Safety Profile and Adverse Event Management for Futibatinib, An Irreversible FGFR1–4 Inhibitor: Pooled Safety Analysis of 469 Patients

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ABSTRACT

Purpose: Futibatinib, a covalently-binding inhibitor of fibroblast growth factor receptor (FGFR)1-4 gained approval for the treatment of refractory, advanced intrahepatic cholangiocarcinoma (iCCA) harboring an *FGFR2* fusion/other rearrangement. An integrated analysis was performed to evaluate safety and provide guidance on the management of futibatinib-associated adverse events (AEs) in patients with unresectable/metastatic tumors, including iCCA.

Patients and Methods: Data from three global phase I or II studies of futibatinib (NCT02052778; JapicCTI-142552) were pooled. AEs were graded per NCI CTCAE v4.03, where applicable. Safety was analyzed for patients receiving any futibatinib starting dose (overall population) and in those receiving the approved starting dose of 20 mg once every day.

Results: In total, 469 patients with one of 33 known tumor types were analyzed, including 318 patients who received futibatinib 20 mg every day. AEs of clinical interest (AECI; any grade/grade ≥3) in the overall population included hyperphosphatemia (82%/19%), nail disorders (27%/1%), hepatic AEs (27%/11%), stomatitis (19%/3%), palmar-plantar erythrodysesthesia syndrome (PPES; 13%/3%), rash (9%/0%), retinal disorders (8%/0%), and cataract (4%/1%). Median time to onset of grade ≥3 AECIs ranged from 9 days (hyperphosphatemia) to 125 days (cataract). Grade ≥3 hyperphosphatemia, hepatic AEs, PPES, and nail disorders resolved to grade ≤2 within a median of 7, 7, 8, and 28 days, respectively. Discontinuations due to treatment-related AEs were rare (2%), and no treatment-related deaths occurred. AE management included phosphate-lowering medication and dose adjustments.

Conclusions: Futibatinib showed a consistent and manageable safety profile across patients with various tumor types. AECIs were mostly reversible with appropriate clinical management.

Introduction

Dysregulated activation of the fibroblast growth factor/fibroblast growth factor receptor (FGF/FGFR) signaling pathway through genomic aberrations in *FGFR* drives oncogenesis in various tumor types (1–3). Accordingly, FGFR-directed therapies, including reversible and covalent small-molecule inhibitors of FGFR, have been evaluated as potential therapeutics across multiple cancer types (4).

Futibatinib is a highly selective, covalently-binding, irreversible inhibitor of FGFR1–4 with activity in a variety of cancer cell lines and xenograft models harboring *FGFR* alterations (5). In a global phase I dose escalation/expansion study and a Japanese phase I trial, futibatinib demonstrated antitumor activity in patients with a broad spectrum of *FGFR*-aberrant tumors, including promising activity in cholangiocarcinoma (CCA; refs. 6–8). The results of the subsequent, pivotal phase II trial (FOENIX-CCA2) in patients with previously treated, advanced intrahepatic CCA (iCCA) harboring *FGFR2* fusions or other rearrangements demonstrated a 42% objective response rate and median duration of response of 9.7 months, leading to the approval of futibatinib at a dose of 20 mg orally once every day for this indication in the United States (September 2022), Japan (June 2023), and Europe (July 2023; refs. 9–11).

Safety and tolerability are key considerations for all FGFR-targeted drugs, since FGFRs are expressed on many different cell types and regulate diverse physiologic processes, including tissue homeostasis, angiogenesis, embryogenesis, and wound repair (1–3). Adverse events (AEs) of clinical interest generally observed with pan-FGFR inhibitors include hyperphosphatemia, an on-target, off-tumor effect resulting from FGFR inhibition in kidneys and bones (12, 13), nail disorders such as onycholysis and paronychia, stomatitis, palmar-plantar erythrodysesthesia syndrome (PPES), rash, and retinal disorders (11, 14–21).

A detailed understanding of the AE profile of FGFR inhibitors is important for optimizing their efficacy, while maintaining patients' quality of life. Here, we conducted a pooled analysis of individuals enrolled across three phase I and II trials of futibatinib to provide more detailed information on the incidence and time course of AEs. Analysis focused on typical FGFR inhibitor–related side effects [hereafter described as AEs of clinical interest (AECI)] and their management, including pharmacologic treatments and dose adjustments. Recommendations for the management of AECIs are also discussed to provide practical guidance for optimizing the treatment of patients with futibatinib in the clinic.

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Translational Relevance

A comprehensive understanding of the safety profile of FGFR inhibitors is important for timely detection and effective management of adverse events (AEs). We report a pooled safety analysis of data from three phase I and II trials of futibatinib to provide detailed information on the incidence and time course of AEs and provide practical recommendations for AE management based on clinical expertise. The data reported herein show that futibatinib has a consistent and manageable safety profile across various tumor types. AEs of clinical interest, such as hyperphosphatemia, nail disorders, and retinal toxicities were resolved effectively with dose modifications and/or supportive care. Education of the clinical care team and patients regarding effective management of AEs is paramount for optimizing patient outcomes. Longer-term follow-up, including from real-world studies, is needed to fully establish the long-term safety profile of FGFR inhibitors and inform AE management in routine clinical practice.

Patients and Methods

Patients and analysis populations

This analysis included patients with an advanced solid tumor who received ≥1 dose of futibatinib in one of the following studies: (i) global phase I study in patients with advanced solid tumors (NCT02052778); (ii) global phase II study in patients with *FGFR2* fusion or rearrangement-positive iCCA (NCT02052778); or (iii) Japanese phase I study (JapicCTI-142552). Patients may have received any number of prior lines of therapy. Full details of the study design and eligibility criteria for those studies have been published previously (6–8, 11). All studies were designed and conducted in compliance with the ethical principles of Good Clinical Practice and in accordance with the Declaration of Helsinki. The study protocols were approved by all the institutional review boards/independent ethics committees at participating centers, and written informed consent was obtained from all patients.

Results were analyzed separately for the overall population, which included patients receiving futibatinib at any starting dose and any dosing schedule (including 2–24 mg every day or 8–200 mg three times per week), and for those receiving futibatinib at the approved starting dose of 20 mg every day (20-mg every day population).

Safety assessments

AEs were recorded from the time of informed consent until 30 days after the last futibatinib dose or new anticancer treatment initiation, whichever occurred first. AEs were graded based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03, except for hyperphosphatemia, which was not included in NCI CTCAE v4.03 and was therefore graded based on serum phosphate levels, defined per protocol (Supplementary Table S1).

AECIs were grouped using Medical Dictionary for Regulatory Activities (MedDRA) labeling groups (MLG), based on a standardized MedDRA query (SMQ) and adjusted by medical judgment to group preferred terms describing a similar medical condition. If there was no appropriate SMQ, MLGs were assembled by medical judgment. The following MLGs were included for AECIs: hyperphosphatemia, nail disorders, hepatic AEs, stomatitis, PPES, rash, retinal disorders, and cataract. Preferred terms of AEs with similar clinical appearance that were included in each of the AECIs are shown in Supplementary Table S2.

