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ADIS DRUG EVALUATION

Futibatinib: A Review in Locally Advanced and Metastatic Cholangiocarcinoma

Sheridan M. Hoy[1]

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Abstract

Futibatinib (LYTGOBI®) is an oral small molecule compound that selectively, irreversibly and potently inhibits the tyrosine kinase activity of fibroblast growth factor receptor (FGFR)1–4. It is approved in the EU, Japan and the USA for the treatment of adults with locally advanced or metastatic cholangiocarcinoma (CCA) harbouring an *FGFR2* fusion or rearrangement who have progressed following systemic therapy. In the phase II part (FOENIX-CCA2) of a multinational phase I/II study in this patient population, monotherapy with futibatinib 20 mg once daily was associated with clinically meaningful and durable responses, sustained health-related quality of life (HR-QOL), and a manageable safety profile with supportive care and as-needed dose modifications. Indeed, hyperphosphataemia (the most common all grade and grade 3 treatment-related adverse event) was manageable with phosphate-lowering therapy and dose reductions or interruptions. Although further efficacy and tolerability data are expected, current evidence indicates that futibatinib is a valuable targeted therapy option for adults with locally advanced or metastatic CCA harbouring an *FGFR2* fusion or rearrangement who have progressed following systemic therapy, a patient population with limited treatment options and poor life expectancy.

Plain Language Summary

Cholangiocarcinoma (CCA) is an invasive tumour arising from the biliary tract. In the early stages it presents silently; this, along with its highly aggressive nature, means it is often diagnosed in the later (advanced) stages when surgery is not a treatment option. Up to half of CCAs have genetic aberrations that can be targeted for treatment. One such abnormality (present in 9–15% of CCAs) is found in fibroblast growth factor receptor (FGFR)2. The presence of this aberration promotes tumour survival and development. Futibatinib (LYTGOBI®) is an oral drug that strongly inhibits the activity of FGFR1–4. When given to adults with unresectable or metastatic CCA harbouring an *FGFR2* aberration who had disease progression after systemic therapy, futibatinib 20 mg once daily produced clinically meaningful and prolonged responses and sustained health-related quality of life; moreover, with supportive care and as-needed dose modifications, futibatinib had a manageable safety profile. In a patient population that has limited treatment options and poor life expectancy, current evidence indicates that futibatinib is a valuable targeted therapy option.

Digital Features for this Adis Drug Evaluation can be found at https://doi.org/10.6084/m9.figshare.25468201.

Futibatinib: clinical considerations in locally advanced and metastatic cholangiocarcinoma

Selectively, irreversibly and potently inhibits the tyrosine kinase activity of FGFR1–4
Administered orally, once daily
Induced clinically meaningful and durable responses and sustained HR-QOL
Manageable safety profile with supportive care and as-needed dose modifications

The manuscript was reviewed by: ***M. A. Morse***, Division of Medical Oncology, Department of Medicine, Duke University Medical Center and Duke Cancer Institute, Durham, NC, USA; ***D. Wekking***, Location Academic Medical Centre, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands.

✉ Sheridan M. Hoy
demail@springer.com

[1] Springer Nature, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand

1 Introduction

Cholangiocarcinomas (CCAs) encompass a heterogenous group of invasive tumours arising from the epithelium of the biliary tree, with their anatomical location [within the liver (intrahepatic), just outside the liver (perihilar) and near the small intestine (distal)] dictating their clinical and molecular features [1–5]. CCAs present asymptomatically at an early stage; this, combined with their highly aggressive nature, results in ≈ 70% of patients being diagnosed with locally advanced (i.e. unresectable) or metastatic disease [4]. As a consequence, these patients have limited therapeutic options (with surgical resection only possible in ≈ 25% of patients) and a poor prognosis (5-year survival rate of 7–20%) [4]. Most patients with advanced or metastatic CCA therefore receive palliative treatment with systemic therapy, with the combination of cisplatin, gemcitabine, and durvalumab or pembrolizumab among the recommended regimens for first-line treatment [1, 2, 4].

