# Practical Management of Adverse Events Associated With FGFR Inhibitors for Cholangiocarcinoma for the Advanced Practice Provider

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Authors' disclosures of conflicts of interest are found at the end of this article.

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https://doi.org/10.6004/jadpro.2024.15.8.2



## Abstract

Cholangiocarcinoma is a cancer of the bile duct frequently diagnosed at a late stage with a poor prognosis. Selective fibroblast growth factor receptor (FGFR) inhibitors have demonstrated efficacy in the treatment of cholangiocarcinoma with *FGFR2* fusions or rearrangements, but are associated with hyperphosphatemia, fatigue, and ocular, dermatologic, and gastrointestinal adverse events (AEs). Treatment adherence and patient outcomes can be improved by anticipating and effectively managing the AEs associated with FGFR inhibitors and providing appropriate intervention and patient education. The multidisciplinary care team for patients with cholangiocarcinoma can involve optometrists and advanced practice providers, including nurse practitioners, physician assistants, pharmacists. This review provides practical insights for advanced practice providers on the management of these common AEs associated with selective FGFR inhibitors in the real-world setting, focusing on pemigatinib and futibatinib. Impacts of renal or hepatic impairment, drug–drug interactions, and drug–food interactions are discussed. Also presented are practical recommendations for prophylaxis and supportive care measures, and resources for health-care professionals and patients.

Cholangiocarcinoma (CCA) is the second most common hepatic cancer, after hepatocellular carcinoma (Banales et al., 2020). Cholangiocarcinomas are classified into intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA) subtypes, based on their site of origin within the biliary tract (Banales et al., 2020). They have a poor prognosis and are frequently diagnosed at a late stage (Banales et al., 2020). Based on Surveillance, Epidemiology, and End Results (SEER)

data from CCA diagnoses between 2001 and 2017, the estimated 5-year mortality rate is 80.1% (Javle et al., 2022). Surgical resection is the sole potentially curative option for CCA (Blechacz, 2017), but a study of patients with iCCA in the US National Cancer Database found only 21.9% underwent surgical resection (Wu et al., 2019). Tumor recurrence rates following surgical resection of iCCA are as high as 71% (Spolverato et al., 2016).

Gemcitabine plus cisplatin (GemCis) has been the first-line standard of care for advanced unresectable CCA, based on results from the ABC-02 trial showing median overall survival and progression-free survival of 11.7 and 8.0 months, respectively (Valle et al., 2010). Results from the phase III TOPAZ-1 trial of durvalumab combined with GemCis in patients with advanced biliary tract cancer showed significantly improved overall and progression-free survival compared with placebo plus GemCis (Oh et al., 2022).

Second-line or later treatments may target genetic alterations in CCA, for example, alterations in the fibroblast growth factor receptor (*FGFR*) gene (Babina & Turner, 2017; Krook et al., 2021). Among patients with CCA, fusions or rearrangements in *FGFR2* occur predominantly in those with iCCA (Lowery et al., 2018); alterations in *FGFR1*, *FGFR3,* and *FGFR4* are also observed in CCA, with less frequency than *FGFR2* alterations (Jain et al., 2018). The development of selective FGFR inhibitors for the treatment of locally advanced or metastatic cancers, such as pemigatinib (Pemazyre) for CCA, futibatinib (Lytgobi) for iCCA, and erdafitinib (Balversa) for urothelial carcinoma, has overcome some of the challenges presented by off-target toxicities associated with less selective FGFR inhibitors including dovitinib, lenvatinib (Lenvima), and ponatinib (Iclusig; Chae et al., 2017).

Despite their demonstrated efficacy, selective FGFR inhibitors are associated with on-target toxicities, such as hyperphosphatemia, fatigue, and ocular, dermatologic, and gastrointestinal adverse events (AEs) requiring effective management for optimal treatment (Kommalapati et al., 2021). Toxicities commonly associated with selective FGFR inhibitors are related to their mechanisms of action and vary depending on the relative selectivity of each inhibitor towards the FGFR receptors. FGFR1 binds FGF23, activating a negative feedback loop that limits phosphate reabsorption by the kidneys and intestines; thus, inhibition of FGFR1 may result in hyperphosphatemia (Kommalapati et al., 2021; Takashi et al., 2021). Hyperphosphatemia is characteristic of FGFR inhibitors and may be difficult to manage for some patients. A multidisciplinary approach including advanced practice providers can improve patient outcomes. Inhibition of FGFR4 may result in diarrhea, because FGFR4 binding to FGF19 inhibits bile acid synthesis. When this binding is inhibited, bile acid synthesis and secretion into the intestine continues, which leads to diarrhea (Farrugia & Arasaradnam, 2021). The pathophysiology of fatigue, ocular, and dermatologic AEs with FGFR inhibitors are less understood.

The management of AEs associated with FGFR inhibitors in the clinical trial setting has been reviewed recently (Kommalapati et al., 2021; Lacouture et al., 2021; Mahipal et al., 2020). However, a review of practical insights on AE management in the real-world setting for advanced practice providers is still needed. We aim to provide a ready reference concerning clinical guidance on the management of AEs associated with selective FGFR inhibitors, drawing from the authors' clinical experience. This review focuses on selective FGFR inhibitors approved for the treatment of CCA with *FGFR2* fusions or other rearrangements (pemigatinib; Hoy, 2020) or iCCA with *FGFR2* fusions or other rearrangements (futibatinib; Taiho Pharmaceutical Co. & Ltd., 2022).

## CLINICAL TRIAL DATA

Pemigatinib was the first selective FGFR1-3 inhibitor to be approved by the US Food & Drug Administration (FDA) for use in adults with previously treated, unresectable, locally advanced or metastatic CCA and an *FGFR2* fusion or other rearrangement (Hoy, 2020), based on results from the phase II FIGHT-202 study (NCT02924376). The most common (≥ 40% of all patients [*N* = 146]) any-grade treatment-emergent AEs (TEAEs) were hyperphosphatemia (60%), alopecia (49%), diarrhea (47%), fatigue (42%), dysgeusia (40%), and nausea (40%; Figure 1; Abou-Alfa et al., 2020).