Statistical analysis

Time to onset of AECIs was defined as the time between the first dose of futibatinib and the earliest onset date of an AE. Time to resolution of grade ≥3 or grade ≥2 AEs was defined as the longest time from onset to documentation of improvement to grade ≤2 or grade ≤1, respectively. Data, including frequencies of AEs, futibatinib dose adjustments, and use of concomitant medications were summarized descriptively; no comparative statistics were performed. Point estimates of AE onset or resolution rates were assessed using Kaplan–Meier methodology, with 95% confidence intervals calculated on the basis of the Greenwood formula.

Data availability

The data analyzed in this study are on file with Taiho Oncology, Inc. and Taiho Pharmaceutical Co., Ltd., and are not publicly available. Data are available from the authors upon reasonable request with the permission of Taiho. Other data generated in this analysis are available within the article and its supplementary data files.

Results

Patients

A total of 469 patients with solid tumors were included in this pooled analysis. Baseline characteristics in the overall ($n = 469$) and 20-mg every day ($n = 318$) populations are presented in **Table 1**. In the overall population, the mean age was 56.9 years, 52.9% were female, and most (70.4%) were enrolled from North America or Europe. A summary of the patient populations and futibatinib dose ranges included in this analysis is provided in Supplementary Fig. S1.

A total of 33 known primary tumor types were represented, the most common (≥5%) being CCA (51.6%), primary central nervous system tumor (7.9%), gastric cancer (7.0%), colorectal cancer (6.0%), and breast cancer (5.3%). Almost all patients (98.1%) had received ≥1 prior anticancer treatment, with 48.9% of patients receiving ≥2 regimens for advanced or metastatic disease. Baseline characteristics in the 20-mg every day population were like those of the overall population.

At the time of data cutoff for this analysis (October 1, 2020), 92.1% and 88.7% of patients in the overall and 20-mg every day populations, respectively, had discontinued study treatment (Supplementary Table S3). The primary reason for discontinuation in both populations was disease progression (78.5% and 74.8%), with a minority of patients in both populations discontinuing treatment due to AEs (4.5% and 6.0%).

Median (range) duration of treatment across all tumor types was 2.8 (0.1−37.9) months in the overall population and 3.7 (0.1–34.5) months in the 20-mg every day population. The median number of treatment cycles (range) was 4.0 (1–54) and 5.0 (1–49), respectively, and the median (range) relative dose intensity was 88.9% (4.8–102.9) and 90.3% (19.0–100.0; Supplementary Table S4).

Safety overview

In the overall and 20-mg every day populations, treatment-emergent AEs (TEAEs) were reported for 99.6% and 99.4% of patients, respectively, including 313 (66.7%) and 228 (71.7%) patients with at least one grade ≥3 TEAE (**Table 2**). Common AEs in the overall population, regardless of causality, included hyperphosphatemia (82.1%), constipation (34.1%), diarrhea (33.7%), and nausea (29.6%; **Table 2**), with similar frequencies in the 20-mg every day population. Overall, 23.7% of patients had fatigue (grade ≥3 treatment-related fatigue in 1.9% of patients). The most common grade ≥3 TEAEs were hyperphosphatemia (18.8%), anemia

Table 1. Baseline patient and clinical characteristics.

Variable	Futibatinib dosing	
	Overall population (*n* = 469)	20-mg every day (*n* = 318)
Mean (SD) age, years	56.9 (12.8)	56.8 (12.8)
Female, *n* (%)	248 (52.9)	167 (52.5)
Race, *n* (%)		
White	233 (49.7)	157 (49.4)
Asian	138 (29.4)	90 (28.3)
Black	15 (3.2)	12 (3.8)
Other/unknown	83 (17.7)	59 (18.6)
Geographical region, *n* (%)		
North America	167 (35.6)	124 (39.0)
Europe	163 (34.8)	112 (35.2)
Japan	97 (20.7)	52 (16.4)
Asia Pacific (excluding Japan)	42 (9.0)	30 (9.4)
ECOG performance status, *n* (%)		
0	197 (42.0)	130 (40.9)
1	272 (58.0)	188 (59.1)
Mean (SD) time from first diagnosis, months	33.5 (41.9)	29.9 (40.1)
Mean (SD) time from most recent recurrence/relapse, months	4.2 (12.5)	4.2 (12.6)
Tumor type		
Cholangiocarcinoma	242 (51.6)	192 (60.4)
Primary CNS	37 (7.9)	36 (11.3)
Gastric	33 (7.0)	28 (8.8)
Colorectal	28 (6.0)	8 (2.5)
Breast	25 (5.3)	13 (4.1)
Esophageal	16 (3.4)	10 (3.1)
Sarcoma	9 (1.9)	7 (2.2)
Brain	7 (1.5)	0
Lung	7 (1.5)	3 (0.9)
Bladder	6 (1.3)	0
Gallbladder	6 (1.3)	4 (1.3)
Head and neck	5 (1.1)	2 (0.6)
Endometrial	5 (1.1)	3 (0.9)
Pancreatic	4 (0.9)	1 (0.3)
Cervical	3 (0.6)	1 (0.3)
GIST	3 (0.6)	0
Mesothelioma	3 (0.6)	1 (0.3)
Neuroendocrine	2 (0.4)	0
Oropharyngeal	2 (0.4)	2 (0.6)
Ovarian	2 (0.4)	1 (0.3)
Parotid	2 (0.4)	1 (0.3)
Skin	2 (0.4)	0 (0)
Thyroid	2 (0.4)	1 (0.3)
Adrenal corticoid	1 (0.3)	1 (0.3)
Other[a]	9 (1.9)	0 (0)
Unknown	8 (1.7)	3 (0.9)
Patients with ≥1 prior anticancer therapy, *n* (%)	460 (98.1)	311 (97.8)
Prior regimens for advanced/metastatic disease, *n* (%)		
1	134 (28.6)	101 (31.8)
2	95 (20.3)	74 (23.3)
≥3	134 (28.6)	86 (27.0)
Median (range) time from last prior anticancer therapy dose to first study dose (months)	1.5 (0.1–173.3)	1.5 (0.1–173.3)

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; GIST, gastrointestinal stromal tumor; SD, standard deviation.
[a]Other tumor types were appendix, duodenal papilla, neuroblastoma, penis carcinoma, prostate, renal cell, tubal, urachal, and uterine myoma, each in 1 patient.

(6.6%), alanine aminotransferase (ALT) increase (6.4%), and aspartate aminotransferase (AST) increase (6.0%). The incidence of treatment-related serious AEs (SAEs) was low in both the overall (5.8%) and 20-mg every day (7.2%) populations. In total, 9 (1.9%) patients discontinued treatment due to treatment-related AEs. No treatment-related deaths occurred in any of the three trials. An overall summary of safety and the most common treatment-related AEs, SAEs, and treatment-related SAEs are summarized in Supplementary Tables S5 to S8.

A total of 401 patients (85.5%) in the overall population had a dose modification during treatment, including 270 patients (84.9%) in the 20-mg every day population. In the overall and 20-mg every day

Table 2. Overview of common TEAEs (MedDRA Preferred Terms; incidence ≥10%) and select AEs of clinical interest irrespective of frequency.

