, and decreasing cell viability in cancer cell lines with FGFR alterations. Findings in rat and dog repeat-dose toxicology studies revealed drug-related effects known to be associated with FGFR inhibition including increases in plasma phosphorus, tissue mineralization, and lesions in bone. The genotoxicity data, including negative *in vivo* studies and a negative mutagenicity assay, indicate that there is a low potential for futibatinib to be genotoxic *in vivo*. Futibatinib was embryofetal toxic in rats at clinically relevant exposures.

Clinical Pharmacology

The recommended dosage of futibatinib is 20 mg administered orally once daily (QD). The systemic exposure of futibatinib (the area under the concentration-time curve, AUC) increased proportionally over the dose range from 4 to 24 mg. There was no accumulation after repeat doses at 20 mg QD. There was no meaningful change in futibatinib AUC when

administered with a high-fat, high-calorie meal, supporting the administration of futibatinib with or without food.

Futibatinib is primarily metabolized by CYP3A and, to a lesser extent, by CYP2C9 and CYP2D6. Futibatinib is a substrate and an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Therefore, avoidance of concomitant administration of futibatinib with dual P-gp and strong CYP3A modulators is recommended.

Data from the dose-finding portion of Study TAS-120–101 showed comparable ORR but increased toxicity at higher doses; patients who received futibatinib 16 mg QD (n=11) appeared to have a lower rate of Grade ≥3 and serious adverse reactions (ARs) and dose reductions due to ARs compared to patients receiving futibatinib 20 mg QD (n=19). Better tolerability of a lower dose is also supported by positive exposure-response relationships for multiple safety outcomes. These findings may suggest an improved safety profile at the 16 mg dose without compromising efficacy compared to the 20 mg dose, though the data are limited by the small numbers of patients in these cohorts and trial design.

Clinical Trial Design

The approval of futibatinib was based upon the results of Study TAS-120–101 (FOENIX-CCA2; NCT02052778) a multicenter, open-label, single-arm trial. The study enrolled patients with previously treated, unresectable advanced or metastatic iCCA harboring an FGFR2 gene fusion or other rearrangement. FGFR2 status was determined by next generation sequencing (NGS) in a central laboratory or by local testing using NGS, fluorescence *in situ* hybridization (FISH), or other assays. Use of local laboratory tests required tumor tissue or circulating tumor DNA (ctDNA) for the purposes of performing central retrospective confirmatory testing for the presence of an FGFR2 rearrangement. Qualifying in-frame fusions and other rearrangements were predicted to have a breakpoint within intron 17/exon 18 of the FGFR2 gene, leaving the FGFR2 kinase domain intact.

The study's major efficacy outcomes were overall response rate (ORR) and duration of response (DoR) as determined by an independent review committee (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [11]. Disease response and progression were measured using computed tomography or magnetic resonance imaging at baseline, end of Cycles 2 and 4, and every 3 cycles thereafter. Key eligibility criteria included the presence of measurable disease, documented disease progression following at least one systemic gemcitabine-and platinum-based chemotherapy, and ECOG performance status of 0–1. Patients received futibatinib 20 mg orally QD until disease progression or unacceptable toxicity.

Results

Efficacy

As of the cutoff date of October 1, 2020, the efficacy evaluable population consisted of 103 patients. Table 1 summarizes the demographic characteristics of the efficacy population. Most patients had in-frame fusions (78%), with the remainder having other FGFR2 rearrangements. Among the patients with in-frame FGFR2 gene fusions, the most common

FGFR2 fusion identified was FGFR2-BICC1 (23%). All patients had received at least one prior line of systemic therapy (30% received 2 prior lines; 23% received 3 or more prior lines). All patients had received prior gemcitabine and platinum-based therapy, including 94 patients (91%) who received gemcitabine in combination with cisplatin.

Table 2 summarizes the efficacy data. In the 103 patients with FGFR2 gene fusion/rearrangement-positive iCCA who received at least one dose of futibatinib, the estimated ORR was 42% (95% confidence interval [CI]: 32%, 52%). All responses were partial responses.