Selecting a subsequent-line systemic therapy depends upon several factors, including molecular testing results [2]. As nearly 40% of patients with biliary tract cancers harbour genetic mutations, amplifications or fusions that are potential targets for precision medicine, both the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) recommend the molecular profiling of patients with advanced or metastatic CCA who are candidates for systemic therapy [1, 2, 4]. Fibroblast growth factors (FGFs) and their receptors (FGFRs) play an integral role in regulating various biological processes that promote survival and proliferative signalling pathways; aberrant FGFR signalling (mostly constitutive FGFR activation) promotes tumourigenesis, supports tumour survival and confers chemotherapeutic resistance via anti-apoptotic signalling [6, 7]. *FGFR2* fusions or rearrangements are present in 9–15% of intrahepatic CCAs but are rare in other CCA subtypes [2]. Inhibitors of FGFR mostly target the FGFR kinase domain, thereby inhibiting FGFR signalling [6]. While selective FGFR inhibitors have demonstrated promising activity in various FGFR-aberrant cancer types, acquired resistance (e.g. the development of secondary mutations in the kinase domain that prevent the FGFR inhibitor from binding) is a concern. Moreover, reversible inhibitors (e.g. pemigatinib) are largely ineffective against these mutations [6].

Futibatinib (LYTGOBI®) is an oral small molecule compound that irreversibly inhibits the tyrosine kinase activity of FGFR1–4 via covalent binding [8–10]. It is approved in various countries worldwide for the treatment of adults with locally advanced or metastatic CCA harbouring an *FGFR2* fusion or rearrangement who have progressed following systemic therapy (Sect. 6). This article discusses pharmacological, therapeutic efficacy and tolerability data relevant to the use of futibatinib in this patient population.

2 Pharmacodynamic Properties of Futibatinib

By binding covalently to a conserved (across all four FGFRs) cysteine residue in the P-loop of the FGFR tyrosine kinase domain within the ATP-binding pocket, futibatinib selectively and irreversibly inhibits the kinase activity of each FGFR isoform [6, 11]. In an enzymatic assay of 296 human kinases, futibatinib potently inhibited the kinase activities of recombinant FGFR1, 2, 3 and 4 [half-maximal inhibitory concentrations (IC_{50}) 1.8 nmol/L, 1.4 nmol/L, 1.6 nmol/L and 3.7 nmol/L, respectively], with only three non-FGFR kinases displaying more than 50% inhibition by futibatinib: mutant RET (S891A; 85.7%), MAPKAPK2 (54.3%) and CK1a (50.7%) [12].

Futibatinib dose-dependently inhibited FGFR phosphorylation (IC_{50} 4.9 nmol/L; ELISA) in gastric cancer cell lines harbouring *FGFR2* amplifications, with the levels of Akt and ERK (downstream signalling components of the FGFR pathway) phosphorylation reduced in proportion to that of FGFR phosphorylation [12]. Moreover, it demonstrated antiproliferative activity against cancer cell lines of diverse tissue origins (including gastric) harbouring various *FGFR* genomic aberrations (amplifications, fusions, point mutations and translocations) regardless of the FGFR isoform or the nature of the genetic aberration; it had no effect on the proliferation of cell lines that did not harbour such aberrations. In a mouse xenograft model of human gastric cancer with activating *FGFR* genetic alterations, oral futibatinib 0.15 mg/mL, 1.5 mg/mL and 5 mg/mL resulted in dose-dependent FGFR2 phosphorylation inhibition following a single dose, and significant ($p < 0.05$ vs vehicle) and dose-dependent tumour growth inhibition following once-daily dosing over 2 weeks [12].

The development of resistant clones appears to be less likely in tumours with *FGFR2* genomic aberrations exposed to futibatinib than in those exposed to the reversible ATP-competitive FGFR inhibitor AZD4547 [12]. Futibatinib inhibited FGFR phosphorylation (IC_{50} 3.1 nmol/L) and suppressed growth (IC_{50} 4.8 nmol/L) in AZD4547-resistant clones, and exhibited activity (IC_{50} 1.3–5.2 nmol/L) against several drug-resistant FGFR mutants, including the gatekeeper mutation (i.e. a mutation encoding amino acids located in the hinge region of the ATP-binding pocket [13]) V565I [12]. Moreover, the drug has demonstrated clinical benefits in patients with advanced refractory *FGFR2* fusion-positive intrahepatic CCA who developed resistance to ATP-competitive FGFR2 inhibitors [14] and in those with intrahepatic CCA harbouring *FGFR2* extracellular domain in-frame deletions [15].

