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Review Article

Futibatinib, an Irreversible FGFR1-4 Inhibitor for the Treatment of *FGFR*-Aberrant Tumors

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Abstract

Fibroblast growth factor receptors (FGFR) are emerging as an important therapeutic target for patients with advanced, refractory cancers. Most selective FGFR inhibitors under investigation show reversible binding, and their activity is limited by acquired drug resistance. This review summarizes the preclinical and clinical development of futibatinib, an irreversible FGFR1-4 inhibitor. Futibatinib stands out among FGFR inhibitors because of its covalent binding mechanism and low susceptibility to acquired resistance. Preclinical data indicated robust activity of futibatinib against acquired resistance mutations in the FGFR kinase domain. In early-phase studies, futibatinib showed activity in cholangiocarcinoma, and gastric, urothelial, breast, central nervous system, and head and neck cancers harboring various *FGFR* aberrations. Exploratory analyses indicated clinical benefit with futibatinib after prior FGFR inhibitor use. In a pivotal phase II trial, futibatinib demonstrated durable objective responses (42% objective response rate) and tolerability in previously treated patients with advanced intrahepatic cholangiocarcinoma harboring *FGFR2* fusions or rearrangements. A manageable safety profile was observed across studies, and patient quality of life was maintained with futibatinib treatment in patients with cholangiocarcinoma. Hyperphosphatemia, the most common adverse event with futibatinib, was well managed and did not lead to treatment discontinuation. These data show clinically meaningful benefit with futibatinib in *FGFR2*-rearrangement-positive cholangiocarcinoma and provide support for further investigation of futibatinib across other indications. Future directions for this agent include elucidating mechanisms of resistance and exploration of combination therapy approaches.

Key words: fibroblast growth factor receptor; FGFR inhibitor; futibatinib; cholangiocarcinoma; safety; clinical trials.

Implications for Practice

Patients with *FGFR*-altered cancers have limited treatment options in advanced stages. Promising responses have been observed with FGFR inhibitors; however, acquired resistance is an emerging concern. This review summarizes data surrounding futibatinib, the only second-generation FGFR1-4 inhibitors in phase II/III clinical development. Futibatinib has shown durable efficacy and tolerability in cholangiocarcinoma with *FGFR2* fusions/rearrangements, and recently received approval from the US Food and Drug Administration for this indication. Futibatinib has demonstrated antitumor activity across several *FGFR*-aberrant tumors, spurring the initiation of several phase II trials of futibatinib or futibatinib-containing combinations in other tumor types.

Introduction

Fibroblast growth factors (FGFs) and their receptors (FGFRs) play an integral role in regulating a wide range of biological processes[1] and dysregulation of the FGFR pathway is associated with oncogenesis.[2-7] Approximately 7% of all cancers harbor *FGFR* aberrations, with type and prevalence varying widely.[8] Thus, FGFR has emerged as an important therapeutic target. Most FGFR inhibitors in development are ATP-competitive, reversible inhibitors, which are associated with acquired resistance.[9,10] Futibatinib, an irreversible FGFR1-4 inhibitor, is the most advanced covalent inhibitor in clinical development for multiple cancer types.[11] Here, we briefly describe the role of FGFR and FGFR inhibitors in cancer and discuss recent data supporting futibatinib as a clinically meaningful, second-generation FGFR inhibitor.

FGFR as an Oncologic Target

The FGFR pathway includes a family of 22 FGF ligands, which primarily convey cellular signals through 4 transmembrane tyrosine kinase receptors (FGFR1-4).[12,13] Typically, FGFR activation induces cell proliferation and migration,[14] but it can also drive cell differentiation or negatively regulate proliferation.[15,16] Aberrant FGFR signaling (generally constitutive FGFR activation) can promote tumorigenesis,

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support tumor survival, and confer resistance to chemotherapy through anti-apoptotic signaling,[2-7,17,18] rendering *FGFR*-altered tumors difficult to treat.[19]

Analysis of 17 different cancer types showed that 7% had *FGFR* aberrations, found most commonly in urothelial, breast, endometrial, and squamous cell lung cancer (Fig. 1). Gene amplifications, mutations, and rearrangements accounted for 66%, 26%, and 8% of *FGFR* aberrations identified, respectively.[8] These findings suggest FGFR inhibition as a potential therapeutic strategy in multiple tumor types.

Selective, Small-Molecule FGFR Inhibitors

FGFR inhibitors mostly target the FGFR kinase domain, inhibiting FGFR signaling. Although several therapeutic modalities are being investigated for FGFR inhibition (reviewed elsewhere[39]), small-molecule FGFR inhibitors remain the most widely investigated. These inhibitors vary in their selectivity (specific to FGFR or multikinase) and mode of binding to the FGFR kinase domain (type I, type II, reversible, or irreversible).[40] Reversible ATP-competitive FGFR inhibitors currently under investigation, including derazantinib, erdafitinib, pemigatinib, and infigratinib (Table 1; Supplementary Table S1), engage primarily in noncovalent interactions with amino acids in the hinge and surrounding regions of the ATP-binding pocket in the FGFR kinase domain. Irreversible inhibitors, such as PRN1371, futibatinib, and fisogatinib, form a covalent bond, generally with a conserved cysteine in the FGFR kinase domain.[40,54]

Selective FGFR inhibitors have shown promising activity in various *FGFR*-aberrant cancer types. To date, the US Food and Drug Administration (FDA) has approved erdafitinib in patients with metastatic urothelial carcinoma harboring *FGFR2/3* aberrations who were previously treated,[55] and pemigatinib and infigratinib for second- or later-line treatment of unresectable cholangiocarcinoma (CCA) with *FGFR2* fusions or rearrangements.[49,55] An emerging concern with these inhibitors is acquired resistance, which leads to disease progression.[9,56,57] One mechanism of acquired resistance is the development of secondary "gatekeeper" mutations in the FGFR kinase domain that "block" FGFR inhibitor binding through steric hindrance.[9,39,56,58] Reversible inhibitors, such as erdafitinib, infigratinib, and pemigatinib, are largely ineffective against these mutations.[56] Second-generation inhibitors that retain activity against these mutations and have a lower susceptibility to resistance are sorely needed.

Futibatinib, a Potent, Irreversible FGFR1-4 Inhibitor

Futibatinib is a structurally novel, highly selective, and potent FGFR inhibitor,[11] which binds covalently and irreversibly to a conserved cysteine residue in the FGFR kinase domain within the ATP-binding pocket[54] (Fig. 2). As this cysteine residue is conserved across all FGFR receptors, futibatinib inhibits the kinase activity of all 4 FGFR isoforms. The distinct binding site and irreversible binding render futibatinib less susceptible to drug resistance mutations than reversible, ATP-competitive inhibitors.