Infigratinib (Truseltiq) was the second FGFR1-3 inhibitor to be approved by the FDA for use in

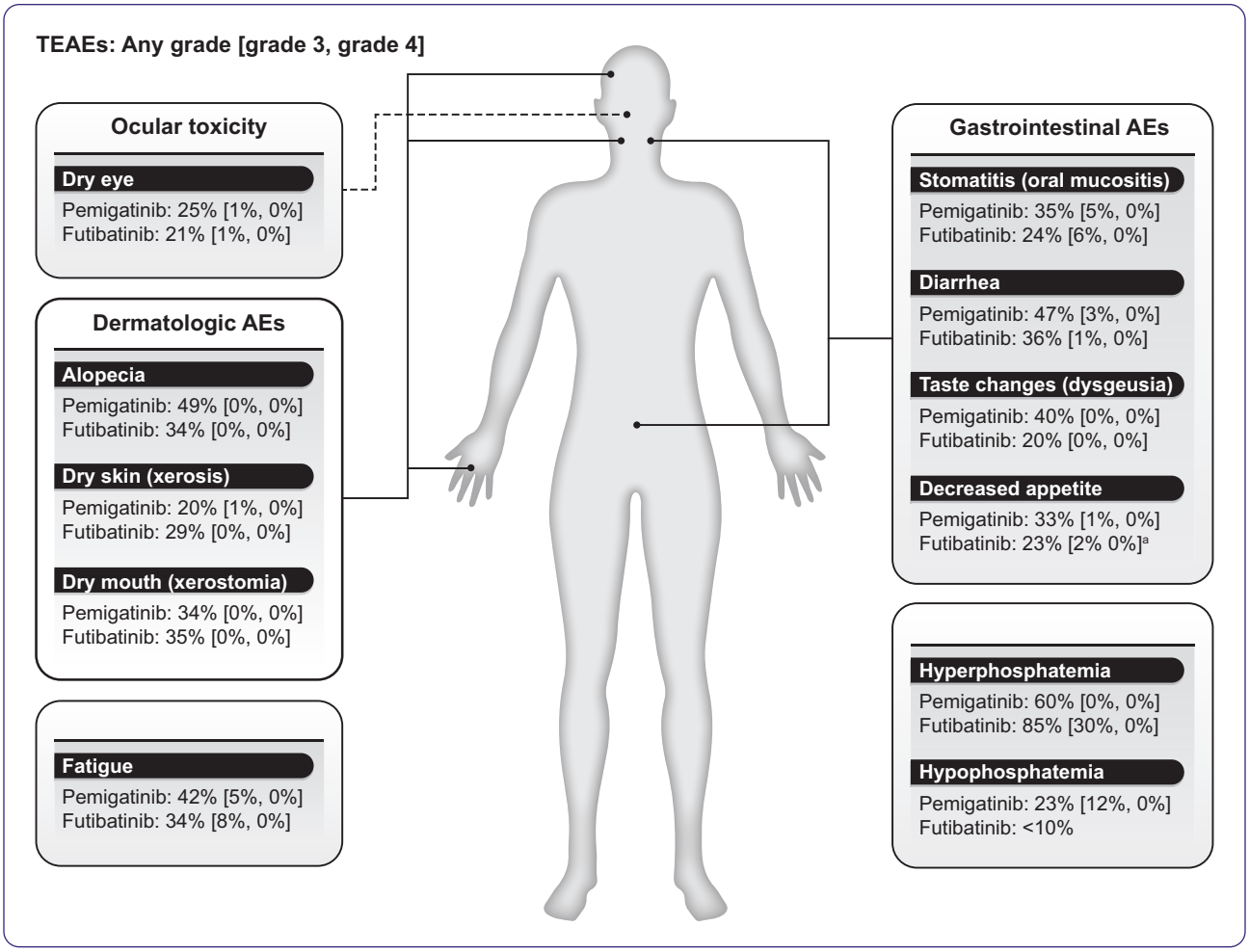


**Figure 1.** Incidence rates for select treatment-emergent AEs experienced by patients receiving the selective FGFR inhibitors in trials of pemigatinib (Abou-Alfa et al., 2020) and futibatinib (Goyal et al., 2023). Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. AE = adverse event; CCA = cholangiocarcinoma; FGFR = fibroblast growth factor receptor; TEAE = treatment-emergent adverse event.
[a]There was one (1%) case of grade 5 decreased appetite with futibatinib (not considered treatment-related).

adults with previously treated, unresectable, locally advanced or metastatic CCA with an *FGFR2* fusion or other rearrangement (Kang, 2021). However, distribution of infigratinib was discontinued as of March 2023.

Futibatinib is an irreversible FGFR1-4 inhibitor approved by the FDA for use in adults with previously treated, unresectable, locally advanced or metastatic iCCA harboring *FGFR2* gene rearrangements, including fusions, based on results from the phase II FOENIX-CCA2 trial (NCT02052778; Goyal et al., 2023; Taiho Pharmaceutical Co. & Ltd., 2022). In FOENIX-CCA2, the most common TEAE of any grade among all patients ($N$ = 103) was hyperphosphatemia (85%; Figure 1; Goyal et al., 2023).

In our experience, AEs associated with these selective FGFR inhibitors can occur early in treatment and may be modifiable through early identification and management. Anticipation and effective treatment of these AEs, including patient education and awareness, are critical for treatment adherence and improved patient outcomes.

## MULTIDISCIPLINARY TEAMS

Management of treatment requires multiple levels of oversight. Ideally, in addition to the medical oncologist, the multidisciplinary care team

should include advanced practice providers, including nurse practitioners, physician assistants, and pharmacists, in addition to ophthalmologists and dieticians. The pharmacy team is involved in treatment procurement, addressing financial toxicity, and ongoing management of AEs, adherence, drug–drug interactions, and refills. In parallel, nurse practitioners and physician assistants manage treatment during follow-up visits to the clinic and often over the phone. Optometrists can serve to diagnose and manage ocular toxicities that may arise on therapy with FGFR inhibitors. Patients should also be in communication with their nurse coordinator and/or nurse navigator throughout their treatment. Additionally, dieticians are involved in patient care, particularly for the management of hyperphosphatemia with a low-phosphate diet. Social workers may also be part of the patient multidisciplinary management team.

Multidisciplinary teams are likely set up differently at individual sites, and responsibilities may overlap. Care should be taken to ensure responsibilities across the team are well understood and that there are no gaps. Team members should also ensure patients communicate openly and often with their primary care provider for additional support.

## PRETREATMENT ASSESSMENTS

Although pemigatinib and futibatinib are approved as second-line treatments, patients should undergo genomic testing as early as possible after diagnosis. This will allow efficient transition to the appropriate targeted therapy when needed. Patients with CCA and *FGFR2* fusions or rearrangements may benefit from treatment with a selective FGFR inhibitor (Abou-Alfa et al., 2020). Before initiating treatment with an FGFR inhibitor, patients should undergo eye examinations and laboratory testing. Comprehensive ophthalmological examination including optical coherence tomography should be performed before treatment and periodically thereafter, as per the label, to monitor for retinal pigment epithelial detachment (RPED) and other ocular toxicities. Laboratory blood testing should be conducted to measure patients' phosphate levels, and obtain baseline measurements of calcium, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and erythrocytes. Patient performance status and self-reported quality of life may be assessed before treatment by using tools such as the Eastern Cooperative Oncology Group (ECOG) performance status scale and patient-reported outcomes questionnaires to monitor changes to patients' level of functioning and health-related quality of life throughout treatment. The ECOG performance status scale is a six-point scale ranging from 0 (fully active, able to carry on all pre-disease performance without restriction) to 5 (dead; Oken et al., 1982) and is widely used in oncology clinical trials.