As FGFRs play a key role in phosphorus homeostasis, increases in phosphate levels are an expected pharmacodynamic effect with futibatinib administration [8, 9, 16]. Indeed, dose-dependent increases in blood phosphate levels

have been observed with the administration of futibatinib 4–24 mg [9] (Sect. 5) and an exposure–response analysis showed a significant relationship between hyperphosphataemia and futibatinib exposure [17].

At therapeutic (20 mg) and supratherapeutic (80 mg) doses, futibatinib did not prolong the Fridericia heart rate-corrected QT interval or affect other cardiac measures (heart rate, other ECG parameters) to a clinically relevant extent in healthy adults [18].

3 Pharmacokinetic Properties of Futibatinib

The pharmacokinetics of futibatinib were not affected by food to a clinically relevant extent in healthy individuals [19], and were linear over a dosage range of 4–24 mg once daily in patients with advanced solid tumours [16]. Following the oral administration of a single 20 mg dose in the advanced solid tumour population, the median time to the peak plasma concentration (C_{max}) of futibatinib was 2 h; there was no accumulation of the drug after multiple doses [16].

In vitro, futibatinib is ≈ 95% bound to human plasma proteins (mainly albumin and α1-acid glycoprotein) and is predominately metabolized by CYP3A and, to a lesser extent, by CYP2C9 and CYP2D6 [8–10, 20]. Unchanged drug was the major drug-related moiety in the plasma of healthy adult males who received a single 20 mg dose of radiolabelled futibatinib; one inactive metabolite was also recovered. The mean elimination half-life of futibatinib 20 mg in patients with advanced cancer is 2.9 h [8–10]. Following a single 20 mg dose of radiolabelled futibatinib in this patient population, ≈ 91% and 9% of the total recovered radioactivity was observed in faeces and urine; negligible unchanged futibatinib was also seen in both faeces and urine [9].

Age (18–82 years), sex, race/ethnicity, body weight (36–152 kg), mild to moderate renal impairment, and mild [8, 9] to severe [8] hepatic impairment do not have a clinically relevant effect on the systemic exposure of futibatinib [8, 9]. Indeed, a single-dose, multicentre, phase I study determined that there was no clinically relevant association between the degree of hepatic impairment (mild, moderate or severe) and futibatinib exposure following a 20 mg dose (based on Child–Pugh scores and liver function tests); thus, no futibatinib dose adjustments are required in these patient populations [21]. The effect of severe renal impairment and renal dialysis in end-stage renal disease on futibatinib exposure is unknown [8, 9].

In vitro studies have shown that futibatinib is a time-dependent inhibitor of CYP3A and likely to be a P-glycoprotein (P-gp) substrate and inhibitor [20]. In drug–drug interaction (DDI) studies in healthy adults, the coadministration of futibatinib with itraconazole (a dual P-gp and strong CYP3A inhibitor) increased futibatinib mean C_{max} and area under the plasma concentration–time curve (AUC) values by 51% and 41% compared with futibatinib alone, while the concomitant administration of futibatinib and rifampin (a dual P-gp and strong CYP3A inducer) reduced futibatinib mean C_{max} and AUC values by 53% and 64% [20]. Accordingly, in the EU [8] and the USA [9], the concomitant administration of futibatinib with dual P-gp and strong CYP3A inhibitors, and dual P-gp and moderate [8] or strong [8, 9] CYP3A inducers should be avoided. If concomitant administration of these agents cannot be avoided, adjusting the dose of futibatinib based on tolerability should be considered [8].