Preclinical Development

In vitro characterization of futibatinib against a panel of 296 kinases demonstrated high selectivity and potent inhibition of all 4 FGFR isoforms with half-maximal inhibitory concentration values ranging from 1.4 nmol/L to 3.7 nmol/L.[11] Futibatinib selectively inhibited cancer cell lines of diverse tissue origins

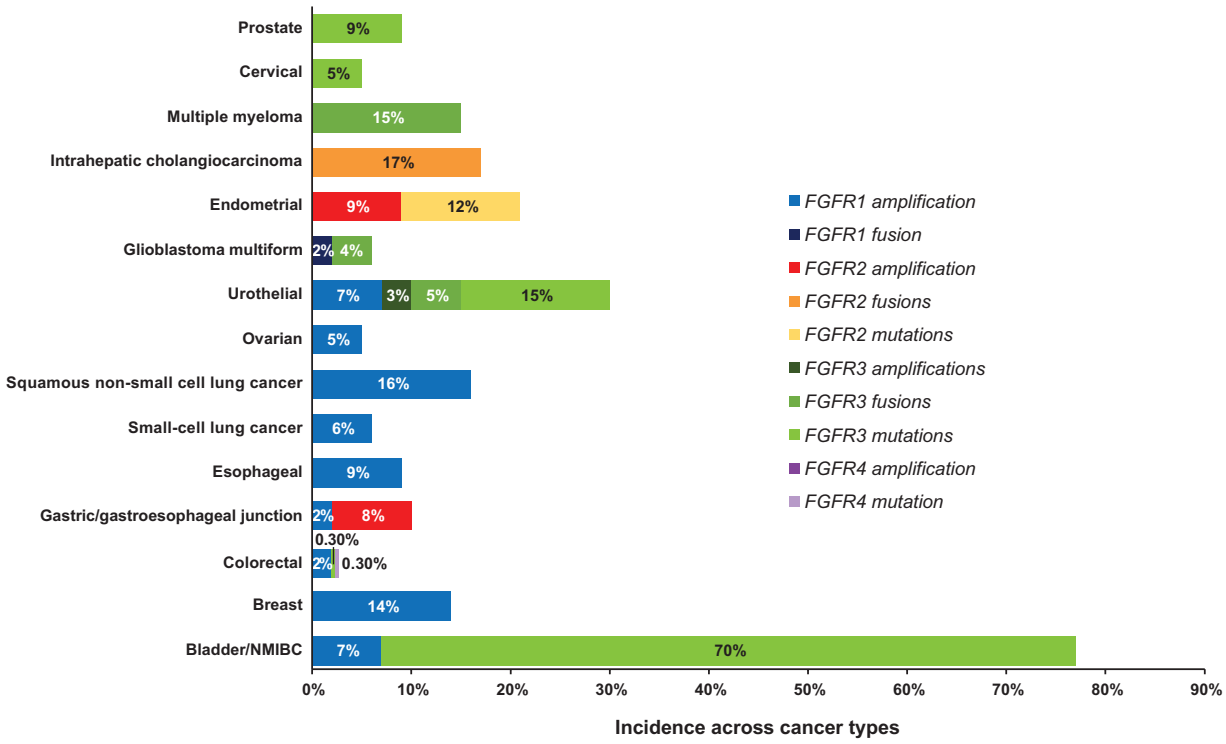
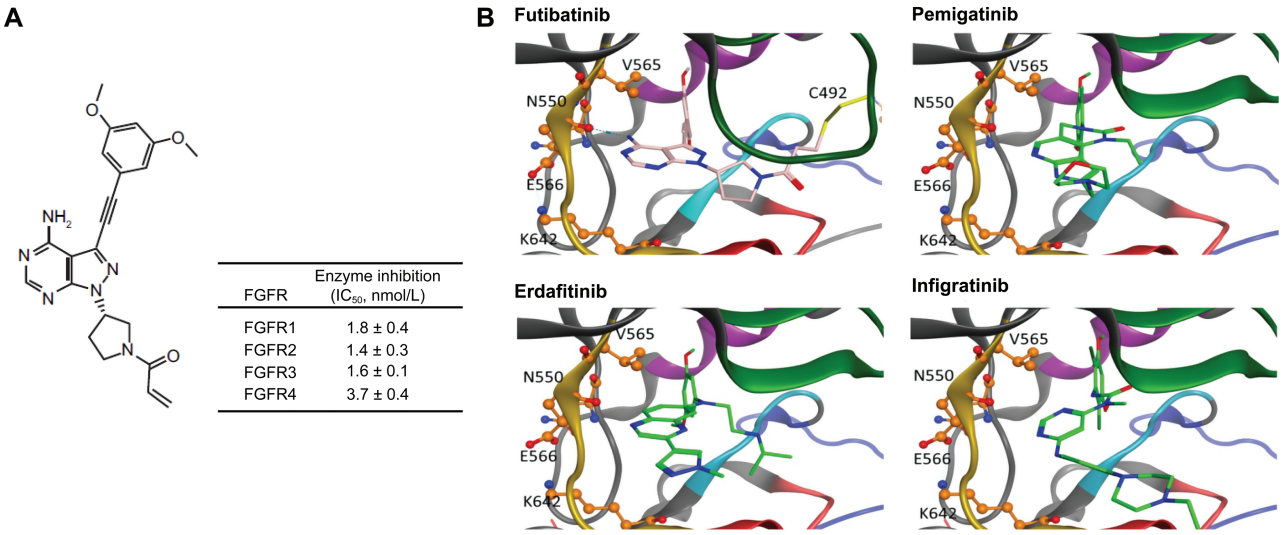


Figure 1. Incidence of *FGFR* aberrations across cancer types. This bar chart shows the incidence of the indicated *FGFR* aberrations across various cancer types, data collated from a number of published reports.[2,8,13,20-38] In cases where a range of incidences were noted, the upper limit of the range is indicated in this chart. Abbreviation: NMIBC, non-muscle invasive bladder cancer.

Table 1. Overview of published studies reporting clinical activity of FGFR inhibitors.

FGFR inhibitor	Type/isoform selectivity	Tumor/*FGFR* aberration	Trial phase/ number	*n*	Results				Ref
					ORR (%)	mDOR (mo)	mPFS (mo)	mOS (mo)	
AZD4547	Reversible FGFR 1-3 inhibitor	Squamous cell non-small cell lung cancer/ *FGFR1-3* amplification, fusion, or substitution	Phase II NCT02965378	27[a]	7	1.5, 2.9[b]	2.7	7.5	41
		Refractory cancers, lymphomas, or myelomas/ Any *FGFR1-3* aberration	Phase II NCT02465060	48	8	7.9	3.4	7.2	42
Derazantinib	Reversible FGFR1-3 inhibitor	iCCA/ *FGFR2* fusions	Phase I/II NCT01752920	29	20.7	4.6	5.7	NR	43
Debio1347	Reversible FGFR1-3 inhibitor	Advanced solid tumors/ *FGFR1-3* aberrations	Phase I NCT01948297	58[c]	10.5	NR	NA	NA	44
Erdafitinib	Reversible FGFR1-4 inhibitor	CCA/ *FGFR2/3* alterations	Phase II NCT02699606	12[d]	50.0	6.8	5.6	NR	45
		Urothelial/*FGFR3* mutation or *FGFR2/3* fusions	Phase II NCT02365597	99	34	5.6	5.5	13.8	46
Fisogatinib	Irreversible FGFR4	Hepatocellular/ FGF19 positive	Phase I	66[e]	17	5.3	3.3	NA	47
Futibatinib	Irreversible FGFR1-4 inhibitor	iCCA/ *FGFR2* fusions/rearr.	Phase II NCT02052778	103	41.7	9.7	9.0	21.7	48
Infigratinib	Reversible FGFR1-3 inhibitor	CCA/ *FGFR2* fusions/rearr.	Phase II NCT02150967	108	23.1	5.0	7.3	12.2	49
		Urothelial/*FGFR3* alterations	Phase I expansion NCT02657486	67	25.4	5.1	3.8	7.8	50
Pemigatinib	Reversible FGFR1-3 inhibitor	CCA/*FGFR2* fusions/rearr.	Phase II NCT02924376	107[f]	35.5	7.5[g]	6.9	21.1	51
		Urothelial/*FGF* or *FGFR* alterations	Phase II NCT02872714	100	25	NR	NR	NR	52
Rogaratinib	Reversible FGFR1-4 inhibitor	Adv cancers/FGFR mRNA-overexpressing	Phase I NCT01976741	126[h]	15	NR	93 d	NR	53

[a]AZD4547-treated evaluable patients.
[b]Partial responses were observed in 2 patients, response durations are listed for each patient.
[c]57 patients were evaluable for response.
[d]12 evaluable patients (Asian population).
[e]Response evaluable patients who were FGF19-positive.
[f]Subgroup of population with *FGFR2* fusions or rearrangements.
[g]Updated median DOR of 9.1 months is reported in the US Prescribing Information.
[h]Total enrollment of 126 pts. A total of 121 pts had available progression-free survival. One hundred pts were evaluable for response assessment.
Abbreviations: Adv, advanced; CCA, cholangiocarcinoma; DOR, duration of response; FGFR, fibroblast growth factor receptors; iCCA, intrahepatic CCA; mo, months; mDOR, median DOR; mOS, median overall survival; mPFS, median progression-free survival; NA, not applicable; NR, not reported; ORR, objective response rate; pts, patients; ref, references.