## COMORBIDITIES

Common comorbidities in patients with CCA include hypertension, liver disease, coronary heart disease, diabetes mellitus, chronic obstructive pulmonary disease, cerebrovascular disease, and ulcer (Chamberlain et al., 2021; Fernández-Ruiz et al., 2009; Qu et al., 2020). Predisposing conditions and risk factors for the development of CCA include bile duct cysts, Caroli disease, cholelithiasis, choledocholithiasis, cirrhosis, hepatitis B and C, hepatolithiasis, liver flukes (*Clonorchis sinensis, Opisthorchis viverrine*), nonalcoholic fatty liver disease/nonalcoholic steatohepatitis, and primary sclerosing cholangitis (Khan et al., 2019). When treating patients with FGFR inhibitors, caution should be used in patients with pre-existing hyperphosphatemia (e.g., end-stage renal disease), and in those with pre-existing eye conditions or taking concomitant drugs causing dry eyes (Incyte Corporation, 2022; Taiho Pharmaceutical Co. & Ltd., 2022).

## DOSING

The approved dosage of pemigatinib for the treatment of CCA is 13.5 mg orally once daily for 14 days followed by 7 days off therapy, in 21-day cycles (Figure 1; Incyte Corporation, 2022). In contrast, the approved dosage of futibatinib is 20 mg (five 4-mg tablets) orally once daily on a continuous basis; intermittent dosing regimens are not approved (Figure 1; Taiho Pharmaceutical Co. & Ltd., 2022). Both medicines are taken until disease progression or unacceptable toxicity occurs. While pemigatinib and futibatinib both have approved dosages at treatment initiation, erdafitinib (indicated for urothelial carcinoma) has an approved starting

dose, which is then increased if serum phosphate concentrations remain < 5.5 mg/dL (Janssen Pharmaceutical Companies, 2019). The dose of each of these selective FGFR inhibitors can be decreased based on tolerability.

## FACTORS AFFECTING TOLERABILITY OF SELECTIVE FGFR INHIBITORS

### Clearance and Exposure

The geometric mean apparent clearance of pemigatinib is 10.6 L/h and geometric mean elimination half-life is 15.4 hours (Incyte Corporation, 2022). For futibatinib, the geometric mean apparent clearance is 20 L/h and mean elimination half-life is 2.9 hours (Taiho Pharmaceutical Co. & Ltd., 2022). Factors, such as renal or hepatic impairment, drug–drug interactions, and drug–food interactions, result in interpatient pharmacokinetic (PK) variability, which may affect the tolerability and efficacy of selective FGFR inhibitors. As outlined in the next sections, it is important to understand the effects of these factors on PK variability of pemigatinib and futibatinib to optimize clinical outcomes.

### Hepatic and Renal Impairment

The PK of pemigatinib was evaluated in patients with impaired hepatic or renal function. No clinically significant differences in pemigatinib exposure were observed between healthy participants and patients with moderate hepatic impairment (Child-Pugh Class B) or end-stage renal disease (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 $m^2$ and on hemodialysis; Ji et al., 2021b). Pemigatinib dose reduction is not needed for patients on hemodialysis. However, a pemigatinib dose of 9 mg is recommended for patients with severe hepatic (Child-Pugh Class C) or renal impairment (eGFR < 30 mL/min/1.73 $m^2$ and not on hemodialysis; Figure 2A; Ji et al., 2021b). For futibatinib, there were no clinically meaningful differences in the systemic exposure of futibatinib in patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and AST > ULN, or total bilirubin > 1 to 1.5 × ULN and any AST) or mild to moderate renal impairment (creatinine clearance 30–89 mL/min by Cockcroft-Gault; Taiho Pharmaceutical Co. & Ltd., 2022). The PK of futibatinib has not been assessed in patients with moderate or severe hepatic impairment, severe renal impairment, or renal dialysis in end-stage renal disease (Taiho Pharmaceutical Co. & Ltd., 2022).

### Drug–Drug Interactions

Pemigatinib and futibatinib are predominantly metabolized by cytochrome P450 (CYP) 3A (CYP3A; Ji et al., 2021a; Yamamiya et al., 2021). Common medications that should be avoided with pemigatinib include strong and moderate CYP3A inducers such as rifampin, which can lead to clinically significant decreases in exposure, and thus reduce the antitumor efficacy of the pemigatinib. Coadministration of pemigatinib with a strong or moderate CYP3A inhibitor such as itraconazole should also be avoided if possible as it can lead to clinically significant increases in pemigatinib exposure (Incyte Corporation, 2022). If coadministration is necessary, however, pemigatinib can be given at a reduced dose (Ji et al., 2021a). For futibatinib, significant drug–drug interactions were also observed with itraconazole and rifampin (Yamamiya et al., 2021). Coadministration of futibatinib with drugs that are dual P-glycoprotein and strong CYP3A inhibitors, or dual P-glycoprotein and strong CYP3A inducers, should be avoided (Taiho Pharmaceutical Co. & Ltd., 2022). Since futibatinib is an inhibitor of P-glycoprotein and breast cancer resistance protein (BCRP), doses of drugs that are substrates of P-glycoprotein and BCRP should be reduced (Taiho Pharmaceutical Co. & Ltd., 2022).

No clinically significant differences in exposure were observed when pemigatinib was coadministered with a proton pump inhibitor (esomeprazole) or a histamine-2 antagonist (ranitidine; Ji et al., 2021a). Coadministration of the proton pump inhibitor lansoprazole had no clinically meaningful effect on futibatinib exposure (Yamamiya et al., 2021).