Safety—The safety analysis was based on 103 patients who received at least one dose of futibatinib. The median duration of treatment was 9.1 months (range: 0.5 to 24.5 months). Grading of adverse events (AEs) was based on CTCAE v4.03 and all patients experienced at least one AE. A total of 40 patients (39%) experienced serious adverse events (SAE), including 34 patients (33%) who experienced a Grade ≥3 SAE.

The most common (≥ 20%) adverse reactions (see Table 3) 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 erythrodysesthesia syndrome, and vomiting.

The most common (≥50%) laboratory abnormalities (see Table 4) were increased phosphate, increased creatinine, decreased hemoglobin, increased glucose, increased calcium, decreased sodium, decreased phosphate, and increased alanine aminotransferase.

Hyperphosphatemia and ocular disorders result from known pharmacodynamic effects of FGFR2 inhibition and were therefore adverse events of special interest for futibatinib. In Study TAS-120–101, hyperphosphatemia was reported in 97% of patients; 39% of patients experienced Grade 3–4 events (serum phosphate > 7 mg/dL).

The median time to onset of hyperphosphatemia was 5 days (range 3–117 days) and 93% of patients received phosphate-lowering therapy. Due to the incidence of hyperphosphatemia following treatment with futibatinib and the need for early identification and intervention to avoid clinical sequelae, hyperphosphatemia is described in Section 5 of the United States package insert (USPI) for futibatinib and management guidelines are included in the dosage modification section.

The analysis of the incidence of ocular events in Study TAS-120–101 included AEs of dry eyes in 25% of patients (including patients who experienced increased lacrimation, keratitis, photokeratitis, punctate keratitis, and ulcerative keratitis) and retinal pigment epithelial detachment (RPED) in 8% of patients. The median time to first onset of RPED was 42 days. Ocular toxicity led to dose interruptions in 6% of patients. Given the significance and sometimes asymptomatic nature of some ocular events, Section 5.1 of the USPI recommends comprehensive ophthalmic examination including optic coherence tomography prior to initiation of futibatinib, every 2 months for the first 6 months of treatment, and every 3 months thereafter and to refer patients for ophthalmic evaluation urgently for onset of visual symptoms.

Skin toxicities were reported in 77% of patients, and included nail disorders, dry skin, and palmar-plantar erythrodysesthesia.

Discussion / Regulatory Insights

The review team concluded that the overall risk:benefit assessment favored approval of futibatinib for the treatment of patients with relapsed/refractory advanced or metastatic iCCA harboring an FGFR2 gene alteration (Table 5). The magnitude and durability of the ORR demonstrated in Study TAS-120–101 were considered clinically meaningful and reasonably likely to predict clinical benefit, thus meeting the evidentiary requirements for accelerated approval. The indication was restricted to patients with iCCA because the TAS-120–101 study restricted eligibility to these patients. The observed safety profile of futibatinib in this patient population was generally consistent with the known toxicity profile of the pharmacological class. The risks of futibatinib are largely manageable with safety monitoring, treatment modifications, and supportive care.

There was a high rate of dose modifications/interruptions (77%) among patients receiving futibatinib at the approved dosage of 20 mg administered once daily. Additionally, data from dose escalation cohorts suggests a similar response rate with an improved safety profile at the lower dose of 16 mg daily, but the small number of patients evaluated precludes a conclusive determination of the benefits and risks of this lower dose and further dose evaluation is needed. As such, a post-marketing requirement (PMR) was issued for a prospective randomized dose optimization study to further characterize the safety and efficacy of futibatinib 16 mg administered once daily compared to the approved 20 mg QD dosage, to determine whether patients receiving the lower dose experience reduced toxicity while preserving efficacy.