FGFR	Enzyme inhibition (IC_{50}, nmol/L)
FGFR1	1.8 ± 0.4
FGFR2	1.4 ± 0.3
FGFR3	1.6 ± 0.1
FGFR4	3.7 ± 0.4

Figure 2. Futibatinib structure and predicted binding of futibatinib and other reversible FGFR inhibitors to the FGFR kinase domain. **(A)** Chemical structure of futibatinib and in vitro inhibitory activity. Adapted from *Cancer Research*, 2020, 80(22), 4986-4997, Sootome H, Fujita H, Ito K, et al., Futibatinib Is a Novel Irreversible FGFR 1-4 Inhibitor That Shows Selective Antitumor Activity against FGFR-Deregulated Tumors, with permission from AACR.[11] **(B)** Predicted interactions of futibatinib, erdafitinib, and pemigatinib with the ATP binding pocket of the FGFR2 wild-type kinase domain. Amino acid residues altered in identified resistance mutations are labeled and shown as ball and stick models. Kinase domain regions are depicted as follows: gold, hinge region; red, catalytic loop; blue, activation domain; purple, c-alpha-helix; green, P-loop; cyan, DFG motif. Futibatinib (pink and blue stick figure) binds covalently to C492 in the P-loop (yellow stick), enabling it to persist in the ATP-binding pocket irrespective of the presence of resistance mutations, which block access of reversible FGFR inhibitors such as erdafitinib, pemigatinib, or infigratinib (green and blue stick figures). Reproduced with permission from Goyal et al. 2023.[48] Abbreviations: DFG, Asp-Phe-Gly; FGFR, fibroblast growth factor receptors; IC_{50}, half-maximal inhibitory concentration. From *The New England Journal of Medicine*, Goyal L, Meric-Bernstam F, Hollebecque A, et al., Futibatinib for FGFR2-Rearranged Intrahepatic Cholangiocarcinoma, 388, 228-239. Copyright © (2023) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

(gastric, lung, multiple myeloma, bladder, endometrial, and breast) harboring a variety of *FGFR* aberrations. Additionally, futibatinib treatment led to significant dose-dependent tumor reductions and sustained FGFR kinase inhibition in *FGFR*-aberrant human tumor xenograft mice models.

In vitro futibatinib treatment of gastric cancer cells was associated with a lower risk of developing drug resistance due to *FGFR* escape mutations than the reversible FGFR inhibitor AZD4547.[11] Futibatinib also demonstrated greater inhibition of secondary *FGFR2* kinase domain drug-resistant mutations, including the gatekeeper mutation V565I/L, than AZD4547, infigratinib, pemigatinib, or erdafitinib.[11]

In an unbiased library-based analysis, the activity of futibatinib and other FGFR inhibitors were examined against drug-resistant *FGFR2* kinase domain mutations generated by random mutagenesis[59] and transfected in a Ba/F3 cell system dependent on FGFR2 signaling for growth. Futibatinib showed the most robust inhibition of drug-resistant *FGFR2* kinase domain mutations (also clinically relevant[9,56,57,60]) as well as the lowest propensity for emergence of resistant clones with prolonged treatment.

Futibatinib Early Clinical Data: Dose Selection and Pharmacology

A first-in-human, phase I dose-escalation study (NCT02052778) evaluated futibatinib safety and pharmacokinetics/pharmacodynamics in 86 patients with advanced solid tumors (83% with *FGF/FGFR* aberrations) who were heavily pretreated.[61] Futibatinib was administered on daily (QD) continuous dosing (4-24 mg QD; n = 44) and 3 times a week (TIW) intermittent dosing (8-200 mg TIW; n = 42) schedules. Dose-limiting toxicities (DLTs), all related to liver enzyme elevations, occurred in 3 patients receiving futibatinib 24 mg QD. No DLTs were observed with TIW dosing. All QD doses tested showed dose-proportional pharmacokinetics, whereas TIW dosing was associated with saturation between 80 mg and 200 mg TIW. As renal handling of phosphorus is mediated by FGF23 signaling,[62] serum phosphorus levels were evaluated as an on-target effect and chosen as a pharmacodynamic marker. While serum phosphorus levels correlated positively with futibatinib dose and exposure for both QD and TIW dosing, this correlation was stronger with QD vs. TIW dosing. Similar data were observed in a phase I dose-escalation study in patients with advanced solid tumors from Japan (JapicCTI-142552).[63] Based on these data, futibatinib 20 mg QD was selected as the recommended phase II dose.

Futibatinib showed a manageable safety profile.[61] The most common treatment-emergent adverse events were hyperphosphatemia, diarrhea, and constipation. In addition, encouraging preliminary antitumor activity was observed in this heavily pretreated population, particularly in those with intrahepatic CCA (iCCA). Across cohorts, 5 patients (6%) experienced partial responses (PRs) and 48% (n = 41) achieved stable disease (SD). Most patients with PRs or SD had tumors harboring *FGF/FGFR* aberrations; those with PRs included 3 patients with iCCA, all harboring *FGFR2* fusions, and 2 patients with *FGFR1*-mutant brain tumors. Among patients with CCA, 75% (18/24) experienced a PR or SD.

Futibatinib pharmacokinetics were evaluated in healthy adult volunteers in multiple open-label, phase I studies. An absorption, distribution, metabolism, and excretion study with [^{14}C]-futibatinib identified futibatinib as the most abundant component circulating in plasma; other

metabolites accounted for 9%-13% of circulating components.[64] [^{14}C]-futibatinib was mainly excreted through the fecal route after metabolism, and no unmetabolized futibatinib was detected in the feces or urine.

In a food-effect and drug-drug interaction (DDI) study with a proton pump inhibitor (PPI; lansoprazole), consuming a high-fat, high-calorie meal slightly lowered futibatinib oral bioavailability, and delayed time to futibatinib maximum plasma concentration, but the differences were not clinically meaningful. Coadministration of lansoprazole had no clinically relevant effect on futibatinib pharmacokinetics, indicating that futibatinib can be coadministered with PPIs.[64,65]

Other phase I studies in healthy adult volunteers evaluated the involvement of futibatinib in the common drug metabolizing CYP3A pathway.[66] DDIs were assessed between futibatinib and midazolam (a sensitive CYP3A substrate), itraconazole (a strong dual inhibitor of CYP3A and P-gp), and rifampin (a strong dual inducer of CYP3A and P-gp).[65] Multiple doses of futibatinib did not affect the pharmacokinetics of midazolam; therefore, futibatinib is not expected to affect the exposure of concomitant medications metabolized via CYP3A. However, itraconazole coadministration resulted in higher peak plasma concentrations and significant increases in plasma exposure of futibatinib compared with futibatinib alone, and coadministration of rifampin decreased futibatinib exposure. Thus, coadministering futibatinib with strong dual inhibitors or inducers of CYP3A and P-gp should be avoided because of potential significant DDIs.