### Drug–Food Interactions

Patients should not eat or drink grapefruit products during treatment with pemigatinib or futibatinib, because furanocoumarins in grapefruit can irreversibly inhibit CYP3A4 and lead to an increase in exposure to these drugs (Bailey et al., 2013; Incyte Corporation, 2022; Taiho Pharmaceutical Co. & Ltd., 2022). Similar consequences

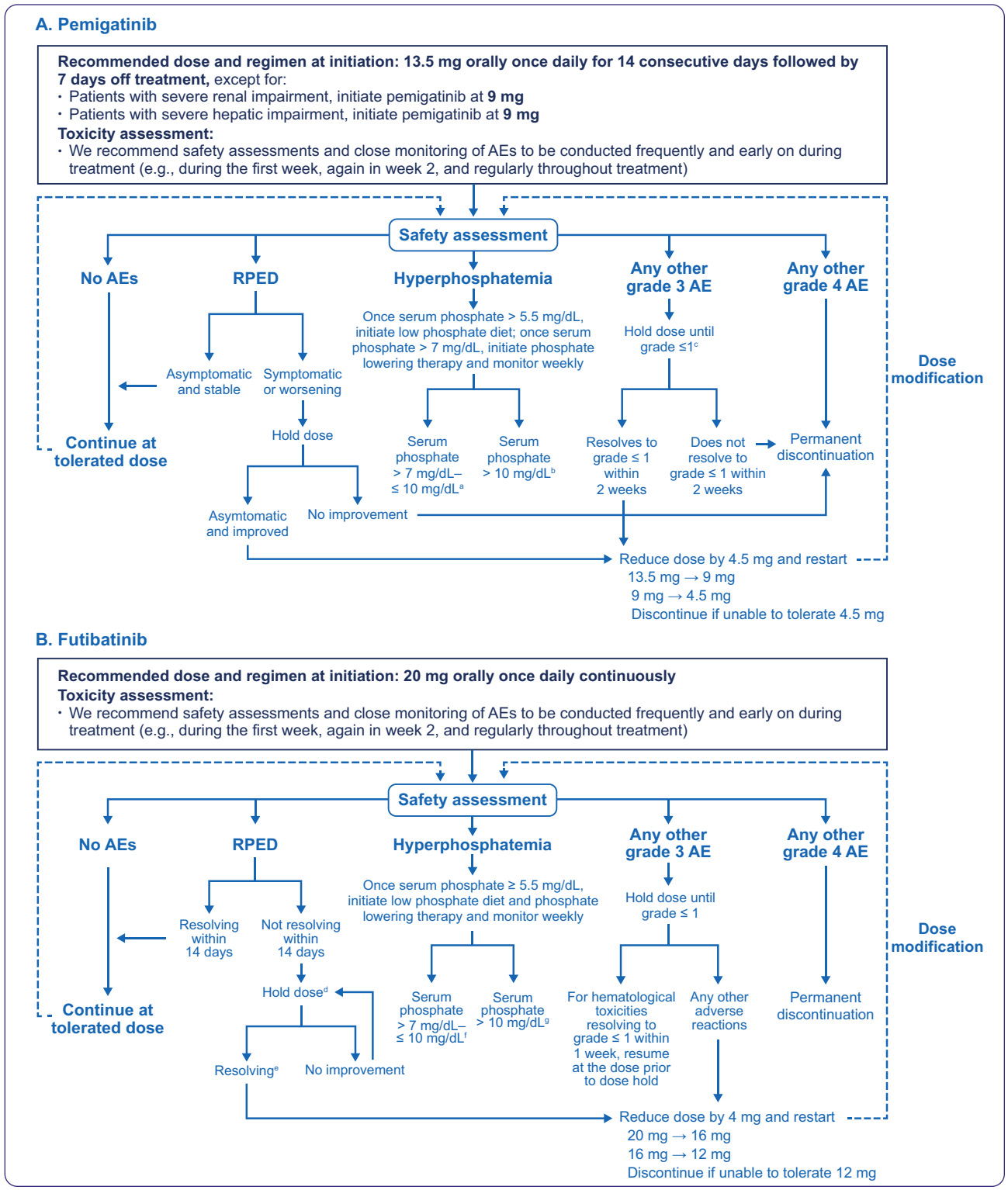


**Figure 2.** Dosing algorithm and toxicity assessment of (A) pemigatinib (Incyte Corporation, 2022) and (B) futibatinib (Taiho Pharmaceutical Co. & Ltd., 2022) based on author's clinical recommendations and the prescribing information. To align with the recommended dose levels, pemigatinib is supplied in three tablet strengths: 13.5 mg, 9 mg, and 4.5 mg; futibatinib is supplied in a single tablet strength of 4 mg and provided in blister cards containing 7-day supplies of 20 mg/day, 16 mg/day, or 12 mg/day.
AE = adverse event; RPED = retinal pigment epithelial detachment.

[a]If serum phosphate concentrations are not < 7 mg/dL within 2 weeks of starting phosphate lowering therapy, then hold dose. When serum phosphate concentrations are < 7 mg/dL in the first occurrence of hyperphosphatemia, resume at same dose. In subsequent occurrences of hyperphosphatemia, resume at a reduced dose when serum phosphate concentrations are < 7 mg/dL. Based on the author's clinical experience, phosphate binder dosing should be held during the week off pemigatinib therapy each cycle (days 15–21) and during pemigatinib dose interruptions for nonhyperphosphatemia AEs.
[b]If serum phosphate concentrations are > 10 mg/dL within 1 week of starting phosphate lowering therapy, then hold dose. When serum phosphate concentrations are < 7 mg/dL, resume at a reduced dose. For recurrence of serum phosphate > 10 mg/dL following two dose reductions, permanently discontinue pemigatinib.
[c]For recurrent grade 3 AEs after two dose reductions, permanently discontinue pemigatinib.
[d]Phosphate binder dosing should be held during futibatinib dose interruptions for nonhyperphosphatemia AEs.
[e]Resume futibatinib at tolerated or lower dose.
[f]Adjust phosphate lowering therapy and reduce dose of futibatinib to next lower dose. If serum phosphate concentrations are ≤ 7 mg/dL within 2 weeks after dose reduction, continue at this reduced dose. If serum phosphate is > 7 mg/dL after 2 weeks, further reduce futibatinib to the next lower dose. If serum phosphate is > 7 mg/dL 2 weeks after the second dose reduction, hold dose until serum phosphate is ≤ 7 mg/dL and resume at the dose before dose hold.
[g]Adjust phosphate lowering therapy and hold dose until serum phosphate is ≤ 7 mg/dL, and then resume at a reduced dose. If serum phosphate is > 7 mg/dL 2 weeks following two dose interruptions and reductions, permanently discontinue futibatinib.

may occur with other citrus fruits such as limes, Seville oranges (in marmalades), and pomelos (Bailey et al., 2013).

Pemigatinib can be taken with or without food, based on findings from the FIGHT-101 study (NCT02393248; Incyte Corporation, 2022; Subbiah et al., 2022). In FIGHT-101, the food effect on pemigatinib PK was evaluated in 12 patients who received pemigatinib 13.5 mg in the fasted and fed state, and administration of a high-calorie and high-fat meal had no clinically meaningful effect on pemigatinib PK (Subbiah et al., 2022). Futibatinib can also be taken with or without food (Taiho Pharmaceutical Co. & Ltd., 2022).