	Futibatinib dosing			
	Overall population ($n = 469$)		20-mg every day ($n = 318$)	
Patients with TEAEs	Any grade, *n* (%)	Grade ≥3, *n* (%)	Any grade, *n* (%)	Grade ≥3, *n* (%)
Any TEAE	467 (99.6)	313 (66.7)	316 (99.4)	228 (71.7)
Hyperphosphatemia	385 (82.1)	88 (18.8)	280 (88.1)	75 (23.6)
Constipation	160 (34.1)	3 (0.6)	112 (35.2)	2 (0.6)
Diarrhea	158 (33.7)	3 (0.6)	106 (33.3)	2 (0.6)
Nausea	139 (29.6)	5 (1.1)	86 (27.0)	3 (0.9)
Decreased appetite	119 (25.4)	11 (2.3)	79 (24.8)	8 (2.5)
Fatigue	111 (23.7)	18 (3.8)	84 (26.4)	17 (5.3)
AST increased	108 (23.0)	28 (6.0)	83 (26.1)	22 (6.9)
Vomiting	105 (22.4)	7 (1.5)	73 (23.0)	5 (1.6)
Dry mouth	102 (21.7)	0 (0)	70 (22.0)	0 (0)
ALT increased	96 (20.5)	30 (6.4)	72 (22.6)	25 (7.9)
Alopecia	87 (18.6)	0 (0)	70 (22.0)	0 (0)
Anemia	85 (18.1)	31 (6.6)	53 (16.7)	19 (6.0)
Dry skin	85 (18.1)	0	57 (17.9)	0
Abdominal pain	73 (15.6)	12 (2.6)	57 (17.9)	8 (2.5)
Blood creatinine increased	63 (13.4)	1 (0.2)	43 (13.5)	1 (0.3)
Weight decreased	59 (12.6)	7 (1.5)	44 (13.8)	5 (1.6)
Arthralgia	58 (12.4)	0	45 (14.2)	0
Dysgeusia	52 (11.1)	0	42 (13.2)	0
Asthenia	51 (10.9)	8 (1.7)	32 (10.1)	7 (2.2)
Pyrexia	51 (10.9)	5 (1.1)	28 (8.8)	3 (0.9)
Hypercalcemia	49 (10.4)	9 (1.9)	39 (12.3)	5 (1.6)
Back pain	48 (10.2)	3 (0.6)	32 (10.1)	3 (0.9)
Dry eye	48 (10.2)	1 (0.2)	39 (12.3)	1 (0.3)
Urinary tract infection	48 (10.2)	6 (1.3)	34 (10.7)	4 (1.3)
Blood alkaline phosphatase increased	46 (9.8)	11 (2.3)	35 (11.0)	7 (2.2)
Edema peripheral	41 (8.7)	1 (0.2)	32 (10.1)	0
AECIs				
Any AECI	409 (87.2)	135 (28.8)	292 (91.8)	109 (34.3)
Hyperphosphatemia	385 (82.1)	88 (18.8)	280 (88.1)	75 (23.6)
Nail disorders	127 (27.1)	5 (1.1)	94 (29.6)	4 (1.3)
Hepatic AEs	126 (26.9)	50 (10.7)	94 (29.6)	38 (11.9)
Stomatitis	89 (19.0)	15 (3.2)	58 (18.2)	11 (3.5)
PPES	62 (13.2)	12 (2.6)	48 (15.1)	11 (3.5)
Rash	40 (8.5)	0 (0)	27 (8.5)	0 (0)
Retinal disorders	38 (8.1)	0 (0)	27 (8.5)	0 (0)
Cataract	15 (3.9)	6 (1.3)	12 (3.8)	4 (1.3)

Abbreviations: AE, adverse event; AECI, adverse event of clinical interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; PPES, palmar-plantar erythrodysesthesia syndrome; TEAE, treatment-emergent adverse event.

populations, 32.0% and 40.3% of patients, respectively, had a dose reduction, and 48.2% and 61.0% of patients had a dose interruption due to AEs. Median time to first dose reduction due to an AE was 42.0 days in both the overall and 20-mg every day populations, and median time to first dose interruption due to an AE was 22.0 and 21.0 days, respectively. Overall, the most common events leading to dose modification were hyperphosphatemia (23.5%), increases in ALT (7.7%) and AST (6.0%), PPES (5.1%), and fatigue (4.5%). Discontinuations due to AEs were rare; only fatigue led to treatment discontinuation in more than 2 patients.

AECIs

Overall, AECIs in order of decreasing incidence were hyperphosphatemia, nail disorders, hepatic AEs, stomatitis, PPES, rash, retinal disorders, and cataract. Time to onset and resolution of AECIs in the overall population is summarized in **Fig. 1** and **Table 3**, and individual AECIs and their clinical management are discussed below and in **Table 4**. Class-effect toxicities for FGFR inhibitors are summarized in **Fig. 2**; **Table 5** summarizes practical recommendations for the management of FGFR inhibitor side effects based on the clinical expertise of investigators involved in futibatinib clinical trials and general guidelines for the management of side effects observed for FGFR inhibitors (22–25).

Hyperphosphatemia

Hyperphosphatemia was the most common AECI, reported in 385 (82.1%) patients in the overall population and in 280 (88.1%) patients in the 20-mg every day population (**Table 2**). In total, 88 (18.8%) patients had grade 3 hyperphosphatemia (serum phosphate >7 to ≤ 10 mg/dL, regardless of any clinical symptoms), including 75