Activity of Futibatinib in CCA

Based on results from the phase I dose escalation study,[61] the phase I dose expansion study evaluated futibatinib in a larger population of patients with advanced solid tumors harboring *FGF/FGFR* aberrations, including a sizeable CCA population.[67] Among 64 patients with *FGFR*-altered CCA who received futibatinib 20 mg QD, the objective response rate (ORR) was 15.6%, and in the subgroup of patients with iCCA harboring *FGFR2* fusions/rearrangements (n = 42), the ORR was 16.7%. Median duration of response (DOR) was 5.3 months and 6.9 months, respectively, and disease control rate (DCR) was 72% and 79%, respectively. In patients with *FGFR2* fusion/rearrangement–positive iCCA treated with either futibatinib 20 mg or 16 mg QD, the overall ORR was 25.4% (15/59). These data formed the basis for further study of futibatinib in patients with *FGFR2*-rearrangement–positive iCCA.

The pivotal phase II FOENIX-CCA2 study investigated futibatinib in 103 patients with advanced unresectable iCCA harboring *FGFR2* fusions or rearrangements after one or more lines of systemic chemotherapy.[48] FOENIX-CCA2 surpassed its primary endpoint target with an ORR of 41.7% (43/103; 95% CI, 32.1-51.9), as assessed by independent central review (Fig. 3A). Responses were rapid and durable: median time to response was 2.5 months (range, 0.7-7.4), median DOR was 9.7 months (95% CI, 7.6-17.0), and 72% (31/43) of responders had responses lasting at least 6 months (Fig. 3B). Objective responses were consistent across subgroups, including patients with poor prognostic factors, such as patients 65 years and older or who were heavily pretreated (≥3 prior therapies). Preliminary survival data were promising; after a median follow-up of 17.1 months, median progression-free survival (PFS) was 9.0 months (95% CI, 6.9-13.1) and median overall survival (OS) was 21.7 months (Fig. 3C, 3D). The 1-year OS rate was 72%. Results were similar at extended follow-up (median 25.0 months) with a confirmed ORR of 41.7%, mature median OS of 20.0 months (12-month OS rate, 73%), and median PFS of 8.9 months.[68] Based on these data, futibatinib was granted accelerated approval by the FDA for patients with previously treated, unresectable, locally advanced, or metastatic *FGFR2*-fusion/rearrangement-positive iCCA.[69]

Genomic Profiling of Futibatinib Clinical Activity in CCA

Exploratory molecular profiling analyses from FOENIX-CCA2 examined futibatinib activity by *FGFR* aberration type or in the context of co-occurring genomic alterations (Fig. 3A).[48] Futibatinib response did not appreciably vary with fusion partner type: ORRs were 41.7% and 44.6% in patients with *BICC1* and non-*BICC1* fusions, respectively.

ORRs were consistent regardless of the presence of co-alterations in *TP53* (ORR, 38.5%; 43.8% with unaltered *TP53*), *CDKN2A* (40.0%; 43.8% with unaltered *CDKN2A*), and *CDKN2B* (43.8%; 42.9% with unaltered *CDKN2B*) (Fig. 3A).[48] Median PFS with futibatinib was 7.0 and 9.0 months in *TP53*-altered and unaltered populations, respectively, 4.9 and 9.7 months in *CDKN2A*-altered and unaltered populations, respectively, and 4.8 and 11.0 months in *CDKN2B*-altered and unaltered populations, respectively.[48] While cross-trial comparisons should be made with caution, a similar analysis of pemigatinib treatment in patients with CCA harboring *FGFR2* fusions/rearrangements found no response to pemigatinib treatment and a lower median PFS (2.8 months) in patients with *TP53* co-alterations, while patients without *TP53* co-alterations experienced an ORR of 38.8% and a median PFS of 9.0 months.[57] Patients with *CDKN2A*/B alterations treated with either pemigatinib or futibatinib had a lower median PFS, and those treated with pemigatinib experienced a lower ORR, than patients without alterations.[48,57] These data provide interesting information about the activity of these treatments in the context of the CCA genetic landscape; however, the findings are limited by the small number of patients with co-alterations and the post hoc exploratory nature of these analyses.

Response to Futibatinib in Patients With iCCA With Prior FGFR Inhibitor Treatment

Preliminary data suggest that futibatinib showed antitumor activity in patients with iCCA with progression after previous FGFR inhibitor treatment. In the dose-escalation study, one responder had a history of disease progression on prior infigratinib before receiving futibatinib treatment for 15.6 months.[61] In the dose expansion study, 5 of 28 patients with prior FGFR inhibitor therapy (17.9%) experienced objective responses with futibatinib.[67] Duration of response ranged from 3.5 months (with response ongoing at data cutoff) to 20.4 months. Of the 5 responders, 3 had *FGFR2* fusions, 1 a *FGFR2* mutation, and 1 a *FGFR2* amplification/rearrangement. An additional 15 patients previously treated with an FGFR inhibitor had stable disease. Of note, mechanisms of acquired resistance to prior FGFR inhibitor therapy were not captured because immediate pretreatment and post-progression biopsies were not required in the study.

In a separate analysis, clonal dynamics using cell-free circulating tumor DNA (ctDNA) were evaluated in 4 patients from a single site within the phase I patient population.[60] These patients received prior infigratinib or Debio 1347, and each