As a condition of accelerated approval, confirmatory studies may be required to verify clinical benefit. FDA guidance states that such trials should be underway at the time of accelerated approval to help ensure timely verification or refutation of clinical benefit. An ongoing randomized controlled clinical trial (FOENIX-CCA3; NCT04093362) comparing the efficacy of futibatinib to gemcitabine plus cisplatin in patients with previously untreated CCA with an FGFR2 fusion or rearrangement was planned as a confirmatory trial and initiated prior to NDA submission. However, the applicant noted accrual to the trial has been slower than anticipated and will likely result in the trial not being completed in a timely fashion. FDA considered what additional investigation could provide confirmatory data to further support a favorable risk-benefit assessment. Among factors FDA considered in this case in addition to the rarity of the population and the unmet medical need, were the magnitude of treatment effect, safety profile of the drug, the (lack of) feasibility of conducting a randomized controlled trial, the treatment landscape for the disease at the time of the marketing authorization, and residual uncertainty regarding the potential need to further mitigate toxicity through additional dose optimization. Ultimately, FDA determined that further characterization of durable ORR in the context of dose optimization could potentially provide these data.

At the time of this accelerated approval, a companion diagnostic test to identify FGFR2 fusions/rearrangements was not available. A post-marketing commitment was requested and agreed to by the applicant to develop a companion diagnostic test for this indication.

Conclusion

Futibatinib received accelerated approval based on durable overall response rate and an acceptable safety profile, providing another therapeutic option for the treatment of patients with relapsed/refractory unresectable or metastatic iCCA with an FGFR2 fusion or other rearrangement. The observed ORR and DoR represents a clinically meaningful improvement over available therapies for second- and later-line treatment, reasonably likely to predict clinical benefit. Available clinical and pharmacologic data suggests that further dose optimization at a lower dosage may provide additional confirmatory evidence of the safety and efficacy of futibatinib. A randomized post-marketing dose-optimization study will evaluate the 16 and 20 mg doses of futibatinib in patients with relapsed/refractory unresectable or metastatic CCA with an FGFR2 fusion or other rearrangement.

References

1. Blechacz B and Gores GJ, Cholangiocarcinoma: advances in pathogenesis, diagnosis, and treatment. Hepatology, 2008. 48(1): p. 308–21. [PubMed: 18536057]
2. Gad MM, et al. , Epidemiology of Cholangiocarcinoma; United States Incidence and Mortality Trends. Clin Res Hepatol Gastroenterol, 2020. 44(6): p. 885–893. [PubMed: 32359831]
3. Blumenthal GM, et al. , Oncology Drug Approvals: Evaluating Endpoints and Evidence in an Era of Breakthrough Therapies. Oncologist, 2017. 22(7): p. 762–767. [PubMed: 28576856]
4. Lamarca A, et al. , Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol, 2021. 22(5): p. 690–701. [PubMed: 33798493]
5. Jain A, et al. , Cholangiocarcinoma With FGFR Genetic Aberrations: A Unique Clinical Phenotype. JCO Precis Oncol, 2018. 2: p. 1–12.
6. Krook MA, et al. , Efficacy of FGFR Inhibitors and Combination Therapies for Acquired Resistance in FGFR2-Fusion Cholangiocarcinoma. Mol Cancer Ther, 2020. 19(3): p. 847–857. [PubMed: 31911531]
7. Liu PCC, et al. , INCB054828 (pemigatinib), a potent and selective inhibitor of fibroblast growth factor receptors 1, 2, and 3, displays activity against genetically defined tumor models. PLoS One, 2020. 15(4): p. e0231877. [PubMed: 32315352]
8. Pemigatinib prescribing information. Drugs@FDA [Database on the Internet]. Silver Spring, MD: U.S. Food and Drug Administration. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213736s001lbl.pdf.
9. Roydhouse JK, et al. , Analyzing patient-reported outcome data when completion differs between arms in open-label trials: an application of principal stratification. Pharmacoepidemiol Drug Saf, 2019. 28(10): p. 1386–1394. [PubMed: 31410963]
10. Goyal L, et al. , Updated results of the FOENIX-CCA2 trial: Efficacy and safety of futibatinib in intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 fusions/rearrangements. Journal of Clinical Oncology, 2022. 40(16_suppl): p. 4009–4009.
11. Eisenhauer EA, et al. , New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer, 2009. 45(2): p. 228–47. [PubMed: 19097774]
12. U.S. Food and Drug Administration. NDA Multi-disciplinary Review and Evaluation (NDA 214665) LYTGOBI (futibatinib). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214801Orig1s000TOC.cfm

13. Lytgobi USPI. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214801Orig1s000lbledt.pdf

Table 1:

Demographics and Baseline Characteristics.