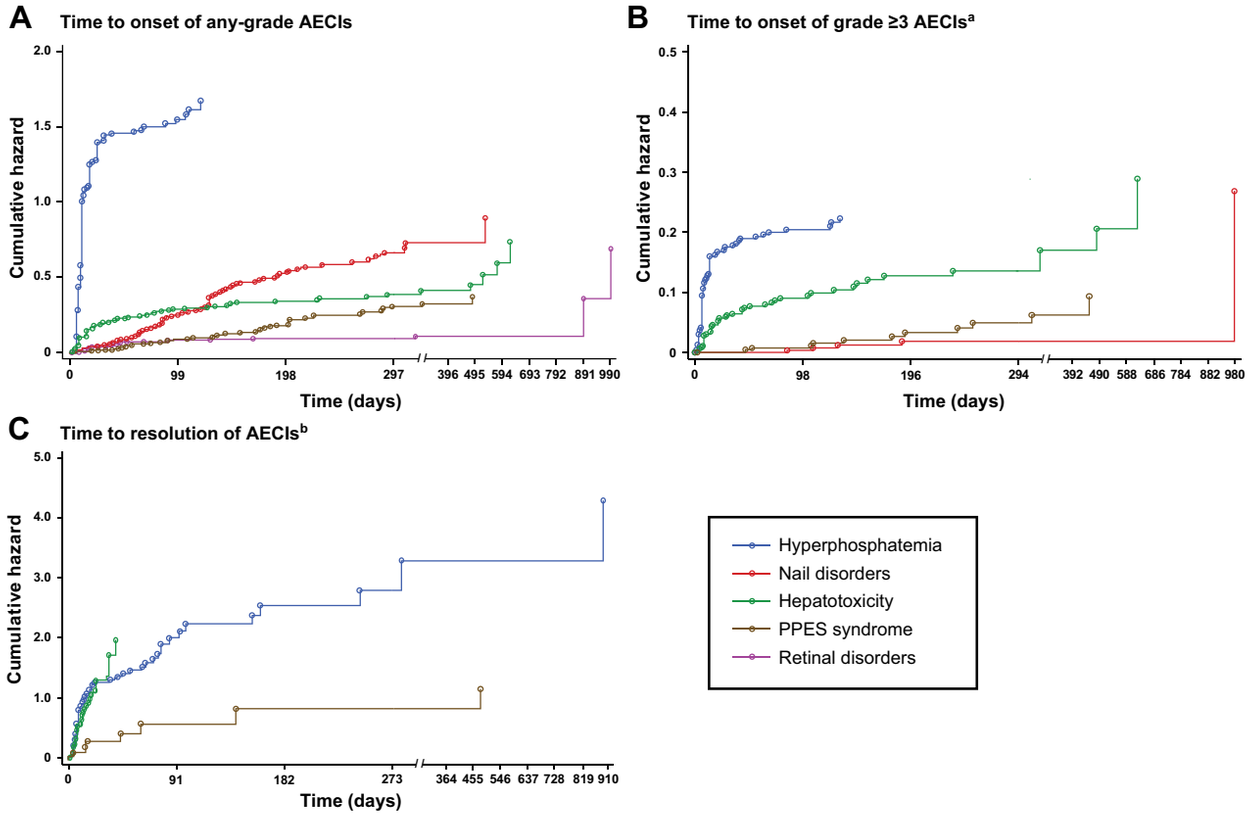

Figure 1.

Time to onset and resolution of AEs of clinical interest among the overall population. **A,** Time to onset of any-grade AECIs. **B,** Time to onset of grade ≥3 AECIs. **C,** Time to resolution of grade ≥3 AECIs to grade <1. [a]No grade ≥3 retinal disorders were reported. [b]At the time of data cutoff, no grade 3 nail disorder had resolved to grade <1; of the 5 patients with grade 3 nail disorder, events resolved to grade 2 in three cases and to grade 1 in two cases. AE, adverse event; AECI, adverse event of clinical interest; PPES, palmar-plantar erythrodysesthesia syndrome.

(23.6%) patients in the 20-mg every day population. All events were considered treatment related. No grade 4 events occurred. In the overall population, median time to onset for any-grade and grade ≥3 hyperphosphatemia was 6 and 9 days, respectively (**Fig. 1A** and **B**; **Table 3**), with a median time to resolution to grade ≤2 of 7 days. All but five cases of grade 3 hyperphosphatemia resolved to grade <1 (**Fig. 1C**), with a median time to resolution to grade <1 of 8 days in both the overall and 20-mg every day populations (**Table 3**).

Table 3. Time to onset and resolution of AEs of special interest.

	Futibatinib dosing					
	Overall population (n = 469)			20-mg every day (n = 318)		
	Median (range) time to onset of any-grade AECIs, days	Median (range) time to onset of grade ≥3 AECIs, days	Median (range) time to resolution grade ≥3 AECIs to grade <1, days	Median (range) time to onset of any-grade AECIs, days	Median (range) time to onset of grade ≥3 AECIs, days	Median (range) time to resolution grade ≥3 AECIs to grade <1, days
Hyperphosphatemia	6.0 (1–117)	9.0 (3–134)	8 (3–903)	5.0 (3–117)	9.0 (3–126)	8 (3–903)
Nail disorders	78.0 (2–547)	127.0 (82–980)	NA[a]	85.0 (5–547)	155.5 (105–980)	NA[a]
Hepatic AEs	15.5 (1–609)	22.0 (4–609)	14 (1–50)	15.5 (3–609)	25.0 (4–609)	14 (1–50)
Stomatitis	45.0 (2–685)	103.0 (27–374)	27 (8–48)	50.0 (2–682)	113.0 (43–374)	NE (8–27)
PPES	93.5 (6–482)	156.0 (44–462)	141 (4–490)	85.0 (6–279)	178.0 (44–462)	141 (4–490)
Rash	48.5 (3–527)	NA	31 (14–60)[b]	43.0 (8–527)	NA	31 (14–60)[b]
Retinal disorders	32.5 (7–990)	NA	21 (1–216)[b]	40.0 (7–902)	NA	23 (1–216)[b]
Cataract	144.0 (39–693)	620.0 (58–775)	NA	124.5 (39–693)	545.0 (58–702)	NA

Abbreviation: AE, adverse event; AECI, AE of clinical interest; NA, not applicable; PPES, palmar-plantar erythrodysesthesia syndrome.

[a]At the time of data cutoff, no grade 3 nail disorder had resolved to grade <1; of the 5 patients with grade 3 nail disorder, events resolved to grade 2 in three cases and to grade 1 in two cases.

[b]Data shown are for resolution of grade ≥2 rash or retinal disorders to grade <1; no grade ≥3 rash or retinal disorders were reported.

Table 4. Frequency of dosing adjustments and supportive medications used to manage AEs of clinical interest in patients who received futibatinib 20 mg once every day ($n = 318$).

AECI (group term)	Dose interruptions, *n* (%)	Dose reductions, *n* (%)	Dose discontinuation, *n* (%)	Supportive meds, *n* (%)
Hyperphosphatemia	67 (21.1)	41 (12.9)	0	248 (78.0)
Nail disorders	13 (4.1)	10 (3.1)	1 (0.3)	74 (23.3)
Hepatic AEs	29 (9.1)	21 (6.6)	0	0
Stomatitis	9 (2.8)	9 (2.8)	2 (0.6)	33 (10.4)
PPES	15 (4.7)	18 (5.7)	0	44 (13.8)
Rash	0	0	0	13 (4.1)
Retinal disorders	4 (1.3)	5 (1.6)	1 (0.3)	0

Abbreviations: AE, adverse event; AECI, adverse event of clinical interest; PPES, palmar-plantar erythrodysesthesia syndrome.