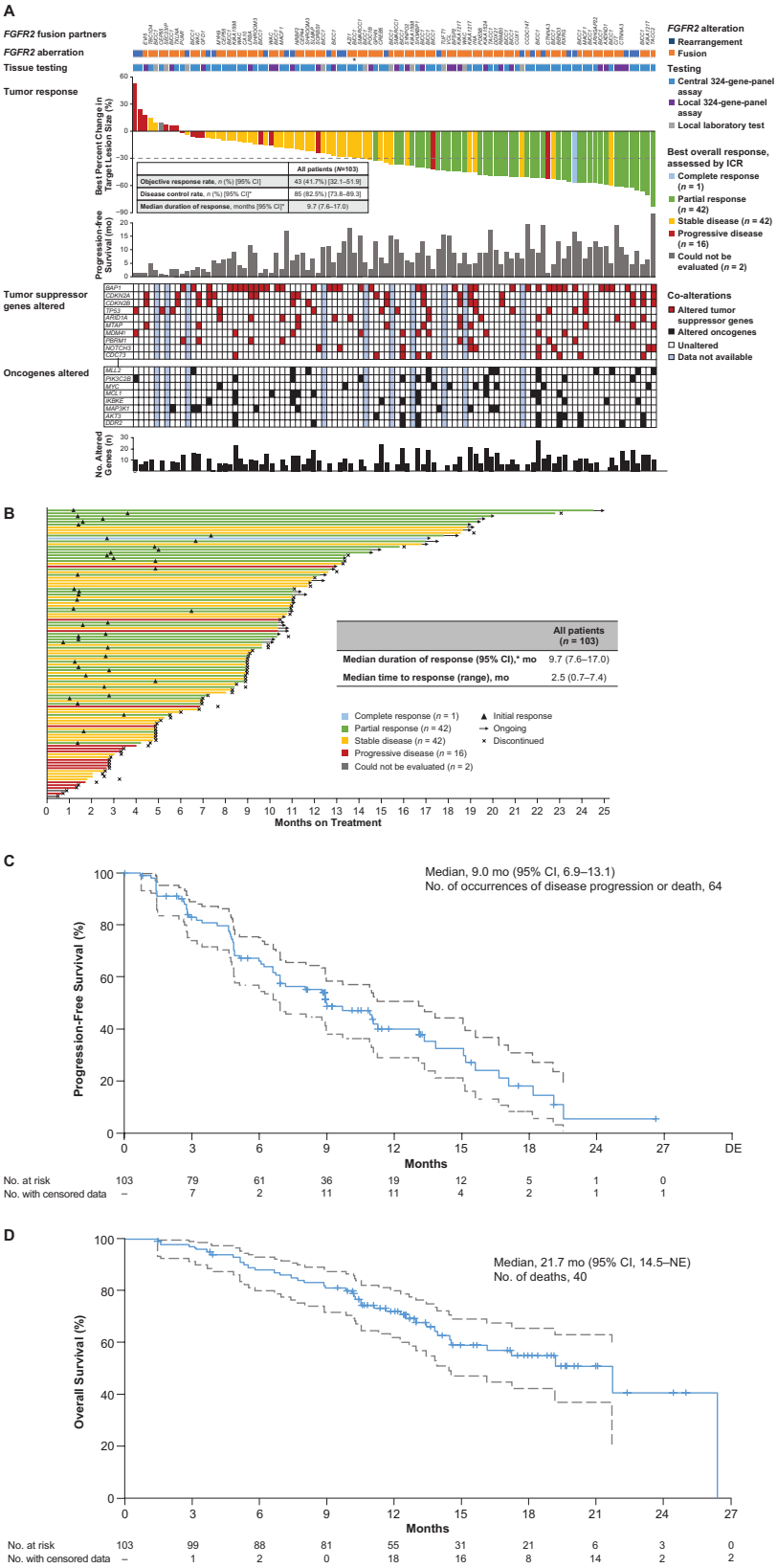


Figure 3. Futibatinib efficacy in the FOENIX-CCA2 study. **(A)** Best percentage change from baseline in target lesion size in individual patients with bars color coded to indicate best overall response assessed per ICR. Horizontal line represents the threshold for PR (≥30% reduction in lesion size) per RECIST v1. *FGFR2* aberrations were assessed by testing of tumor tissue in local labs or using FoundationOne CDx (FoundationOne) assays in central or local labs as shown. The *FGFR2* aberration for each patient (rearrangement or fusion) is indicated along with the fusion partner where identified. One patient had an *FGFR2* S799fs*22 mutation in addition to an *FGFR2* fusion (indicated with an asterisk). The most frequently altered oncogene or tumor suppressor genes are indicated. Three patients were not included in the figure because they were missing tumor assessments: 1 did not have a post-baseline assessment, and 2 had no target lesions available per ICR. **(B)** Duration and type of response per patient. **(C)** Kaplan-Meier plot of PFS.

experienced clinical benefit with futibatinib (2 PR, 2 SD) with SD or PR lasting 5.1-17.2 months. In 3 patients, analysis of ctDNA at progression on the prior FGFR inhibitor indicated the development of acquired resistance mutations: E566A, H683L, K660M, K715R, M538I, N550H, N550K, N550T, and V565F.[60] Analyses of ctDNA at the start of futibatinib treatment and upon subsequent progression in all 4 patients suggested that futibatinib had differential activity against individual *FGFR2* secondary mutations compared with the prior FGFR inhibitors. The mutation allele frequency of V565F increased upon futibatinib treatment, whereas levels of E566A and N550K were unchanged. These results suggest that the spectrum of acquired resistance mutations varies and may influence choice of therapy. In follow-up experiments, futibatinib retained activity against *FGFR2* kinase domain mutations in preclinical iCCA models. The investigators concluded that these preliminary investigations support the clinical utility of futibatinib in patients with acquired resistance to ATP-competitive reversible FGFR inhibitors.

These analyses were consistent with preclinical experiments showing superior activity of futibatinib against acquired resistance mutations.[11,59] However, data on mechanisms of futibatinib resistance remain limited and further research is needed to understand the role of futibatinib after progression on FGFR inhibitors.

Activity of Futibatinib in Tumor Types Other Than CCA

In addition to CCA, futibatinib activity has been observed in at least 7 other tumor types harboring 10 different categories of *FGFR1-4* aberrations (Table 2). Among 19 patients with urothelial cancer in the phase I expansion study,[67] 3 patients had PRs (16% ORR), all with *FGFR1/3*-mutant tumors. The ORR in this urothelial cohort was numerically lower than that in trials of other selective FGFR inhibitors,[46,71] possibly because these patients were heavily pretreated: 58% received ≥3 prior regimens, with 42% previously treated with an FGFR inhibitor. Based on these data, a phase II study (NCT04601857) was initiated to study futibatinib in combination with pembrolizumab in patients with advanced or metastatic urothelial cancer.[72]

Futibatinib showed activity in gastric cancer in 2 phase I studies. In the phase I expansion study, 2 of 9 patients achieved a PR (ORR 22%).[67] One responder had an *FGFR2* amplification and the other had an *FGFR3* fusion. In the Japanese phase I dose-expansion study, patients with gastric cancer harboring an *FGFR2* amplification with a copy number ≥10 experienced an ORR of 36.4% and DCR of 54.5% vs. 0% and 10% in those with *FGFR2* amplification copy number <10.[63]

Responses to futibatinib were also observed in primary central nervous system (CNS), breast, and head and neck tumors (Table 2).[67] In the phase I dose-escalation study, 2 patients with primary CNS tumors (glioblastoma and anaplastic oligodendroglioma) harboring *FGFR1* mutations experienced PRs,[61] while in the phase I expansion study, 1 patient with glioblastoma harboring an *FGFR1* fusion experienced a PR. A patient with triple-negative breast cancer with *FGFR2* amplification from the phase I expansion study (16-mg cohort) and another with *FGFR2*-amplified breast cancer from the phase I study in Japan experienced durable responses with futibatinib.[63,67] In a compassionate use program, a patient with an *FGFR1*-rearranged myeloid neoplasm treated with futibatinib had complete hematologic and cytogenetic remission.[70] Notably, these phase I trials helped to identify previously uncharacterized *FGFR* aberrations and tumor types as potential FGFR inhibitor targets, including *FGF*-amplified and *FGFR1*-mutated urothelial carcinoma and *FGFR*-fusion positive head and neck cancer.

Altogether, these data support further investigation of futibatinib in multiple *FGFR*-aberrant tumor types and as a disease-agnostic treatment for patients with *FGFR*-altered advanced solid tumors.

Futibatinib Safety and Tolerability

Safety data in the 2 largest populations of patients who received futibatinib 20 mg QD, the phase I expansion 20-mg cohort (n = 170)[67] and the phase II iCCA study (n = 103),[48] indicated a manageable safety profile for futibatinib consistent with that of other FGFR inhibitors.[43,44,46,51,73] Adverse events (AEs) were common in both studies (reported in >98% of patients), including hyperphosphatemia, diarrhea, constipation, fatigue, dry mouth, and alopecia (Table 3). In the phase I expansion and phase II iCCA studies, any-cause grade ≥3 AEs were reported in 72% and 77% of patients, respectively; grade ≥3 treatment-related AEs (TRAEs) occurred in 43% and 57% of patients, respectively, with grade 3 hyperphosphatemia most commonly reported in ≥10% of patients (phase I expansion, 22%; phase II, 30%). One grade 4 TRAE was reported in each study (increased gamma glutamyl-transferase and increased alanine aminotransferase). Serious TRAEs were reported in 6% and 10% of patients in the phase I expansion and phase II iCCA studies, respectively; no treatment-related deaths occurred in either study.