In a further DDI study in healthy adults, the coadministration of futibatinib with midazolam (a sensitive CYP3A substrate) had no effect on midazolam pharmacokinetics compared with midazolam alone [20]. Moreover, futibatinib did not affect the exposure of total 1-OH-midazolam (which reflects in vivo CYP3A activity), suggesting that futibatinib can be concomitantly used with other drugs metabolized by CYP3A [20]. Futibatinib has demonstrated a potential to induce CYP1A2 in vitro, and thus its coadministration with CYP1A2 sensitive substrates (e.g. olanzapine, theophylline) may reduce their exposure [8]. It is an inhibitor of breast cancer resistance protein (BCRP) in vitro, and thus may increase the exposure of drugs that are BCRP substrates [8, 9]. The coadministration of futibatinib and the proton pump inhibitor lansoprazole had no clinically relevant effect on futibatinib exposure [8, 9]. Consult local prescribing information for further details of potential DDIs involving futibatinib.

4 Therapeutic Efficacy of Futibatinib

Data from patients with advanced solid tumours (most of whom harboured ≥ 1 *FGF*/*FGFR* aberration) participating in the dose-escalation portion of the first-in-human, phase I part of a noncomparative, multinational, phase I/II study [16] and a two-part, noncomparative, multicentre, Japanese phase I study [22] determined that the recommended dosage of futibatinib for further studies was 20 mg once daily. This section discusses the therapeutic efficacy of this dosage of oral futibatinib in adults with unresectable or metastatic intrahepatic CCA harbouring an *FGFR2* fusion or rearrangement, and disease progression after systemic therapy (including ≥ 1 previous regimen of gemcitabine plus platinum-based chemotherapy) participating in the phase II part (FOENIX-CCA2) of the noncomparative, multinational, phase I/II study [23].

Enrolled patients had radiologically measurable disease [according to Response Evaluation Criteria in Solid

Tumors (RECIST) version 1.1]; no previous treatment with an FGFR inhibitor; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 [scores range from 0 (no disability) to 5 (death)]; and adequate organ function [23]. The *FGFR2* fusion or rearrangement was prospectively identified. Among the exclusion criteria were a history of or current clinically relevant retinal disorder or altered nontumour-related calcium–phosphorus homeostasis [23].

Patients received futibatinib 20 mg once daily continuously in a repeating 21-day cycle, with treatment continuing until imaging-based or clinical disease progression, unacceptable toxicity or meeting any other discontinuation criterion [23]. Patients with continued clinical benefit were permitted to continue treatment following disease progression after discussion between the investigators and study sponsors. The dose of futibatinib was modified in patients with adverse events (AEs) and those with hyperphosphataemia, with dose modifications and the initiation of phosphate-lowering therapies implemented following the detection of a serum phosphate level of ≥ 5.5 mg/dL (≥ 1.8 mmol/L). Treatment in these patients was discontinued if the toxic effects did not resolve following two dose reductions (from 20 mg to 16 mg, then to 12 mg) or if the toxic effects resulted in treatment delays of ≥ 21 days [23].

The primary endpoint was objective response (OR) rate [ORR; defined as the proportion of patients with a confirmed best overall response of complete response (CR) or partial response (PR) according to RECIST version 1.1] as assessed by independent central review [23]. The target ORR was 20%. Best overall response was assessed from the start of treatment until disease progression, the initiation of a subsequent new anticancer treatment or the clinical data cutoff, whichever was earliest. A confirmed OR required a minimum of two radiological assessments. Secondary endpoints were duration of response (DOR; defined as the time from first CR or PR until tumour progression or death), disease control rate (DCR; defined as the proportion of patients with CR, PR or stable disease), progression-free survival (PFS; defined as the time from first study dose to the first documented disease progression or death, whichever occurred first), overall survival (OS; defined as the time from the first dose of study drug to death) and patient-reported outcomes. The widths of the confidence intervals for the secondary endpoints were not adjusted for multiplicity. Patients who did not have disease progression, die or begin a subsequent therapy without progression were censored on the date of their last tumour assessment. A prespecified interim efficacy analysis was performed when 67% of all the patients who received futibatinib had ≥ 6 months' follow-up. The primary analysis was performed when ≥ 50% of the patients with an OR had ≥ 6 months' follow-up from the onset of responses. At baseline, patients ($n = 103$) had a median age of 58 years; 78% and 22% of patients had *FGFR2* fusions or rearrangements and 53% of patients had received ≥ 2 previous lines of systemic therapy [23].

Monotherapy with futibatinib induced clinically meaningful and durable responses in adults with unresectable or metastatic intrahepatic CCA harbouring an *FGFR2* fusion or rearrangement, and disease progression after systemic therapy [23].