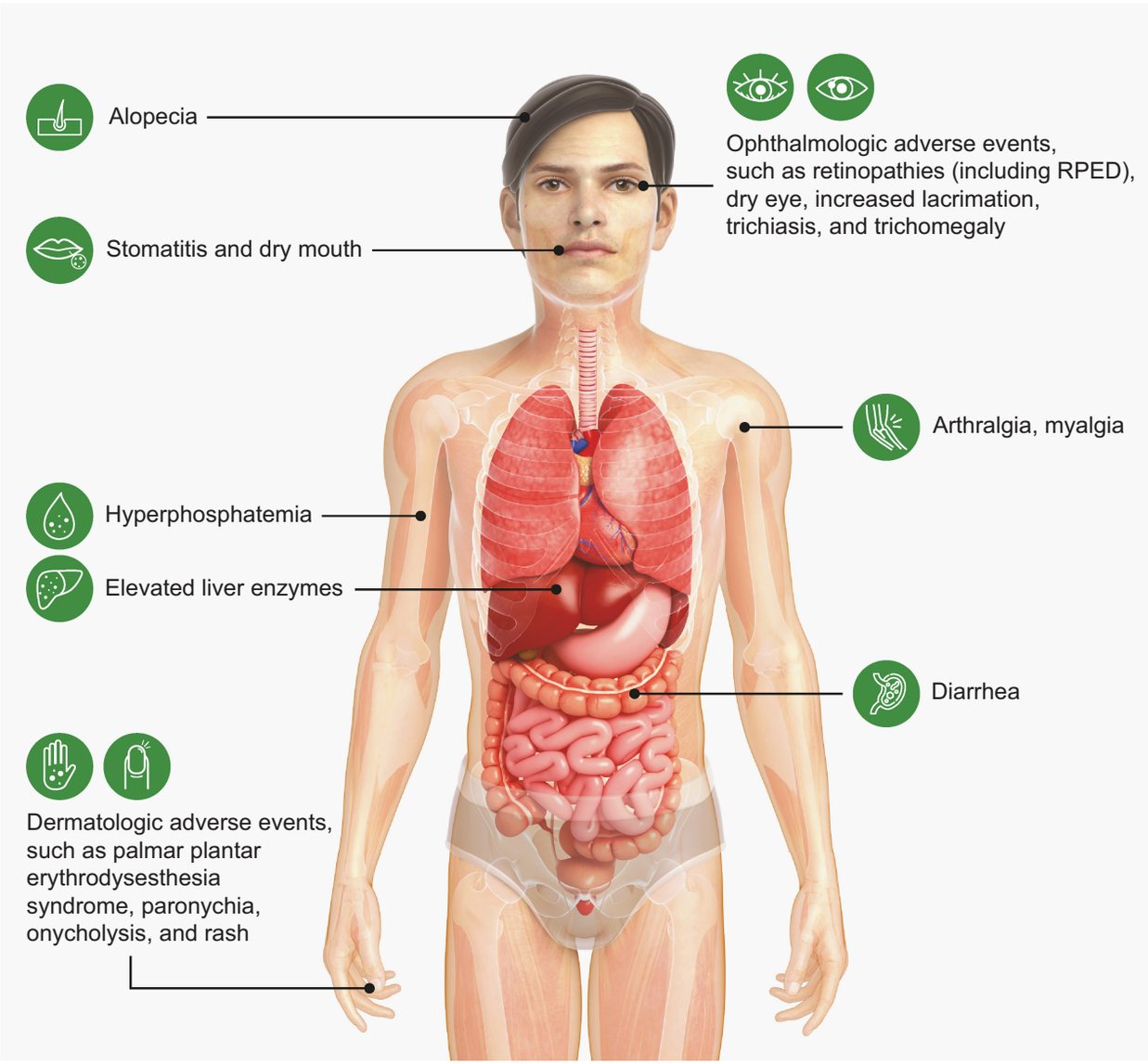

Figure 2.
Side effects of FGFR inhibitors. FGFR, fibroblast growth factor receptor; RPED, retinal pigment epithelial dystrophy.

Table 5. Practical recommendations for the management of FGFR inhibitor side effects.

Clinical presentation or CTCAE grade	Recommendations[a]
Hyperphosphatemia	
Serum phosphate ≥5.5 to ≤7 mg/dL	• Continue FGFR inhibitor at standard dose • Initiate phosphate binder • Reinforce low-phosphate diet and monitor serum phosphate weekly
Serum phosphate >7 to ≤10 mg/dL	• Initiate or increase dose of phosphate binder and/or add phosphaturic acid • Reinforce low-phosphate diet and monitor serum phosphate weekly • Dose reduction of FGFR inhibitor should be considered once the phosphate levels reach >7 mg/dL on two separate occasions despite optimization of diet and phosphate binding agents ○ If the serum phosphate resolves to ≤7 mg/dL within 2 weeks after dose reduction, continue at reduced dose ○ If serum phosphate is not ≤7 mg/dL within 2 weeks, further reduce to next lower dose ○ If serum phosphate is not ≤7 mg/dL within 2 weeks after the second dose reduction, withhold FGFR inhibitor until serum phosphate is ≤7 mg/dL and resume at the dose prior to interruption
Serum phosphate >10 mg/dL	• Initiate or adjust phosphate lowering therapy • Reinforce low-phosphate diet and monitor serum phosphate weekly • Hold FGFR inhibitor until serum phosphate is ≤7 mg/dL ○ When serum phosphate reaches <7 mg/dL, restart FGFR inhibitor at one dose reduction ○ Consider permanently discontinuing FGFR inhibitor if serum phosphate is not ≤7 mg/dL within 2 weeks following two dose interruptions and reductions
Nail disorders	
Onycholysis	
Grade 1	• If infected, begin oral antibiotics with anti-*S. aureus* and Gram-positive coverage
Grade 2	• If infected, begin oral antibiotics with anti-*S. aureus* and Gram-positive coverage • If painful hematoma or subungual abscess is suspected, partial or total nail avulsion is required • Refer to a dermatologist for intolerable grade 2 events, or grade 2 events that have not responded to 4 weeks of therapy
Grade ≥3	• Withhold FGFR inhibitor until onycholysis has resolved to grade ≤1 • If infected, begin oral antibiotics with anti-*S. aureus* and Gram-positive coverage • If painful hematoma or subungual abscess is suspected, partial or total nail avulsion is required • Reassess after 2 weeks; if necessary, interrupt treatment until severity decreases to grade ≤1; if reactions worsen or do not improve, consider withdrawing treatment • Refer to a dermatologist
Paronychia	
Grade 1	• Clindamycin 1% solution (or other topical antibiotic) around and under nails TID, or antibiotic ointment • Topical povidone iodine 2% (antiseptic) • Soak for 15 min daily in a 1:1 mix of white vinegar and water
Grade 2	• Clindamycin 1% solution (or other topical antibiotic) around and under nails TID, or antibiotic ointment • Topical povidone iodine 2% (antiseptic) and soak in mix of white vinegar and water • Cefadroxil 500 mg BID or TMP/SMX DS BID (oral antibiotics) for 14 days • Refer to a dermatologist for intolerable grade 2 events, or grade 2 events that have not responded to 4 weeks of therapy
Grade ≥3	• Withhold FGFR inhibitor until paronychia has resolved to grade ≤1 • Obtain bacterial cultures to confirm sensitivity to antimicrobial agents • Clindamycin 1% solution (or other topical antibiotic) around and under nails TID, or antibiotic ointment • Cefadroxil 500 mg BID or TMP/SMX DS BID (oral antibiotics) for 14 days • Consider partial nail avulsion • Refer to a dermatologist
Stomatitis	
Grade 1	• Dexamethasone elixir (corticosteroid) 0.5 mg/mL swish and spit 1 teaspoon (5 mL) TID • Alcohol-free mouthwash for oral hygiene
Grade 2	• Dexamethasone elixir 0.5 mg/mL swish and spit 5 mL TID *AND* doxepin 10 mg/mL solution (analgesic) or "magic mouthwash" (i.e., diphenhydramine plus lidocaine plus antacid) swish and spit 5 mL PRN for pain • Consider intralesional triamcinolone acetonide (corticosteroid) 10 mg/mL to area if localized
Grade ≥3	• Withhold FGFR inhibitor until stomatitis has resolved to grade ≤1, and restart at one dose reduction • Dexamethasone elixir 0.5 mg/mL swish and spit 5 mL TID *AND* doxepin 10 mg/mL solution or "magic mouthwash" swish and spit 5 mL PRN for pain • Clotrimazole (antifungal) 10 mg lozenges QID
PPES	
Grade 1	• Apply topical urea 20% or ammonium lactate 12% lotion BID to hands and feet
Grade 2	• Apply topical urea 20% or ammonium lactate 12% lotion BID to hands and feet • Fluocinomide 0.05% or other high-potency corticosteroid cream BID to hands and feet • Refer to a dermatologist for intolerable grade 2 events, or grade 2 events that have not responded to 4 weeks of therapy
Grade ≥3	• Withhold FGFR inhibitor until PPES has resolved to grade ≤1, and restart at one dose reduction • Apply topical urea 20% or ammonium lactate 12% lotion BID to hands and feet • Fluocinomide 0.05% or other high-potency corticosteroid cream BID to hands and feet • Refer to dermatologist