	TAS-120-101 Phase 2 20 mg QD (N=103) n (%)
Age (years)	
Mean (SD)	55.7 (12.23)
Median (min, max)	58.0 (22, 79)
Age Groups	
<65 years	80 (77.7)
≥65 years	23 (22.3)
Sex, n (%)	
Male	45 (43.7)
Female	58 (56.3)
Race, n (%)	
Caucasian/White	51 (49.5)
Black or African American	8 (7.8)
Asian/Oriental	30 (29.1)
Native Hawaiian or Other Pacific Islander	1 (1.0)
Unknown	13 (12.6)
Region, n (%)	
North America	47 (45.6)
Europe	28 (27.2)
Asia Pacific *	14 (13.6)
Japan	14 (13.6)
Ethnicity, n (%)	
Hispanic or Latino	2 (1.9)
Not Hispanic or Latino	89 (86.4)
Unknown	12 (11.7)
ECOG Performance Status, n (%)	
0	48 (46.6)
1	55 (53.4)

* Includes the following countries: Hong Kong, Korea, and Taiwan.

Source: U.S. Food and Drug Administration. NDA Multi-disciplinary Review and Evaluation (NDA 214801) (12).

Table 2:

Efficacy Results in TAS-120–101.

Efficacy Parameter	**Futibatinib 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)
DoR ≥6 months, n (%)	31 (72%)
DoR ≥12 months, n (%)	6 (14%)

Source: U.S. Food and Drug Administration. NDA Multi-disciplinary Review and Evaluation (NDA 214801) (12).

[a]The 95% confidence interval (CI) was calculated using Clopper–Pearson method.

[b]The 95% confidence interval (CI) was constructed based on a log-log transformed CI for the survival function.

Table 3:

Adverse Reactions (≥15%) in Study TAS-120–101.

	Futibatinib N = 103	
Adverse Reaction	**All Grades[a] (%)**	**Grade 3 (%)**
Skin and subcutaneous tissue disorders		
Nail toxicity[b]	47	1.9
Alopecia	34	0
Dry skin	29	0
Palmar-plantar erythrodysesthesia syndrome	21	4.9
Gastrointestinal disorders		
Constipation	39	0
Diarrhea[c]	39	1
Dry mouth	35	0
Stomatitis[d]	30	6
Abdominal pain[e]	30	2.9
Nausea	24	1.9
Vomiting[f]	20	1
General disorders		
Fatigue[g]	37	8
Metabolism and nutrition disorders		
Decreased appetite	23	2.9
Musculoskeletal and connective tissue disorder		
Musculoskeletal pain[h]	43	3.9
Arthralgia[i]	25	0
Eye disorders		
Dry eye[j]	25	1
Nervous system disorders		
Dysgeusia[k]	25	0
Infections		
Urinary tract infection[l]	23	2.9
Investigations		
Weight decreased	18	3.9

Source: LYTGOBI USPI (13).

[a] Graded per NCI CTCAE 4.03.

[b] Includes nail toxicity, nail disorder, nail discoloration, nail dystrophy, nail hypertrophy, nail infection, nail pigmentation, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, and paronychia.

[c] Includes diarrhea, colitis, and gastroenteritis.

[d] Includes stomatitis, glossitis, mouth ulceration, mucosal inflammation, pharyngeal inflammation, and tongue ulceration.

[e] Includes abdominal pain, abdominal discomfort, abdominal pain upper, gastrointestinal pain, and hepatic pain.

[f] Includes vomiting and hematemesis.