At the time of the prespecified interim analysis (data cutoff date 31 January 2020), over one-third (37%) of 67 patients had achieved an OR [24, 25]. The median DOR was 8.3 months and the DCR was 82%. In patients with confirmed *FGFR2* fusions and rearrangements ($n = 58$ and 9), the ORRs were 36.2% and 44.4%; in those with the *FGFR2–BICC1* fusion ($n = 15$), the ORR was 33.3% [24, 25]. At the time of the primary analysis (data cutoff date 1 October 2020; median follow-up duration 17.1 months; median treatment duration 9.1 months), 43 (42%; 95% CI 32–52) of 103 patients had achieved an OR (primary endpoint; Table 1), with 1 patient achieving a CR and 42 patients achieving a PR [23]. This result was considered clinically relevant as the lower limit of the 95% confidence interval for the ORR exceeded an historical ORR of 10% for chemotherapy in previously treated patients with CCA [23, 26]. At this timepoint, the ORRs were consistent across the patient subgroups, including those based on age (< 65 vs ≥ 65 years) and previous regimens (1 vs 2 vs ≥ 3) [23]. Secondary endpoint results are also reported in Table 1. Among the 43 patients who achieved a response with futibatinib monotherapy, 72% and 14% had responses lasting ≥ 6 and ≥ 12 months, respectively, and the median time to response was 2.5 months. An ongoing response was observed in 21 of the 43 patients who had a response. The 6- and 12-month PFS rates were 66%

Table 1 Efficacy of futibatinib in the phase II part (FOENIX-CCA2) of a phase I/II study [23]

Endpoint	
Objective response rate[a] (% of pts)	42 (95% CI 32–52)
Median duration of response (mo)	9.7 (95% CI 7.6–17.0)[b]
Disease control rate (% of pts)	83 (95% CI 74–89)[b]
Median progression-free survival (mo)	9.0 (95% CI 6.9–13.1)[b]
Median overall survival (mo)	21.7 (95% CI 14.5–NE)[b]

Pts in FOENIX-CCA2 were adults with unresectable or metastatic intrahepatic cholangiocarcinoma harbouring a fibroblast growth factor receptor 2 fusion or rearrangement, and disease progression after systemic therapy ($n = 103$). Data cutoff date 1 October 2020

mo months, *NE* not evaluable, *pts* patients

[a]Primary endpoint

[b]The widths of the confidence intervals were not adjusted for multiplicity

and 40%, respectively; the 12-month OS rate was 72%. Of note, there was no correlation between the responses and *FGFR2* fusion partner status or co-occurring alterations in tumour-suppressor genes or oncogenes [23].

The clinical benefits of futibatinib monotherapy appear to be durable, according to preliminary data from the final analysis [27]. At the final data cutoff date (29 May 2021; median follow-up duration 25.0 months; median treatment duration 9.1 months), the confirmed ORR [41.7% (43 of 103 patients)] and the DCR (82.5%) were unchanged from those seen in the primary analysis. ORRs were also consistent across the patient subgroups. Median DOR was 9.5 months, with 74% of the responses lasting ≥ 6 months; median PFS was 8.9 months, with a 12-month PFS rate of 35.4%; and mature median OS was 20.0 months, with a 12-month OS rate of 73.1% [27].

Health-related quality of life (HR-QOL) was sustained throughout 9.0 months of futibatinib monotherapy [23]. There were no clinically meaningful (i.e. ≥ 10 points) mean changes from baseline in European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 global health status, individual functional scale and symptom scale scores at cycles 2, 4, 7, 10 and 13 (assessed $n = 84$, 80, 66, 59 and 48, respectively) except for the constipation scale score in cycle 4 (which worsened by 10.0 points). Moreover, the status across all EuroQol 5-Dimension 3-Level dimensions was unchanged or had improved in ≥ 71.8% of patients and mean EuroQol visual-analogue scale scores were sustained from baseline at cycle 13. ECOG performance status was also maintained or improved from baseline at cycles 2, 4, 7, 10 and 13, respectively ($n = 91$, 89, 77, 66 and 54) in 94.5%, 88.8%, 84.4%, 83.2% and 81.5% of patients [23].