(Continued on the following page)

Table 5. Practical recommendations for the management of FGFR inhibitor side effects. (Cont'd)

Clinical presentation or CTCAE grade	Recommendations[a]
Rash	
Grade 1	• Initiate topical agents such as emollients, lidocaine cream, super-potent topical steroids (clobetasol), and nonsteroid anti-inflammatory agents • Reassess after 2 weeks (either by clinician or patient self-report)
Grade 2	• Initiate or escalate topical agents such as emollients, lidocaine cream, super-potent topical steroids (clobetasol), and nonsteroid anti-inflammatory agents • Reassess after 2 weeks (either by clinician or patient self-report) • Refer to a dermatologist for intolerable grade 2 events, or grade 2 events that have not responded to 4 weeks of therapy
Grade ≥3	• Withhold FGFR inhibitor until rash has resolved to grade ≤1, and restart at one dose reduction • Continue topical agents • Initiate oral antibiotics and consider a short course of systemic corticosteroids • Reassess after 2 weeks; if reactions worsen or do not improve, dose interruption or discontinuation per protocol may be necessary • Refer to a dermatologist
Retinal pigment epithelial dystrophy/retinopathy	
	• Recommend comprehensive ophthalmologic examination prior to initiation of treatment • Recommend detailed ophthalmologic evaluation every 2 months for the first 6 months, and every 3 months thereafter that includes optical coherence tomography, and fundus examination along with routine slip lamp and visual acuity testing • If RPED asymptomatic and stable on serial examination, continue FGFR inhibitor and continue periodic ophthalmic evaluation • If RPED symptomatic AND visual acuity is 20/40 or better, or ≤3 lines of decreased vision from baseline ○ Withhold FGFR inhibitor until resolution of symptoms and significant examination findings ○ If condition resolves within 4 weeks, resume FGFR inhibitor at one dose reduction ○ If condition recurs with rechallenge, withhold FGFR inhibitor again; if condition resolves within 4 weeks, resume FGFR inhibitor at two reductions ○ Continue close monitoring with an ophthalmologist • If RPED symptomatic and visual acuity is worse than 20/40 or >3 lines decreased vision from baseline ○ Withhold FGFR inhibitor until resolution of symptoms and significant examination findings ○ If condition resolves within 4 weeks, resume FGFR inhibitor at two dose reductions ○ If condition recurs, consider permanently discontinuing FGFR inhibitor ○ Continue close monitoring with an ophthalmologist • If visual acuity severely compromised (e.g., worse than 20/200 in affected eye; limiting activities of daily living), consider permanently discontinuing the FGFR inhibitor, and continue close monitoring with an ophthalmologist

Note: Table adapted from Lacouture and colleages (22), Kommalapati and colleagues (23), and Mahipal and colleagues (24) based on clinical expertise of futibatinib investigators.

Abbreviations: AE, adverse event; AECI, adverse event of clinical interest; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; FGFR, fibroblast growth factor receptor; PPES, palmar-plantar erythrodysesthesia syndrome; PRN, as required; QID, four times a day; RPED, retinal pigment epithelial dystrophy; TID, three times a day; TMP/SMX DS, trimethoprim/sulfamethoxazole double strength.

[a]For all AECIs, continue FGFR inhibitor without dose reduction unless otherwise specified. Management may differ based on regulatory approval. For more information on the use of individual FGFR inhibitors, please refer to the corresponding US Prescribing Information or European Summary of Product Characteristics.

Management of hyperphosphatemia included the use of phosphate-lowering agents, such as phosphate binders and phosphaturic agents, and futibatinib dose modifications according to study protocols (6–8, 11). Patients were also educated on dietary modifications to minimize intake of foods with high phosphorus content. In the 20-mg every day population, 248 (78.0%) patients received at least one concomitant supportive medication for the management of hyperphosphatemia (**Table 4**). Supportive medications (used either alone or in combination) included sevelamer ($n = 225$, 70.7%), acetazolamide ($n = 84$, 26.4%), and lanthanum carbonate ($n = 39$, 12.3%). In addition, management of hyperphosphatemia included futibatinib dose interruptions in 21.1% of patients and dose reductions in 12.9% of patients in the 20-mg every day population (**Table 4**). No patients discontinued treatment because of hyperphosphatemia.

Soft-tissue mineralization was rare, nonserious, and grade ≤2 in severity in all instances; events in the 20-mg every day population included lymph node calcification (0.2%), tendon calcification (0.2%), and arteriosclerosis of the coronary artery (0.2%); all were radiographically detected and asymptomatic.

Nail disorders

A total of 127 patients (27.1%) in the overall population, including 94 patients (29.6%) in the 20-mg every day population had nail disorders (**Table 2**), most of which were treatment related in both populations (96.9% and 96.8% of patients, respectively). Common diagnoses of nail disorders (preferred terms) in the overall population included onycholysis (8.1%), nail disorder (7.9%), paronychia (5.8%), and nail discoloration (5.5%). Five (1.1%) patients in the overall population had a grade 3 nail disorder [reported as nail disorder, onychalgia, onychomadesis (all $n = 1$), and paronychia ($n = 2$); all treatment related]. In the overall population, median times to onset for any-grade and grade ≥3 nail disorders were 78 and 127 days, respectively (**Fig. 1A** and **B**; **Table 3**). In the 20-mg every day population, median times to onset were 85 and 156 days, respectively. Of the 5 patients with a grade 3 nail disorder, events resolved to grade ≤2 in three cases, and to grade 1 in two cases. Median time to resolution to grade ≤2 and grade 1 was 28 days and not reached, respectively.

Management of nail disorders involved dose modifications, patient education on preventive nail care strategies, and the use of topical

steroids, antibacterials, and emollients. In the 20-mg every day population, 74 (23.3%) patients received ≥1 supportive medication for nail disorders (**Table 4**), including analgesics (n = 52, 16.4%), systemic antibacterials (n = 25, 7.9%), topical corticosteroids (n = 17, 5.3%), topical antifungals (n = 17, 5.3%), and emollients (n = 14, 4.4%). Dose interruptions and reductions for the management of nail disorders were reported in 4.1% and 3.1% of patients, respectively, in the 20-mg every day population (**Table 4**). One patient discontinued treatment due to grade 2 onycholysis.