## ADVERSE EVENT MANAGEMENT

The AE profiles of pemigatinib and futibatinib are generally similar, with hyperphosphatemia, fatigue, and ocular, dermatologic, and gastrointestinal AEs being the most common (Kommalapati et al., 2021). Patients should be informed about the potential risk of experiencing these AEs (Kommalapati et al., 2021; Lacouture et al., 2021). Educational handouts can be useful resources for patients. Medication information sheets are available from www.oralchemoedsheets.com (National Community Oncology Dispensing Association Inc (NCODA) et al., 2020) including for pemigatinib (http://www.oralchemoedsheets.com/sheets/Pemigatinib_Patient_Education.pdf). Educational sheets on specific AEs are also available at this site. Additionally, the patient education databases Lexicomp (https://www.wolterskluwer.com/en/solutions/lexicomp) and Clinical Pharmacology (https://www.clinicalkey.com/pharmacology/login) contain useful information on pemigatinib and futibatinib that can be provided to patients.

We recommend safety assessments and close monitoring of AEs to be conducted frequently and early during treatment (Figure 2). Conduct follow-up calls with patients during treatment to identify any issues promptly and provide advice, particularly in the first few treatment cycles (Cope, 2022). Specific prophylactic and supportive care measures for the practical management of these AEs are discussed in the following sections, with advice specific to advanced practice providers and patients in Tables 1 and 2, respectively.

### Hyperphosphatemia and Hypophosphatemia

Hyperphosphatemia is the most common any grade TEAE associated with FGFR inhibitors, reported by 60% to 85% of patients in clinical trials (Abou-Alfa et al., 2020; Goyal et al., 2023). Although hyperphosphatemia is the most common any grade TEAE, all events were grade 1 or 2 in severity in patients treated with pemigatinib (Abou-Alfa et al., 2020). In contrast, 30% of futibatinib-treated patients experienced a TEAE of grade 3 hyperphosphatemia (Goyal et al., 2023).

**Table 1. FGFR Inhibitor Adverse Event Management Strategies for Advanced Practice Providers**

| Type | AE | Strategy |
|---|---|---|
| *Hyperphosphatemia and Hypophosphatemia* | | |
| Prevention and mitigation strategies | | • Determine patient baseline serum phosphate concentration<br>• Discuss the risks of hyperphosphatemia and hypophosphatemia with patients<br>• Discuss food labels and dietary sources of phosphorus with patients<br>• Based on patient baseline serum phosphate concentration and dietary habits, determine whether the patient should be advised to make any dietary changes when initiating treatment with an FGFR inhibitor<br>• Let patients on intermittent treatment regimens know that they may not need to follow phosphate-lowering diets on days when they are not taking the FGFR inhibitor; this could help them avoid hypophosphatemia<br>• Assess patient's serum phosphate concentration regularly and look for trends of increasing or decreasing serum phosphate |
| Supportive strategies | | • Assess patient's serum phosphate concentration weekly<br>• Advise patients to follow low- or high-phosphate diets, as needed (see Table 3)<br>• If serum phosphate is higher than 7 mg/dL in patients receiving pemigatinib or 5.5 mg/dL or higher in patients receiving futibatinib, consider use of phosphate-lowering therapies such as phosphate binders (that decrease phosphate absorption) and phosphaturic agents (that increase phosphate elimination; see Figure 2; Incyte Corporation, 2022, 2023)<br>• If patients experience hypophosphatemia, they should discontinue or reduce phosphate-lowering therapies |
| *Dermatologic AEs* | | |
| Prevention and mitigation strategies | Alopecia | • Prescribe minoxidil 5% foam or liquid (Kommalapati et al., 2021; Lacouture et al., 2021) |
| | Nail changes | • Provide suggestions for topical emollients (moisturizing creams) that may reduce or slow the development of symptoms (Lacouture et al., 2021) |
| | Xerosis (dry skin) | • Provide suggestions for emollients and fragrance-free soaps or detergents (Lacouture et al., 2021) |
| | Xerostomia (dry mouth) | • Advise patients to visit the dentist regularly and use a high-fluoride toothpaste (Lacouture et al., 2021) |
| | Palmar–plantar erythrodysesthesia (Hand–foot syndrome) | • Provide suggestions for emollients containing ≥ 10% urea (Huynh Dagher et al., 2021; Lacouture et al., 2021)<br>• Advise patients to have regular pedicures and to cushion callused areas using soft or padded shoes (Huynh Dagher et al., 2021; Lacouture et al., 2021)<br>• Advise patients to avoid activities that cause force or rubbing on the feet (such as long walks) and hands during the first 6 weeks of treatment and to limit contact with harsh chemicals and sources of heat (Huynh Dagher et al., 2021; Lacouture et al., 2021) |
| Supportive strategies | Alopecia | • Advise patients to use minoxidil 5% foam or liquid and high-potency topical corticosteroids (such as fluocinonide 0.05% solution; Kommalapati et al., 2021; Lacouture et al., 2021) |
| | Nail changes | • Refer patients to a dermatologist to ensure they do not have an underlying fungal infection, particularly for grade ≥ 2 paronychia (Lacouture et al., 2021)<br>• For paronychia, advise patients to soak their nails for 15 minutes daily in water and vinegar (1:1; Lacouture et al., 2021)<br>• For onycholysis and grade 1 paronychia, advise patients to apply topical povidone iodine 2%–10% twice a day (Lacouture et al., 2021)<br>• For grade 2 or 3 paronychia, patients should be prescribed a 2-week course of oral antibiotics (Lacouture et al., 2021) |
| | Xerosis (dry skin) | • Advise patients to moisturize regularly with emollients containing ≥ 10% urea, or colloidal oatmeal, or 3% salicylic acid, and exfoliate scaly patches of dry skin<br>• Severe grade 3 dry skin (which can lead to asteatotic dermatitis) can be treated with low-potency (such as hydrocortisone 2.5% cream/ointment) or medium-potency (such as triamcinolone 0.1% cream) topical steroids (Lacouture et al., 2021) |