The most common AE across studies was hyperphosphatemia (Table 3)[48,59,63,67] similar to findings with pemigatinib and infigratinib.[49,51,74] Hyperphosphatemia is an on-target effect of FGFR inhibition because decreased FGF23–FGFR1 signaling leads to increased phosphate reabsorption and hyperphosphatemia in proximal tubules.[62] The numerically higher rates of hyperphosphatemia reported with futibatinib vs. pemigatinib and infigratinib[49,51,74] may be related to between-study differences in dosing schedules, safety assessments, and grade definitions. Hyperphosphatemia was not defined in the National Cancer Institute Common Criteria for Adverse Events version 4.03, the version used for safety assessments in

Upper and lower 95% CIs indicated as dotted lines. Tick marks represent data censored at the time of the last tumor assessment for patients who did not progress or die. **(D)** Kaplan-Meier plot of OS. Upper and lower 95% CIs indicated as dotted lines. Tick marks represent data censored at the date of the last follow-up (or data cutoff date, whichever is earlier) for patients who were alive or whose death was not confirmed. *The widths of the CIs have not been adjusted for multiplicity. Abbreviations: CR, complete response; ICR, independent central review; mo, month; NE, not evaluable; no, number; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease. From *The New England Journal of Medicine*, Goyal L, Meric-Bernstam F, Hollebecque A, et al, Futibatinib for FGFR2-Rearranged Intrahepatic Cholangiocarcinoma, 388, 228-239. Copyright © (2023) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Table 2. Futibatinib activity in patients receiving futibatinib once daily.

Tumor type	Study	QD dose (mg)	*n*	FGF/FGFR aberrations[a]	PR (*n*)	SD (*n*)	ORR (%)	DCR (%)
CCA	Global phase I expansion[67]	20	64	*FGFR1* fusion/rearr. (*n* = 1) *FGFR2* fusion/rearr. (*n* = 43) *FGFR2* mutation (*n* = 13) *FGFR3* fusion/rearr. (*n* = 1) *FGF1* amplification (*n* = 7) *FGF3* amplification (*n* = 6) *FGF4* amplification (*n* = 5) *FGF19* amplification (*n* = 8)	10	36	16	72
		16	19	*FGFR2* fusion/rearr. (*n* = 8)[b] *FGFR2* amplification (*n* = 1)[b]	8	8	42	NR
	Global phase II[48]	20	103	*FGFR2* fusion/rearr. (*n* = 103)	43[c]	42	42	83
	Global phase I escalation[61]	4-24	17	*FGFR2* fusion (*n* = 3)[b]	3[d]	NR	NR	NR
	Japanese phase I expansion/ escalation[63]	16-20	3	*FGFR2* mutation (*n* = 1) FGFR2 fusion/rearr. (*n* = 2)	1	NR	NR	NR
Gastric	Global phase I expansion[67]	20	9	*FGFR2* fusion/rearr. (*n* = 1) *FGFR2* amplification (*n* = 8) *FGFR3* fusion/rearr. (*n* = 1) *FGF1* amplification (*n* = 2) *FGF3* amplification (*n* = 2) *FGF4* amplification (*n* = 1) *FGF19* amplification (*n* = 2)	2	3	22	56
	Japanese phase I expansion/ escalation[63]	20[e]	21	*FGFR2* amplification CNV ≥10 (*n* = 11)[e] *FGFR2* amplification CNV <10 (*n* = 10)	4[e] 0	2 1	36 0	54 10
Urothelial	Global phase I expansion[67]	20	19	*FGFR1* mutation (*n* = 1) *FGFR1* amplification (*n* = 1) *FGFR3* mutation (*n* = 13) *FGFR3* fusion/rearr. (*n* = 3) *FGF1* amplification (*n* = 5) *FGF3* amplification (*n* = 5) *FGF4* amplification (*n* = 2) *FGF19* amplification (*n* = 4)	3	6	16	47
Primary CNS	Global phase I expansion[67]	20	36	*FGFR1* fusion/rearr. (*n* = 2) *FGFR1* mutation (*n* = 9) *FGFR2* mutation (*n* = 1) *FGFR3* fusion/rearr. (*n* = 23) *FGFR3* mutation (*n* = 1) *FGFR3* amplification (*n* = 1)	1	6	3	19
	Global phase I escalation[61]	4-24 (PR: 24)	4	*FGFR1* mutation (*n* = 1)[f]	2	NR	NR	NR

Table 2. Continued

Tumor type	Study	QD dose (mg)	*n*	FGF/FGFR aberrations[a]	PR (*n*)	SD (*n*)	ORR (%)	DCR (%)
Breast[g]	Global phase I expansion[67]	20	11	*FGFR1* mutation (*n* = 1) *FGFR1* amplification (*n* = 1) *FGFR2* fusion/rearr. (*n* = 2) *FGFR2* amplification (*n* = 5) *FGFR3* amplification (*n* = 1) *FGFR4* mutation (*n* = 1)	0	3	-	27
		16	1	*FGFR2* amplification (*n* = 1)	1	-	-	-
Head and neck	Global phase I expansion	20	2	*FGFR1* fusion/rearr. (*n* = 1)[b]	1	-	-	-
Myeloid neoplasm	Single patient protocol[70]	20	1	*FGFR1* fusion/rearr. (*n* = 1)	1	-	-	-

Only tumor types with either at least one responder reported or DCR reported are shown.
[a]In the global phase I expansion study, patients may have more than one *FGFR* or *FGF* aberration.
[b]*FGFR* aberrations were only reported for responders.
[c]One patient experienced a complete response.
[d]The 3 responding patients received the following doses of futibatinib: 16 mg, 16 mg, and 24 mg once daily.
[e]One patient had received futibatinib 80 mg TIW.
[f]A second patient with anaplastic oligodendroglioma experienced a PR with futibatinib 160 mg TIW dosing.
[g]The Japanese phase I expansion/escalation study included one patient with breast cancer harboring *FGFR2* amplifications who had a partial response with futibatinib.
Abbreviations: CCA, cholangiocarcinoma; CNS, central nervous system; CNV, copy number variant; DCR, disease control rate; FGFR, Fibroblast growth factor receptors; NR, not reported; ORR, objective response rate; PR, partial response; QD, once daily; rearr, rearrangements; SD stable disease; TIW, 3 times a week.

these trials. In the futibatinib studies, hyperphosphatemia was graded by serum phosphate levels regardless of symptoms,[48,67] which was not the case for the pemigatinib trial.[49,51,74] In the 2 futibatinib studies, hyperphosphatemia was managed with phosphate binders (75%-78%), dose interruptions (17%-20%), or dose reductions (8%-20%). All grade 3-4 events of hyperphosphatemia resolved, except in 2 patients in the phase I expansion study in whom resolution could not be assessed as they discontinued the study because of disease progression and withdrawal of consent.

Eye and nail toxicities are also considered AEs of special interest for FGFR inhibitors.[48,49] Similar to agents targeting the MAPK pathway, FGFR inhibitors can cause central serous retinopathy (CSR)/retinal pigment epithelial dystrophy (RPED). Patients with CSR/RPED can be asymptomatic; however, more severe cases manifest with acute central vision decrease/loss and metamorphopsia.[75] In the phase I expansion study, 26% of patients had eye-related AEs, most commonly dry eye (9%), and blurred vision (6%). All but 2 cases (grade 3 cataract [treatment-related]; grade 3 macular fibrosis/grade 4 ocular ischemic syndrome [unrelated]) were grade 1-2. Seven patients experienced grade 1-2 central serous retinopathy.[67] In the phase II iCCA study, retinal disorders were reported in 8% of patients (grade 1-2 events).[48] In the phase I expansion study, 20% of patients had nail toxicities, all but one (grade 3 onychalgia) grade 1 or 2. In the phase II study, 47% of patients developed nail toxicities (including nail disorder, onycholysis, nail discoloration, and paronychia), with grade 3 cases in 2%.[48] Similar data on eye and nail-related toxicities have been reported with other FGFR inhibitors.[76,77]

Palmar-plantar erythrodysesthesia syndrome, clinically notable in patients treated with FGFR inhibitors, was reported in 13% (grade ≥3, 4%) and 21% (grade ≥3, 5%) of patients in the phase I expansion and phase II studies, respectively. No grade 5 AEs of special interest were reported in either study.