Hepatic AEs

Hepatic AEs were reported in 126 (26.9%) patients in the overall population, and 94 (29.6%) patients in 20-mg every day population (**Table 2**); of these, 93 (19.8%) and 74 (23.3%) patients had treatment-related events, respectively. The most common hepatic AEs in both the overall population and 20-mg every day population were AST increased (23.0% and 26.1%) and ALT increased (20.5% and 22.6%). Other increased liver enzymes included γ-glutamyltransferase and bilirubin in 2.3% and 0.6% patients in the overall population, and 2.5% and 0.9% of patients in the 20-mg every day population, respectively. Grade ≥3 hepatic AEs were reported in 50 (10.7%) patients overall and in 38 (11.9%) patients in the 20-mg every day population. Median time to onset for any-grade hepatic AEs was 16 days in both populations; for grade ≥3 hepatic AEs, median time to onset was 22 and 25 days in the overall and 20-mg every day populations, respectively (**Fig. 1A** and **B**; **Table 3**). Grade ≥3 hepatic AEs resolved to grade <1 in 39/50 (78.0%) patients in the overall population (**Fig. 1C**; 81.6% in the 20-mg every day population), with a median time to resolution of 14 days in both patient populations (**Table 3**).

In the 20-mg every day population, dose interruptions and reductions due to any-grade hepatic AEs were reported for 9.1% and 6.6% of patients, respectively (**Table 4**). No patients discontinued study treatment due to hepatic AEs.

Two patients (both with CCA who started futibatinib 20 mg every day in the global phase I study) had grade 5 hepatic failure due to disease progression and unrelated to futibatinib.

Stomatitis

Overall, 89 (19.0%) patients in the overall population and 58 patients (18.2%) in the 20-mg every day population experienced an event of stomatitis, including 15 (3.2%) and 11 (3.5%) patients, respectively, with grade ≥3 events (**Table 2**). No grade 4 or 5 events were reported. Stomatitis was considered treatment related in most patients in both populations [73 (15.6%) overall and 49 (15.4%) in the 20-mg every day population]. Median time to onset of any-grade stomatitis and grade ≥3 stomatitis was 45 and 103 days, respectively. Grade 3 stomatitis resolved to grade 1 in 14/15 (93.3%) patients, with a median time to resolution of 13 days, and resolved completely (to grade <1) in 9 patients in a median of 27 days (**Table 3**).

Management of stomatitis included the use of prophylactic mouthwash and other measures, such as oral hygiene, avoidance of triggers, and use of corticosteroids. In the 20-mg every day population, stomatitis led to dose interruptions and dose reductions in 2.8% of patients each (**Table 4**). Two patients, each of whom received a starting dose of 20-mg every day futibatinib, discontinued futibatinib due to grade 2 and grade 3 stomatitis, respectively.

PPES

PPES was reported for 62 patients (13.2%) in the overall population, including 48 (15.1%) patients receiving futibatinib 20 mg every day (**Table 2**). Events were assessed as being related to treatment in all but 2 patients. Grade 3 events were reported in 12 patients (2.6%) overall and 11 (3.5%) patients in the 20-mg every day population. No patients experienced a grade 4 or 5 event. Overall, median time to onset for any-grade and grade 3 PPES was 93.5 and 156 days, respectively (**Fig. 1A** and **B**; **Table 3**), and 85 and 178 days in the 20-mg every day population. In all 12 patients with grade 3 events, PPES resolved to grade ≤2 or grade ≤1 after a median of 8 and 13 days, respectively. Results were similar for the 20-mg every day population (8 and 12 days, respectively). Complete resolution of grade 3 PPES was observed in 7 patients, with a median time to resolution of 141 days (**Fig. 1C**; **Table 3**).

Management of PPES included preventive management, use of topical and oral steroids, and dosing modifications. In the 20-mg every day population, 44 (13.8%) patients received supportive medication for PPES (**Table 4**), including analgesics (n = 34; 10.7%), emollients and protectives (n = 22; 6.9%), and topical corticosteroids (n = 22; 6.9%). Dose interruptions and reductions for any-grade PPES were reported in 4.7% and 5.7% of patients, respectively (**Table 4**), with dose interruptions and reductions for grade ≥3 PPES each reported in 2.2% of patients. No patients permanently discontinued futibatinib treatment due to PPES.

Rash

Rash, including erythematous, macular, maculopapular, papular, and pustular forms, was reported in 40 (8.5%) patients in the overall population and was considered treatment related in 20 (4.3%) patients. The incidence was similar in the 20-mg every day population (**Table 2**). The AECIs of rash were mostly grade 1 (7.5%), with 5 (1.1%) patients experiencing grade 2 rash. No grade ≥3 events were reported. Median time to onset for any-grade rash was 49 days in the overall population and 43 days in the 20-mg every day population (**Table 3**). Of the 5 patients with grade 2 rash, 4 had resolution to grade ≤1, with a median time to resolution of 15 days (grade <1 in 31 days). In the 20-mg every day population, 13 (4.1%) patients received supportive medication (**Table 4**), predominantly topical corticosteroids (n = 10, 3.1%). No patients had dose modifications or discontinued treatment due to rash.

Retinal disorders

Retinal disorders were reported in 38 patients in the overall population, including 27 patients in the 20-mg every day population (**Table 2**). Overall, retinal disorders were grade 1 in 31 patients (6.6%) and grade 2 in 7 (1.5%) patients and were considered related to treatment in almost all patients (n = 36, 7.7%). Similar findings were observed for the 20-mg every day population. Among patients with retinal disorders, median time to onset was 32.5 days (**Fig. 1A**) and 40 days in the overall and 20-mg every day populations, respectively (**Table 3**). All cases of grade 2 retinal disorders resolved to grade ≤1, over a median of 21 days (overall population) and 23 days (20-mg every day population). Other treatment-related eye disorders (non-AECIs) of any grade that occurred in the overall population included preferred terms of dry eye [n = 40 (8.5%)], blurred vision [n = 21 (4.5%)], cataract [n = 7 (1.5%)], growth of eyelashes [n = 7 (1.5%)], increased lacrimation [n = 5 (1.1%)], trichiasis [n = 5 (1.1%)], and trichomegaly [n = 5 (1.1%)].

Per protocol, comprehensive ophthalmologic examination was required at baseline and any time in case of visual symptoms. Examination encompassed external ocular examination, routine slit-lamp biomicroscopy, and retinal examination. Retinal disorders were managed through dose modifications. In the 20-mg every day population,

dose interruptions occurred in 4 (1.3%) patients and dose reductions in 5 (1.6%) patients (**Table 4**). With one exception, no patients had recurrent retinal issues after restarting futibatinib. One patient discontinued futibatinib 20 mg every day because of a worsening grade 2 retinal detachment.