**Table 1. FGFR Inhibitor Adverse Event Management Strategies for Advanced Practice Providers (cont.)**

| Type | AE | Strategy |
|---|---|---|
| *Dermatologic AEs (cont.)* | | |
| Supportive strategies (cont.) | Xerostomia (dry mouth) | • Advise patients to use mucosal lubricants, chewing gum, saliva stimulants and substitutes, and topical and systemic medicines that stimulate saliva (sialagogues) such as cevimeline or pilocarpine (Kommalapati et al., 2021; Lacouture et al., 2021) |
| | Palmar–plantar erythrodysesthesia (Hand–foot syndrome) | • Advise patients to moisturize palms and soles regularly with emollients containing ≥ 10% urea (consider increasing to 40% for grade 2 hand–foot syndrome; Lacouture et al., 2021)<br>• Grade ≥ 2 hand–foot syndrome can be treated with high-potency topical steroids such as fluocinonide 0.05% (Lacouture et al., 2021)<br>• Systemic pain management should be initiated as required |
| *Gastrointestinal AEs* | | |
| Prevention and mitigation strategies | Stomatitis (oral mucositis) | • Advise patients to visit the dentist and have any necessary dental work to eliminate existing tooth or gum disease before starting treatment (Lacouture et al., 2021) |
| | Diarrhea | • Prescribe loperamide so patients may take it as needed (Mahipal et al., 2020)<br>• Discuss diet and nutrition with patients to ensure they understand the ways their diet can affect their risk of diarrhea (Mahipal et al., 2020) |
| | Dysgeusia (taste changes) | • Encourage patients to optimize oral hygiene and regular tongue brushing (Togni et al., 2021) |
| | Decreased appetite | • Encourage patients to increase their physical activity to help stimulate their appetite |
| | Constipation | • Advise an increase in dietary fiber (e.g., fruit pastes), fluids, and exercise for healthy patients who are not taking opioid analgesics (these actions may be harmful for patients with progressive or advanced disease; Wickham, 2017) |
| | Nausea and vomiting | • Provide patients with instructions to ensure adequate follow-up, including who to contact to report uncontrolled nausea and vomiting and any side effects or problems with antiemetic medication (Cope, 2022)<br>• In patients prone to nausea and vomiting, a single antiemetic agent (e.g., dexamethasone, a 5-HT3 receptor antagonist such as ondansetron, or a dopamine receptor antagonist such as metoclopramide) may be considered to prevent acute nausea and vomiting (Roila et al., 2016)<br>• Advise patients that although there is less or insufficient evidence to confirm their effectiveness, some people have found ginger, acupuncture, acupressure, and relaxation techniques (yoga, music therapy, guided imagery, progressive muscle relaxation, and systematic desensitization) may help to prevent nausea and vomiting (Cope, 2022) |
| Supportive strategies | Stomatitis (oral mucositis) | • For grade 1 or 2 stomatitis, advise patients to use dexamethasone 0.5 mg/mL elixir as a mouthwash, or an augmented betamethasone dipropionate 0.05% gel applied for 15 minutes (Lacouture et al., 2021)<br>• Lidocaine-based mouthwashes can also be prescribed for the treatment of stomatitis<br>• For grade 2 or 3 stomatitis, prescribe patients with doxepin 10 mg/mL solution as a mouthwash (Lacouture et al., 2021)<br>• You can also recommend nonalcoholic mouthwashes with sucralfate, doxycycline, or steroids to patients; anti-microbial treatment may also be needed (Kommalapati et al., 2021) |
| | Diarrhea | • Assess the patient to see if there could be any other causes of diarrhea (such as infection or diet-related causes), and consider recommending probiotics if appropriate (Kommalapati et al., 2021; Mahipal et al., 2020)<br>• For grade 1 diarrhea, advise patients to take loperamide 4 mg when it starts and another 2 mg with each subsequent loose stool until they have been free from diarrhea for 12 hours (they should not take more than 20 mg loperamide in total per day; Mahipal et al., 2020) |

**Table 1. FGFR Inhibitor Adverse Event Management Strategies for Advanced Practice Providers (cont.)**

| Type | AE | Strategy |
|---|---|---|
| *Gastrointestinal AEs (cont.)* | | |
| Supportive strategies (cont.) | Diarrhea (cont.) | • Another option to consider is diphenoxylate/atropine, administered as two tablets four times daily, not to exceed 20 mg diphenoxylate hydrochloride per day, and then at a reduced dose based on individual requirements (Pfizer, 2017)<br>• For grade 2 diarrhea, measure and treat electrolyte imbalances (Kommalapati et al., 2021; Mahipal et al., 2020)<br>• Provide urgent fluid and electrolyte resuscitation in patients with grade ≥ 3 diarrhea (Kommalapati et al., 2021) |
| | Dysgeusia (taste changes) | • Provide patients with mucosal lubricants or saliva substitutes, and medicines that increase the flow of saliva (sialagogues), such as pilocarpine or cevimeline (Kommalapati et al., 2021)<br>• Suggest that patients take supplements containing zinc, which could reduce the severity and duration of the taste changes (Spencer et al., 2021; Togni et al., 2021)<br>• Treat patients with glutamine, biotin, alpha-lipoic acid, or lactoferrin supplements (Togni et al., 2021) |
| | Decreased appetite | • Refer patients to a dietician to ensure they are consuming enough nutrients and calories (Dev et al., 2017)<br>• Consider treating patients with mirtazapine and megestrol acetate (Hariyanto & Kurniawan, 2021; Zhang et al., 2018) |
| | Constipation | • Assess the patient to see if there could be any other causes of constipation (such as hypercalcemia or diabetes; Wickham, 2017)<br>• Examine the patient to check for and eliminate fecal impaction (Wickham, 2017)<br>• Recommend that patients increase their intake of dietary fiber if they have mild to moderate constipation but are otherwise generally healthy and have a good prognosis (Wickham, 2017)<br>• Treat patients with stimulant laxatives (orally or by suppository) or osmotic agents (e.g., nonabsorbable sugars or polyethylene glycol; Wickham, 2017)<br>• Consider rectal laxatives (suppositories or enemas) when fast and predictable evacuation of a stool is preferred (e.g., in patients with fecal impaction; Wickham, 2017)<br>• As a supplement to laxatives, show patients/caregivers how to carry out abdominal massage to help with self-management and relaxation (explaining that effects may not be immediate but are likely to help in the long term; Wickham, 2017) |
| | Nausea and vomiting | • Prophylactic use with an antiemetic agent before oral dosing of the FGFR inhibitor should be administered if patients have persistent nausea or vomiting |
| *Fatigue or asthenia* | | |
| Prevention and mitigation strategies | | • Encourage patients to use a range of strategies to prevent fatigue before they start treatment, such as participating in regular to moderate physical exercise throughout treatment, and prioritizing sleep and nutrition (particularly if they have decreased appetite; Bower et al., 2014)<br>• Conduct regular blood tests to monitor for abnormalities that may lead to asthenia (such as anemia) |
| Supportive strategies | | • Perform blood tests to check for any abnormalities such as anemia, and treat any problems found (Kommalapati et al., 2021)<br>• Encourage patients to prioritize sleep and nutrition, and participate in moderate physical activity, mental relaxation programs, and/or yoga (Bower et al., 2014) |
| *Ocular toxicity* | | |
| Prevention and mitigation strategies | Retinal pigment epithelial detachment (RPED) and central serous retinopathy | • Refer patients for comprehensive eye examination, including optical coherence tomography (OCT), before starting FGFR inhibitor treatment (Incyte Corporation, 2022; Kommalapati et al., 2021; Taiho Pharmaceutical Co. & Ltd., 2022)<br>• Patients taking pemigatinib or futibatinib should have a comprehensive eye examination and OCT scan every 2 months for the first 6 months, and every 3 months thereafter during treatment (Incyte Corporation, 2022; Taiho Pharmaceutical Co. & Ltd., 2022) |