AEs were mostly managed with dosing interruption and reductions. In the phase I expansion study, TRAEs led to dosing modifications in 44% of patients and treatment discontinuation in 4% of patients. In the phase II study, TRAEs led to dose interruption, dose reduction, or treatment discontinuation in 50%, 54%, and 2% of patients, respectively.

An integrated analysis of futibatinib safety in 318 patients across the global phase I/II and Japanese phase I studies showed a consistent safety profile: grade ≥3 hyperphosphatemia occurred in 23% of patients, but nearly all grade ≥3 events resolved and only 3% discontinued because of TRAEs.[78]

Collectively, these results indicate a monitorable and manageable safety profile for futibatinib, rarely requiring treatment discontinuation due to AEs.

Quality of Life with Futibatinib Treatment

Across therapies for iCCA, little data are available on how treatment affects patient quality of life (QoL).[79] The phase II study of futibatinib in patients with iCCA harboring *FGFR2* fusions/rearrangements was among the first to report patient-reported outcomes (PROs) with an FGFR inhibitor. PROs were measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and Euro QoL Visual analog scale (EQ-VAS).[48] Ninety-two of 103 patients (89%) had PRO data with at least one follow-up assessment, with 48 patients (47%) having PRO data at cycle 13 (final cycle assessed). Through 9 months of futibatinib treatment,

Table 3. Treatment-emergent AEs occurring in ≥10% of all patients in futibatinib studies.

TEAE (%)	Phase I dose escalation combined QD cohort[61] (*n* = 44)		Phase I dose expansion 20 mg QD cohort[67] (*n* = 170)		Japanese phase I expansion/escalation QD cohort (n=43)		Phase II iCCA 20 mg QD[48] (*n* = 103)	
	Any-grade	Grade 3[a]	Any-grade	Grade ≥3[b]	Any-grade	Grade ≥3	Any-grade	Grade ≥3[c]
Hyperphosphatemia	68	16	81	22.4	100	5	85	30
Constipation	41	2	32	1.2	40	0	39	0
Diarrhea	34	2	33	<1	30	0	36	1
Nausea	30	5	28	0	30	0	24	2
ALT increased	25	7	24	10	21	0	17	6
AST increased	25	5	24	5	21	2	25	10
Dry mouth	25	0	18	0	-	-	35	0
Vomiting	25	5	25	1	23	2	19	1
Anemia	20	5	14	5	19	12	16	5
Asthenia	20	0	16	4	-	-	-	-
Stomatitis	20	2	15	3	16	0	24	6
Decreased appetite	16	0	19	2	58	5	23	3
Fatigue	16	2	25	5	9	0	34	8
Abdominal pain	14	2	19	3	-	-	21	3
Alopecia	14	0	19	0	-	-	34	0
Dry skin	14	0	13	0	14	0	29	0
Back pain	11	0	-	-	-	-	17	2
Cough	11	0	-	-	-	-	-	-
Dry eye	11	0	-	-	-	-	21	1
PPE syndrome	-	-	13	4	-	-	21	5
Increased blood creatinine	-	-	12	0	16	2	15	0
Arthralgia	-	-	11	0	5	0	22	0
Hypercalcemia	-	-	11	1	-	-	16	2
Dysgeusia	-	-	11	0	14	9	20	0
Decreased weight	-	-	10	<1	12	9	18	4
Urinary-tract infection	-	-	-	-	-	-	19	3
Hyponatremia	-	-	-	-	14	0	16	11
Nail disorder	-	-	-	-	-	-	16	0
Onycholysis	-	-	-	-	-	-	16	0
Muscle spasms	-	-	-	-	-	-	15	1
Myalgia	-	-	-	-	-	-	15	0
Onychomadesis	-	-	-	-	-	-	15	1
Nail discoloration	-	-	-	-	-	-	14	0

Table 3. Continued

TEAE (%)	Phase I dose escalation combined QD cohort[61] (*n* = 44)		Phase I dose expansion 20 mg QD cohort[67] (*n* = 170)		Japanese phase I expansion/escalation QD cohort (n=43)		Phase II iCCA 20 mg QD[48] (*n* = 103)	
	Any-grade	Grade 3[a]	Any-grade	Grade ≥3[b]	Any-grade	Grade ≥3	Any-grade	Grade ≥3[c]
Peripheral edema	-	-	-	-	14	2	14	0
Pyrexia	-	-	-	-	7	0	14	0
Blood alkaline phosphatase increase	-	-	-	-	-	-	13	3
Hypophosphatasemia	-	-	-	-	7	5	13	5
Dizziness	-	-	-	-	-	-	11	1
Thrombocytopenia	-	-	-	-	-	-	11	2
Blood creatine phosphokinase increase	-	-	-	-	16	2	10	3
Oropharyngeal pain	-	-	-	-	-	-	10	0
Peripheral sensory neuropathy	-	-	-	-	-	-	10	1
Hypoalbuminemia	-	-	-	14	9	-	-	-
Insomnia	-	-	-	12	0	-	-	-
Tumor pain	-	-	-	14	0	-	-	-

Dashed lines (-) indicate the TEAE was reported in fewer than 10% of patients.
[a]None of the TEAEs reported in this table were grade 4 or 5. Among patients treated with the once daily dose in this study, 3 patients had grade 4 TEAEs (one of which was considered treatment-related [increased creating phosphokinase]) and 4 patients had grade 5 events (none of which were considered treatment related).
[b]Among any-grade TEAEs reported in >10% of patients, there was one grade 4 event (increased ALT) and there were no grade 5 events. Overall, 9 patients had grade TEAEs, one of which was considered treatment-related (increased gamma glutamyltransferase). None of the grade 5 TEAEs (*n* = 16) were considered treatment related.
[c]Among any-grade TEAEs reported in ≥10% of patients, 4 grade 4 events were reported (1 patient each of increased ALT, hypercalcemia, hyponatremia, and hypophosphatasemia), and 1 grade 5 event was reported (decreased appetite). Overall, 6 patients had grade 4 TEAEs, 1 of which was considered treatment-related (increased ALT). None of the grade 5 TEAEs (*n* = 5) were treatment related.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartine aminotransferase; iCCA, intrahepatic cholangiocarcinoma; PPE, Palmar–plantar erythrodysesthesia syndrome; QD, once daily; TEAEs, treatment-emergent adverse events.

Table 4. Ongoing clinical studies with futibatinib.