5 Safety of Futibatinib

The primary analysis of data from FOENIX-CCA2 in adults with unresectable or metastatic intrahepatic CCA harbouring an *FGFR2* fusion or rearrangement, and disease progression after systemic therapy showed futibatinib to have a manageable safety profile with supportive care and as-needed dose modifications [26]. Moreover, the safety profile was shown to be consistent with the patient population studied (i.e. patients with advanced cancer) [dry mouth, dry skin, fatigue], the drug's mechanism of action (hyperphosphataemia, palmar–plantar erythrodysesthesia syndrome, gastrointestinal symptoms) and other drugs targeting the same pathway [25, 26].

TRAEs occurred in 99% of 103 patients; the most common TRAEs of any grade (in ≥ 25% of patients) were hyperphosphataemia, alopecia, dry mouth, diarrhoea, dry skin and fatigue (Fig. 1). The most frequently reported grade 3 TRAEs were hyperphosphataemia (defined as a serum phosphate level of ≥ 7 mg/dL), an increased aspartate aminotransferase level, stomatitis and fatigue (occurring in 30%, 7%, 6% and 6% of patients, respectively). One grade 4 TRAE (increased alanine aminotransferase level) and no grade 5 TRAEs were observed [23].

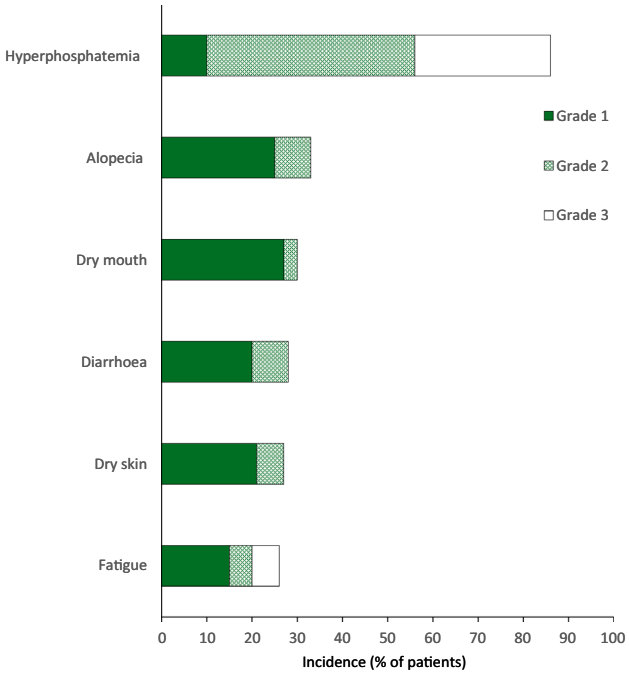

Fig. 1 Treatment-related adverse events of any grade reported in ≥ 25% of 103 patients with unresectable or metastatic intrahepatic cholangiocarcinoma harbouring a *fibroblast growth factor receptor 2* fusion or rearrangement, and disease progression after systemic therapy in the phase II part (FOENIX-CCA2) of a phase I/II study [23]

The median time to the onset of hyperphosphataemia was 5 days; all grade 3 hyperphosphataemia cases resolved in a median of 7 days [23]. Hyperphosphataemia was manageable with phosphate-lowering therapy, dose reductions and dose interruptions in 78%, 20% and 17% of patients, respectively. None of the patients discontinued therapy because of hyperphosphataemia. Other AEs frequently reported in patients receiving FGFR inhibitors were generally mild following futibatinib therapy, including nail toxic effects (any grade: 47% of patients; grade ≥ 3: 2%) and retinal disorders (any grade: 8%; grade ≥ 3: 0%) [23].

Serious TRAEs (grades 1–3) occurred in 10% of patients, with only one [migraine (grade 1/2): $n = 2$] occurring in more than one patient, but treatment discontinuation owing to TRAEs was rare [23]. TRAEs resulted in dose reductions and dose interruptions in 54% and 50% of 103 patients. Two patients permanently discontinued futibatinib: one due to grade 2 stomatitis, grade 3 oral dysesthesia and grade 2 pharyngeal inflammation, and one due to grade 3 oesophagitis [23].