**Table 1. FGFR Inhibitor Adverse Event Management Strategies for Advanced Practice Providers (cont.)**

| Type | AE | Strategy |
|---|---|---|
| *Ocular toxicity (cont.)* | | |
| Prevention and mitigation strategies (cont.) | RPED and central serous retinopathy (cont.) | • Recommend other tests such as a fundoscopic examination, visual acuity testing and routine slit lamp as necessary (Mahipal et al., 2020) |
| | Dry eye | • Recommend preservative-free artificial tears (lubricants) to prevent and reduce eye dryness (Mahipal et al., 2020) |
| Supportive strategies | RPED and central serous retinopathy | • If visual symptoms begin (such as floaters or blurry vision), immediately refer patients for ophthalmic examination, with follow-up every 3 weeks until the symptoms resolve, or the patient discontinues the FGFR inhibitor (Incyte Corporation, 2022; Taiho Pharmaceutical Co. & Ltd., 2022)<br>• Consider holding, reducing, or discontinuing the dose of the FGFR inhibitor |
| | Dry eye | • Encourage patients to treat dry eye with preservative-free artificial tears (lubricants) as needed (Incyte Corporation, 2022; Taiho Pharmaceutical Co. & Ltd., 2022) |
| | Central serous retinopathy | • Monitor for central serous retinopathy so it can be identified early and, if needed, discontinue the FGFR inhibitor as soon as possible. FGFR inhibitors can be restarted at a reduced dose under the close supervision of an ophthalmologist in the case of grade ≤ 3 ocular toxicities that were resolved after 4 weeks following onset. Permanent discontinuation should be considered in the event of any grade ≥ 4 ocular side effects, or a grade ≥ 2 ocular side effect at a reduced dose (Kommalapati et al., 2021) |
| *Laboratory abnormalities* | | |
| Prevention and mitigation strategies | Hypercalcemia | • Conduct routine blood tests to check for hypercalcemia so that it can be detected early<br>• Ensure that patients and their caregivers are familiar with the symptoms of hypercalcemia, such as fatigue, confusion, dehydration, nausea, constipation, and abdominal pain, so that they can receive appropriate treatment promptly (Carroll & Schade, 2003) |
| | Blood creatinine concentration increased | • Explain to patients that FGFR inhibitors may be associated with an increase in serum creatinine (Incyte Corporation, 2022) |
| | Aspartate aminotransferase (AST) concentration increased | • Conduct routine liver function tests to check for elevated liver enzymes (Newsome et al., 2018) |
| | Anemia | • Conduct routine blood tests to check for anemia<br>• Advise patients to report symptoms of anemia, such as fatigue, lethargy, shortness of breath, reduced appetite, and difficulty concentrating (Madeddu et al., 2018) |
| Supportive strategies | Hypercalcemia | • Conduct a thorough history and physical evaluation to determine the cause of hypercalcemia (e.g., hypercalcemia related to treatment with FGFR inhibitor or other medications, hypercalcemia of malignancy, or primary hyperparathyroidism; Zagzag et al., 2018)<br>• Check levels of serum calcium, intact parathyroid hormone, creatinine, and conduct a 24-hour urine collection for calcium and creatinine (Zagzag et al., 2018)<br>• Stabilize patients who are in hypercalcemic crisis with intravenous fluid resuscitation; once calcium levels are corrected, consider treatment with corticosteroids, bisphosphonates, calcitonin, or denosumab (Zagzag et al., 2018)<br>• Correct hypophosphatemia as this may worsen hypercalcemia<br>• Advise patients to stop all oral calcium intake, including in supplements and food (Zagzag et al., 2018)<br>• Routinely monitor calcium levels to check for hypocalcemia (this is particularly relevant in patients with hypoparathyroidism, renal insufficiency, and vitamin D deficiency (Zagzag et al., 2018) |

**Table 1. FGFR Inhibitor Adverse Event Management Strategies for Advanced Practice Providers (cont.)**

| Type | AE | Strategy |
|---|---|---|
| *Laboratory abnormalities (cont.)* | | |
| Supportive strategies (cont.) | Blood creatinine concentration increased | • Dose interruptions, reductions, or permanent discontinuation of the FGFR inhibitor may be considered based on the level of blood creatinine |
| | AST concentration increased | • If blood tests indicate abnormal liver function, determine whether this is due to treatment or possible concomitant liver disease; this decision will be influenced by the pattern of liver blood tests and the timing of medication use in relation to when the liver blood abnormality was detected (Newsome et al., 2018)<br>• Dose reductions of the FGFR inhibitor may be necessary to reduce AST levels (Incyte Corporation, 2022) |
| | Anemia | • Careful characterization of anemia and associated clinical parameters is required to identify its cause and to establish a management strategy (Madeddu et al., 2018)<br>• Treatment should be tailored to the individual patient (Gilreath & Rodgers, 2020); conventional treatments include the use of erythropoiesis-stimulating agents, red blood cell transfusions, and iron therapy (Madeddu et al., 2021)<br>• Nutritional support may also be recommended, including supplementation with amino acids, folic acid, vitamins B, C, and D, polyphenols, and L-carnitine (Madeddu et al., 2021) |
| *Abdominal pain, back pain, or arthralgia* | | |
| Prevention and mitigation strategies | | • Explain to patients that abdominal pain and back pain can be side effects of FGFR treatment and ask them to report these symptoms if they occur<br>• Advise patients on appropriate over-the-counter pain relievers |
| Supportive strategies | | • Carry out a comprehensive assessment of the pain to understand whether it is related to the underlying cancer, to treatment, or if there is a separate cause of the pain (Yoong & Poon, 2018)<br>• In patients with moderate-to-severe cancer pain opioid therapy should be considered (Aman et al., 2021); opioid-induced constipation should be anticipated (Wickham, 2017)<br>• Opioid rotation may be necessary if analgesia is inadequate, or if rapid tolerance or toxicity is seen; this should be carried out cautiously in consultation with an experienced pain or palliative care specialist (Yoong & Poon, 2018)<br>• Screening tools can be used to assess a patient's risk of substance use disorder, so that pharmacologic and nonpharmacologic options can be tailored to lower the risk of misuse (Scarborough & Smith, 2018)<br>• Nerve blocks may be considered based on the location of the cancer-related pain, and epidural/intrathecal analgesics may be considered in patients who have inadequate pain control or intolerable side effects from conventional medical management (Aman et al., 2021)<br>• Nonpharmacologic management strategies should also be discussed with patients, including hypnosis, acupuncture, music therapy, mindfulness-based stress reduction, and massage therapy (Deng, 2019)<br>• In combination with other treatments, low-intensity ultrasound can also be considered for treating joint pain in the knee, hip, and shoulder (Aiyer et al., 2020) |

**Table 2. FGFR Inhibitor Adverse Event Management Strategies for Patients**

**Side effects during treatment with FGFR inhibitors**

Tests have determined that the cancer cells in your body are making too much or an altered form of a type of protein called FGFR. The medication prescribed for you, _____, is an FGFR inhibitor. Many patients experience side effects with this type of medication. These side effects may include changes to the amount of phosphate in your blood, changes in your hair, skin, and nails, or nausea, diarrhea, or constipation. This list provides information on how you can help reduce symptoms or treat symptoms if they occur.