Study	Cancer type	Study design	Intervention(s)[a]	Primary outcome(s)	Estimated enrollment	Start date; estimated end date	NCT identifier
FOENIX-CCA3 (phase III)	Advanced CCA with *FGFR2* rearrangements	Randomized (1:1)	Futibatinib or gemcitabine-cisplatin (control)	PFS	216	March 1, 2020; April 2028	NCT04093362
Phase II study in metastatic breast cancer (MBC)	MBC harboring *FGFR2* amplifications (cohorts 1-3)	Open label	Futibatinib	ORR or CBR	168 across cohorts	August 30, 2019; June 30, 2023	NCT04024436
	MBC harboring *FGFR1* amplifications (cohort 4)		Futibatinib + fulvestrant	PFS at 6 months			
Phase II study in patients with specific *FGFR* aberrations	Solid tumors with *FGFR1-4* rearrangements (cohort A)	Open label	Futibatinib	ORR	115 across cohorts	August 24, 2020; December, 2022	NCT04189445
	Gastric/gastroesophageal junction tumors with *FGFR2*-amplifiication (cohort B)		Futibatinib	ORR			
	Myeloid/lymphoid neoplasms with *FGFR1*-rearrangement (cohort C)		Futibatinib	CR rate			
Phase II study of advanced/metastatic UC (mUC)	mUC with *FGFR3* mutation or *FGFR1-4* fusions/rearrangements (cohort A)	Open label	Futibatinib + pembrolizumab	ORR	46 across cohorts	January 21, 2021; December 30, 2023	NCT04601857
	All other mUC not included in cohort A[b] (cohort B)						
Phase II study in advanced or metastatic hepatocellular carcinoma	Advanced or metastatic *FGF19*-positive BCLC stage A, B, or C hepatocellular carcinoma	Open-label	Futibatinib + pembrolizumab	PFS at 6 months	25	May 7, 2021; May 6, 2024	NCT04828486
Phase I/II study of combination therapy	Advanced solid tumors	Open label, dose escalation (TAS-117)	Futibatinib + TAS-117	Safety and efficacy	137	May 1, 2019; June 30, 2023	Japic CTI-194864
Phase Ib/II study of advanced *KRAS* mutant non-small cell lung cancer	Advanced or metastatic solid tumors (part 1)	Open-label	Futibatinib + binimetinib	RP2D (part 1)	36 across cohorts	September 20, 2021; December 2024	NCT04965818
	Advanced non-small cell lung cancer with *KRAS* mutation (part 2)			ORR (part 2)			

[a]Futibatinib to be administered as 20 mg once daily in all studies.
[b]Includes patients with other *FGFR*/non-*FGFR* genetic aberrations and patients with wild-type tumors.
Abbreviations: BCLC, Barcelona clinic liver cancer; CBR, clinical benefit rate; CCA, cholangiocarcinoma; CR, complete response; NCT, National Clinical Trials; ORR, objective response rate; PFS, progression-free survival; RP2D, recommended phase II dose; UC, urothelial carcinoma.

patient global health status was maintained, with no clinically meaningful changes in individual functional measures (physical, role, cognitive, emotional, and social). Individual symptom measures on the EORTC QLQ-C30 were also stable except for constipation, which met criteria for a clinically meaningful change at cycle 4 only. Mean EQ-VAS scores were sustained and the status across all EQ-5D-3L dimensions remained the same or improved over this period. Most patients (82%-95%) maintained the same or better Eastern Cooperative Oncology Group performance status score relative to baseline. Overall, these data suggest patient QoL was not negatively impacted by AEs while on futibatinib treatment.

Ongoing Studies and Future Directions for Development of Futibatinib

Based on phase I data, phase II studies are examining the safety and activity of futibatinib in various *FGFR*-aberrant cancer types including metastatic breast cancer and urothelial cancer (Table 4). A tumor-agnostic phase II study will investigate futibatinib as a disease-agnostic treatment option for patients with *FGFR*-rearranged advanced solid tumors. Building on the phase II iCCA study results, an ongoing open-label, randomized phase III study will assess futibatinib as a first-line treatment vs. gemcitabine–cisplatin for patients with *FGFR2* fusion/rearrangement-positive iCCA.

Futibatinib combination studies are another important future prospect. The combination of FGFR inhibitors with immunotherapy is supported by preclinical evidence,[80] and phase II trials are evaluating futibatinib combined with pembrolizumab in metastatic urothelial carcinoma (NCT04601857) and metastatic hepatocellular carcinoma (NCT04828486). In preclinical models, futibatinib combined with cytotoxic chemotherapy, MEK inhibitors, or PI3K pathway inhibitors induced synergistic tumor regression[81-83]; trials evaluating the combination of futibatinib with AKT and MEK inhibitors are ongoing (JapicCTI-194864; NCT04965818). There is also rationale for the combination of FGFR inhibitors with VEGF inhibitors.[84] Future exploration of futibatinib combined with other treatments could yield additional clinical benefits, particularly to combat tyrosine kinase inhibitor resistance.

Summary

FGFR dysregulation drives oncogenesis across a broad range of tumor types. Although many FGFR inhibitors are currently in clinical development, futibatinib has a unique mechanism of action as an irreversible FGFR1-4 inhibitor with potential activity against acquired secondary FGFR kinase domain mutations. In early studies, futibatinib demonstrated activity in diverse tumor types harboring various *FGFR* aberrations. Based on durable responses and manageable safety in the phase II FOENIX-CCA2 study futibatinib was approved for patients with iCCA harboring *FGFR2* fusions/rearrangements. These data, combined with the unique irreversible mechanism of action, set futibatinib apart as a leading second-generation FGFR inhibitor, while both preclinical evidence and exploratory clinical results suggest a role for futibatinib after failure of prior FGFR inhibitor treatment. Further studies are required to assess mechanisms of futibatinib resistance and combination therapy approaches using this agent.

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Conflict of Interest

Milind Javle reported consulting fees from QED, Incyte, Taiho, Merck, EMD Serono, Basilea, Oncosil, BMS, and AstraZeneca; fees for promotional services from Incyte; institutional research funding from Bayer, Koo Foundation, Sanofi, Cyclacel; and advisory/consulting relationships with Tempus Inc, Pfizer, QED, and Novartis. Gentry King reported institutional funding from Bayer, Koo Foundation, Sanofi, and Cyclacel, and advisory/consulting relationships with Tempus Inc, Pfizer, QED, and Novartis.. Kristen Spencer reported advisory board member with QED Therapeutics and Caris Life Sciences. Mitesh Borad reported stock and other ownership interests with AVEO, Gilead Sciences, Intercept Pharmaceuticals, and Spectrum Pharmaceuticals; consulting or advisory role with Agios (Inst), ArQule (Inst), Celgene (Inst), De Novo Pharmaceuticals, Exelixis, Fujifilm (Inst), G1 Therapeutics, Genentech, Halozyme (Inst), Immunovative Therapies, Imvax, Inspyr Therapeutics, Insys Therapeutics (Inst), Klus Pharma, Lynx Group, Merck, Novartis (Inst), Pieris Pharmaceuticals (Inst), Taiho Pharmaceutical (Inst), and Western Oncolytics; research funding from Adaptimmune (Inst), Agios (Inst), ARIAD (Inst), AstraZeneca (Inst), Basilea (Inst), BiolineRx (Inst), Boston Biomedical (Inst), Celgene (Inst), Dicerna (Inst), Eisai (Inst), EMD Serono (Inst), Halozyme (Inst), ImClone Systems (Inst), Incyte (Inst), Isis Pharmaceuticals (Inst), MedImmune (Inst), Merck Serono (Inst), miRNA Therapeutics (Inst), Puma Biotechnology (Inst), QED Therapeutics (Inst), RedHill Biopharma (Inst), Senhwa Biosciences (Inst), Sillajen (Inst), Sun Biopharma (Inst), Taiho Pharmaceutical (Inst), Threshold Pharmaceuticals (Inst), and Toray Industries (Inst).

Author Contributions

All authors contributed to the conception, design, data analysis, interpretation, manuscript writing, and final approval of manuscript.

Data Availability

No new data were generated or analyzed for this manuscript.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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