Results from the final analysis were consistent with those of the primary analysis, with no new safety signals identified [23, 27]. The most frequently reported TRAEs included hyperphosphataemia (85% of 103 patients), alopecia (33%), dry mouth (30%), diarrhoea (28%), dry skin (27%) and fatigue (25%) [27]. Treatment discontinuation because of TRAEs occurred in four patients [27].

6 Dosage and Administration of Futibatinib

Futibatinib is conditionally approved for the treatment of adults with locally advanced or metastatic CCA with an *FGFR2* fusion or rearrangement who have progressed after ≥ 1 prior line of systemic therapy in the EU [8] and with previously treated, unresectable, locally advanced or metastatic intrahepatic CCA harbouring *FGFR2* gene fusions or other rearrangements in the USA [9]. In Japan, futibatinib is approved for the treatment of adults with unresectable biliary tract cancer harbouring *FGFR2* gene fusions who have progressed after chemotherapy [10]. Where reported, the presence of *FGFR2* fusions or rearrangements should be confirmed by an appropriate diagnostic test [8, 10]. A US FDA-approved test for detecting *FGFR2* fusions or rearrangements is not available [9].

Futibatinib is available as 4 mg tablets and should be taken with or without food at approximately the same time each day [8, 9], or on an empty stomach [10]. The recommended dosage is 20 mg once daily [8–10], with treatment continued until disease progression or unacceptable toxicity [8, 9].

Local prescribing information should be consulted for detailed information, including regarding dose adjustments due to drug interactions or AEs, the management of hyperphosphataemia, contraindications, warnings and precautions, and use in specific patient populations.

7 Current Status of Futibatinib in the Management of Locally Advanced and Metastatic Cholangiocarcinoma

Complete surgical resection with negative margins and lymphadenectomy is a potential curative option for CCA [1–4]. Regrettably, the disease often presents at a later (advanced) stage (Sect. 1) and has a high recurrence rate (up to 80% in 3 years) following curative-intent resection [1], both of which limit the therapeutic options of patients with unresectable disease to palliative treatment [4].

The EMSO [1] and NCCN [2] Clinical Practice Guidelines for biliary tract cancer both recommend that molecular profiling (with the gene panel including *BRAF*, *FGFR2*, *HER2* and *IDH1*) be carried out in patients with unresectable or metastatic CCA who are candidates for systemic therapy. In this patient population, the EMSO guideline lists chemotherapy as the current standard of care for first-line treatment, with clinical trials advocated for when available [1], while the NCCN guidelines recommend systemic therapy, a clinical trial or best supportive care [2]. The combination of cisplatin, gemcitabine and durvalumab is recommended in the EMSO guideline [1] for first-line treatment and is listed alongside pembrolizumab plus gemcitabine and cisplatin (both category 1 treatments) in the NCCN guidelines [2] as preferred regimens for first-line treatment. The NCCN guidelines also recommend gemcitabine plus cisplatin (category 1) as another recommended regimen and cisplatin plus gemcitabine and durvalumab as a recommended treatment option for patients who developed recurrent disease > 6 months post-surgery with curative intent and > 6 months after completing adjuvant therapy [2]. The British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma [3] recommend that CCAs should be subjected to molecular profiling at the earliest opportunity. The combination of cisplatin and gemcitabine is recommended as first-line therapy in patients with advanced biliary tract cancer, with immunotherapy able to be added upon the consideration of benefits and toxicities [3].

Targeted therapies come into play in patients with CCA who require subsequent-line systemic therapy and have a targetable genomic alteration [1, 2, 4]. Such alterations have been identified in ≈ 40% of biliary tract cancers, with *IDH1* mutations and *FGFR2* fusions or rearrangements the most common (being present in 10–20% and 9–15% of intrahepatic CCAs but rare in other CCA subtypes) [2, 13]. In patients with unresectable or metastatic CCA harbouring an *FGFR2* fusion or rearrangement who have progressed after one prior line of systemic therapy, FGFR inhibitors are recommended: the EMSO guideline [1] recommends futibatinib, infigratinib and pemigatinib while the NCCN guidelines [2] recommend futibatinib and pemigatinib (with infigratinib removed). As noted in the EMSO guideline, futibatinib and infigratinib were approved in the USA but not in the EU at the time of publication [1]. The British Society of Gastroenterology guidelines state that while molecular and in vitro data suggest that futibatinib has shown activity against emergent mutations, any survival impact is currently uncertain [3].