Cataract

Overall, 15 patients had a cataract detected, including 12 patients (3.8%) in the 20-mg every day population (**Table 2**); of these, 5 patients had a grade 3 cataract, and 1 patient had a grade 4 cataract (all treatment related). Among the 12 patients with a cataract in the 20-mg every day population, 2 had cataracts at baseline, and 3 patients had abnormal ophthalmologic results that were considered nonsignificant at baseline (nuclear sclerosis in left eye and nuclear sclerosis and posterior vitreous detachment in right eye, few punctate erosions in both eyes, and nuclear cataract in both eyes). Median time to onset of any-grade and grade ≥3 cataract was 125 and 545 days, respectively (**Table 3**). Two patients required surgery (both restarted futibatinib the next day), and 1 patient enrolled in the global phase I study discontinued futibatinib due to grade 3 cataract.

Discussion

A comprehensive understanding of the safety profile of newly approved drugs such as futibatinib is important to facilitate timely detection and effective management of AEs. In this pooled safety analysis, futibatinib demonstrated a consistent and manageable safety profile in more than 450 patients with a variety of solid tumors. To our knowledge, this is one of the largest safety datasets analyzed for a targeted therapy used in the treatment of CCA. Most AEs were mild or moderate in severity, treatment-related discontinuations were rare, and no treatment-related deaths occurred. The most common AEs with futibatinib were monitorable, and grade 3 and 4 AEs generally resolved with dosing modifications and/or supportive medications.

Among the AECIs, hyperphosphatemia was the most common, consistent with reports for other FGFR inhibitors (14, 18, 20, 24, 26, 27). Pan-FGFR inhibition disrupts signaling of FGF23, a bone-derived endocrine regulator of phosphate metabolism that inhibits phosphate reabsorption by the renal tubules, leading to increased phosphate serum levels (28–30); furthermore, if inadequately managed, hyperphosphatemia can theoretically induce calcium-phosphate precipitation, with calcifications potentially presenting in skin, soft tissue, and periarticular regions (30). In most cases reported in this analysis, hyperphosphatemia was an asymptomatic laboratory value of no/minimal clinical consequence, with very low rates of soft-tissue mineralization and nephrolithiasis reported. The rates of hyperphosphatemia (any grade/grade 3) in the FOENIX-CCA2 trial of futibatinib for patients with iCCA were 85%/30% (11). In a similar trial of the FGFR1–3 inhibitor, pemigatinib, corresponding rates were 60%/0% and, with infigratinib, the rates were 72%/16% (14, 31). Such differences may result, in part, from the different dosing schedules of the inhibitors and/or differences in their binding mechanisms. However, a more significant cause is likely the varied grading of hyperphosphatemia across the trials. In this analysis, grading of hyperphosphatemia was defined by a laboratory value alone, whereas it was dependent on clinical impact and severity in other studies. Indeed, no patients treated with futibatinib had grade 3 or 4 hyperphosphatemia if derived based on new definitions in NCI CTCAE v5.0, where grade 3 is defined as severe or medically significant with hospitalization or prolongation of existing hospitalization indicated, and grade 4 is defined as life-threatening (32).

In the eye, FGFR signaling is vital to the development, survival, stress response, and repair of retinal pigment epithelium cells, ganglion cell maturation and survival, and the regulation of Müller cells in the retina (33, 34). Furthermore, FGFR signaling has been implicated in lens induction, lens cell proliferation and survival, lens fiber differentiation, and lens regeneration (35). Consequently, treatment with FGFR inhibitors can lead to ocular toxicities, including retinopathies, dry eyes, and cataracts (36–38). FGFR inhibitor–induced retinopathies are characterized by subretinal fluid foci similar to the ones observed for other MAPK pathway inhibitors. In one case series, these retinopathies did not cause irreversible loss of vision, were self-limiting, and did not require medical intervention. Moreover, across 26 eyes with follow-up, the subretinal fluid resolved without FGFR inhibitor drug interruption in all but 1 patient (39). In the current analysis, ocular toxicities, including dry eye, retinal disorders, and cataract, were reported in less than 10% of the overall population. Most events were grade 1 or 2 and managed effectively with dose modification. Specifically, there were no grade ≥3 retinal disorders, and grade 2 retinal disorders recovered to grade ≤1 in just over 3 weeks on average, with the timing interval of ophthalmologic examinations possibly contributing to the slightly longer time to resolution versus other AECIs. Owing to the risk of ocular toxicity, patients receiving futibatinib should undergo a comprehensive ophthalmologic examination prior to initiation of futibatinib treatment and as scheduled per local regulations and must be referred for ophthalmologic evaluation upon the onset of visual symptoms, with close follow-up until resolution or discontinuation of treatment.

Other AECIs, including nail disorders, hepatic AEs, stomatitis, PPES, and rash were also managed effectively with dose modifications and/or supportive care interventions, with very few patients discontinuing treatment due to AECIs. The effective management of AECIs was reflected in the short time to clinically meaningful resolution to grade ≤1 or ≤2 within a median of 1 to 2 weeks.

Compared with other pan-FGFR inhibitors, treatment with futibatinib resulted in numerically lower rates of discontinuation due to AEs and of certain important class-related AEs that may affect patients' quality of life, such as stomatitis, PPES, and fatigue (14, 18, 20, 22, 23, 27). Although conclusions cannot be drawn from cross-trial comparisons, this finding is notable since the median duration of treatment was longer with futibatinib in the FOENIX-CCA2 trial than it was with other pan-FGFR inhibitors in comparable pivotal CCA trials (futibatinib, 9.1 months; pemigatinib, 7.2 months; infigratinib, 5.5 months; refs. 11, 14, 16). Patients also attest to a preserved quality of life throughout treatment with futibatinib, as conveyed by the patient-reported outcome (PRO) analysis in the pivotal phase II FOENIX-CCA2 study, the first analysis of its kind in a trial of a selective FGFR inhibitor (11).

As next-generation FGFR inhibitors are being designed to improve efficacy, a focus on safety and tolerability, as well as PROs, will be critical for maximizing the duration of treatment. Drug design features that allow sparing of FGFR1 and FGFR4 may lead to lower rates of hyperphosphatemia and diarrhea, respectively, compared with pan-FGFR inhibitors. FGFR2-specific and FGFR2/3-specific inhibitors currently in development may provide insights into which class-related toxicities can be attributed to inhibition of these specific receptors. This study may therefore serve as a benchmark for reporting the safety and tolerability of FGFR inhibitors, enabling newer drugs in this class to be compared with currently approved therapies.

Overall, the data from this pooled analysis show that futibatinib has a consistent, manageable, and monitorable safety profile, with good tolerability in patients with a variety of tumor types. Practical

recommendations have been provided herein (**Table 5**) for the management of side effects observed with FGFR inhibitors, based on the clinical expertise of investigators. Education of the clinical care team and patients regarding effective management of AEs with FGFR inhibitors will benefit overall clinical outcomes for patients treated with FGFR inhibitors. Longer follow-up is needed to fully establish the long-term safety profile of futibatinib. In this respect, the accumulation of real-world data will be particularly informative for the use of FGFR inhibitors, including futibatinib, in routine clinical practice.

Authors' Disclosures

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Note

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