[g] Includes fatigue and asthenia.

[h] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and spinal pain.

[i] Includes arthralgia and arthritis.

[j] Includes dry eye, keratitis, lacrimation increased, photokeratitis, punctate keratitis, and ulcerative keratitis.

[k] Includes dysgeusia, ageusia, and taste disorder.

[l] Includes urinary tract infection, cystitis, and dysuria.

Table 4:

Laboratory Abnormalities (≥10%) Worsening from Baseline in TAS-120–101.

	Futibatinib N = 103	
Laboratory Abnormality[a]	**All Grades[b] (%)**	**Grades 3 or 4 (%)**
Hematology		
Decreased hemoglobin	52	6
Decreased lymphocytes	46	10
Decreased platelets	42	1
Decreased leukocytes	33	1.1
Decreased neutrophils	31	1.6
Chemistry		
Increased phosphate[c]	97	39
Increased creatinine[d]	58	0
Increased glucose	52	4.9
Increased calcium	51	1.2
Decreased sodium	51	15
Decreased phosphate	50	20
Increased alanine aminotransferase	50	7
Increased alkaline phosphatase	47	4.9
Increased aspartate aminotransferase	46	13
Decreased albumin	31	2.4
Increased creatine kinase	31	5
Increased bilirubin	28	0
Decreased glucose	25	0
Decreased potassium	22	2.1
Increased potassium	16	2
Coagulation		
Increased activated partial thromboplastin time	36	8
Increased prothrombin international normalized ratio	25	0

Source: LYTGOBI USPI (13).

[a] Graded per NCI CTCAE 4.03.

[b] Percentages are based on patients with data at both baseline and at least one post-baseline data value.

[c] NCI CTCAE 4.03 does not define grades for increased phosphate. Laboratory value shift table categories were used to assess increased phosphorus levels (Grades ≥3 defined as >7 mg/dL).

[d] Graded based on comparison to upper limit of normal.

Table 5.

FDA Benefit-Risk Analysis.

Dimension	Evidence and uncertainties	Conclusions and reasons
Analysis of condition	• FGFR2 fusions/rearrangements are present in 10-20% of patients with iCCA.	iCCA with FGFR2 fusions/rearrangements is a rare, serious, and life threatening disease.
Current treatment options	• Treatment options after first-line gemcitabine + cisplatin chemotherapy are limited. • No treatment has received regular FDA approval for relapsed CCA. • FGFR inhibitors pemigatinib and infigratinib were approved under the accelerated approval pathway and therefore are not considered available therapy.	Patients with CCA with a FGFR2 gene fusion or other rearrangement who have received at least one prior line of treatment have an unmet medical need.
Benefit	• The ORR benefit in 103 patients with iCCA enrolled in Study TAS-120-101 was 42% (95% confidence interval [CI]: 32, 52) • The median DoR was 9.7 months (95% CI: 7.6, 17.1) • 43 patients had confirmed PR; 31/43 patients (72%) had a response duration ≥6 months.	There is a meaningful improvement in the magnitude of ORR observed in patients treated with futibatinib in Study TAS-120-101 compared to available therapy. The DoR is also clinically meaningful in the context of a disease with estimated survival of 5-6 months. PMRs have been issued for dose optimization studies.
Risk and risk management	• The most common AEs (≥ 30%) were nail toxicity, musculoskeletal pain, constipation, diarrhea, fatigue, dry mouth, alopecia, stomatitis, and abdominal pain. • The most common laboratory abnormalities (≥ 50%) were increased phosphate, increased creatinine, decreased hemoglobin, and increased glucose. • Ocular toxicity (including dry eye, keratitis, and retinal epithelial detachment), and hyperphosphatemia are important risks associated with futibatinib.	A PMR was issued for further characterization of ocular toxicity. Information in the Warnings and Precautions and Dosage and Administration sections of product labeling address these toxicities adequately.

Source: U.S. Food and Drug Administration. NDA Multi-disciplinary Review and Evaluation (NDA 214801) (12).