Futibatinib is an oral small molecule compound that selectively (with inhibition generally similar across all four FGFR isoforms and minimal activity demonstrated against other kinases) and irreversibly inhibits the tyrosine kinase activity of FGFR1–4 by covalently binding to a conserved cysteine residue in the P-loop of the FGFR tyrosine kinase domain within the ATP-binding pocket (Sect. 2). The low risk of drug resistance and robust activity against

drug-resistant FGFR mutants demonstrated by futibatinib (Sect. 2) may reflect the agent's binding mechanism (i.e. its distinctive binding site and irreversible mode of binding) [6]. Conversely, reversible FGFR inhibitors (e.g. infigratinib and pemigatinib) primarily engage in noncovalent interactions with amino acids in the hinge and surrounding regions of the ATP-binding pocket; thus, access to their binding sites can be blocked by resistance mutations (e.g. secondary 'gatekeeper' mutations in the FGFR tyrosine kinase domain can prevent FGFR inhibitor binding via steric hindrance) [6]. The key role of FGFRs in phosphorus homeostasis results in elevated phosphate levels with futibatinib administration (Sect. 2); thus, dose adjustments may be required to manage the resultant hyperphosphataemia (Sect. 6).

In adults with unresectable or metastatic intrahepatic CCA harbouring an *FGFR2* fusion or rearrangement who had disease progression after systemic therapy, monotherapy with oral futibatinib 20 mg once daily induced clinically meaningful and durable responses in FOENIX-CCA2 (Sect. 4). Moreover, the ORRs were consistent across the patient subgroups, including those based on age and previous regimens. HR-QOL in the patients participating in FOENIX-CCA2 was sustained throughout the futibatinib treatment period (Sect. 4).

Futibatinib demonstrated a manageable safety profile with supportive care and as-needed dose modifications in patients participating in FOENIX-CCA2 (Sect. 5). Moreover, the safety profile was consistent with the patient population studied, the mechanism of action of futibatinib, and other drugs targeting the same pathway [25, 26]. Indeed, hyperphosphataemia (an expected pharmacodynamic effect with futibatinib administration; Sect. 2), while the most frequently reported all grade and grade 3 TRAE, was manageable with phosphate-lowering therapy, dose reductions and dose interruption (Sect. 5).

FOENIX-CCA2 was associated with some limitations, including the noncomparative design (which therefore required the study's results to be compared with the variable estimates of the natural history of *FGFR* fusion-positive disease) and the small sample size [23]. Given the conditional EU and US approval of futibatinib (Sect. 6), an open-label, multinational, phase II study in patients with advanced, unresectable CCA with *FGFR2* fusions or rearrangements who have received ≥ 1 prior systemic therapy has been proposed [25, 26]. In the absence of head-to-head trials, a simulated indirect treatment comparison of patient data from FOENIX-CCA2 and published aggregated data from comparator studies suggests that the PFS and OS benefits did not significantly differ between futibatinib and pemigatinib but that there was a significant reduction in the risk of disease progression or death with futibatinib relative to chemotherapy [28]. Given the limitations of indirect comparisons, the findings should be interpreted with caution.

Although further (confirmatory) efficacy and tolerability data are expected, current evidence indicates that futibatinib is a valuable targeted therapy option for adults with locally advanced or metastatic CCA harbouring an *FGFR2* fusion or rearrangement who have progressed following systemic therapy, who have limited treatment options and poor life expectancy.

Data Selection Futibatinib: 151 records identified	
Duplicates removed	1
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	105
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	17
Cited efficacy/tolerability articles	5
Cited articles not efficacy/tolerability	23
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Futibatinib, Lytgobi, TAS-120, Cholangiocarcinoma, Cholangiocellular carcinoma, bile duct neoplasms. Records were limited to those in English language. Searches last updated 29 April 2024	

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11523-024-01059-8.

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Declarations

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