**Please always let your healthcare providers (HCP) know about any symptoms that you experience.** Your HCP may prescribe or recommend treatments to help with these symptoms. **Always follow your HCP's instructions for the use of these treatments.** For some symptoms, your HCP may change the dose of your FGFR inhibitor medication or stop it altogether.

**Managing side effects of treatment**

*Too much phosphate in the blood (hyperphosphatemia) or too little phosphate in the blood (hypophosphatemia)*

FGFR inhibitors often increase the amount of phosphate in the blood. Too much phosphate can cause muscle cramps, bone or joint pain, numbness or tingling around the mouth, itchy skin, or a rash. Sometimes patients receiving FGFR inhibitors have too little phosphate in their blood. A symptom of too little phosphate is muscle weakness or pain. Your healthcare team will test your blood phosphate regularly.

| | |
|---|---|
| Ways to prevent or postpone symptoms | • Discuss what you eat with a dietician or HCP. Look for ways to decrease how much phosphate you eat, but **do not** start a strict low-phosphate diet unless your HCP tells you to<br>• Look at food labels to see which of the foods that you eat contain phosphate or phosphorus (Mahipal et al., 2020)<br>• If the FGFR inhibitor prescribed for you is not taken every day, you can be less careful about phosphates on the days you are not taking it |
| If symptoms occur | • If your blood phosphate does get too high, your HCP may tell you to follow a low-phosphate diet or prescribe medicine to reduce the phosphate in your blood<br>• If you are not scheduled to take your FGFR inhibitor every day, ask your HCP whether you should follow the diet and take the phosphate-lowering medicine on the days when you are not taking the FGFR inhibitor |

*Skin, nail, and hair-related symptoms*

FGFR inhibitors can cause changes to your skin, nails, and hair. You may experience redness, swelling, peeling or tenderness, mainly on the hands or feet.

| | | |
|---|---|---|
| Ways to prevent or postpone symptoms | Hair loss | • You may be prescribed foams or liquids that can be used once a day to help prevent hair loss (Kommalapati et al., 2021; Lacouture et al., 2021)<br>• Unfortunately, the scalp cooling, scalp compression, and medications which are used to prevent hair loss in patients receiving traditional chemotherapy do not work for patients treated with FGFR inhibitors (Lacouture et al., 2021) |
| | Nail changes | • Avoid having your nails wet for long periods, avoid friction or pressure on the nail beds and nails, limit the use of nail hardeners and nail polish removers, and do not bite your nails or cut them too short (Lacouture et al., 2021)<br>• Use gloves for protection, wear loose socks and shoes, and use thick moisturizing creams (Lacouture et al., 2021) |
| | Dry skin | • Moisturize your skin regularly, and use fragrance-free lotions, soaps and detergents (Lacouture et al., 2021) |
| | Dry mouth | • Visit your dentist regularly, practice good oral hygiene, and use a high-fluoride toothpaste (Lacouture et al., 2021) |
| | Hand–foot syndrome (palmar–plantar erythro-dysesthesia) | • Moisturize your hands and feet regularly with a urea-based cream<br>• Keep your toenails trimmed, and use soft or padded shoes to cushion callused areas (thickened/hardened skin) (Lacouture et al., 2021)<br>• During the first 6 weeks of treatment, avoid activities that cause force or rubbing on the hands and feet, such as long walks (Huynh Dagher et al., 2021; Lacouture et al., 2021)<br>• Limit contact with harsh chemicals and sources of heat, such as saunas or sunshine (Lacouture et al., 2021) |

**Table 2. FGFR Inhibitor Adverse Event Management Strategies for Patients (cont.)**

| | | |
|---|---|---|
| *Skin, nail, and hair-related symptoms (cont.)* | | |
| If symptoms occur | Hair loss | • Consider using hair camouflaging methods or wigs and hats (Lacouture et al., 2021)<br>• Look for programs such as "Look Good Feel Better" which can help with the appearance-related side effects of cancer treatment: https://lookgoodfeelbetter.org/<br>• Use the foams, liquids, or steroid creams prescribed to you as instructed by your HCP (Kommalapati et al., 2021; Lacouture et al., 2021) |
| | Nail changes | • If you get a skin infection around your nails, ask your HCP about using an antiseptic or soaking your nails for 15 minutes daily in water and vinegar (1:1; Lacouture et al., 2021)<br>• If your nail separates from the nail bed, trim the affected nails, and avoid nail hardeners and nail polish removers (Lacouture et al., 2021) |
| | Dry skin | • Moisturize your skin regularly with fragrance-free lotions and emollients<br>• Gently exfoliating scaly patches of skin may help reduce dry skin (Lacouture et al., 2021) |
| | Dry mouth | • Ask your HCP about mucosal lubricants, chewing gum, saliva stimulants and substitutes, and topical and systemic medicines that increase the flow of saliva in the mouth (Lacouture et al., 2021) |
| | Hand–foot syndrome | • Use moisturizers or steroid creams as instructed by your HCP (Lacouture et al., 2021) |
| *Gastrointestinal symptoms* | | |
| You may experience symptoms related to your stomach and intestines, or the inside of your mouth. | | |
| Ways to prevent or postpone symptoms | Inflamed and sore mouth (stomatitis/ oral mucositis) | • Have any needed dental work done before starting treatment (Lacouture et al., 2021)<br>• Maintain good oral hygiene (Kommalapati et al., 2021)<br>• Clean your mouth thoroughly and often using mouthwashes, for example, using bicarbonate of soda and saltwater mouth rinses (1/4 to 1/2 teaspoon of each in 1 cup of warm water, depending on how sensitive your mouth is)<br>• Minimize or avoid hot drinks or salty, spicy, or citrus-based foods (Lacouture et al., 2021)<br>• Avoid mouthwashes with alcohol as an ingredient |
| | Diarrhea and constipation | • Discuss your diet and nutrition with your HCP to assess your risk of developing diarrhea or constipation |
| | Taste changes | • Maintain good oral hygiene, incorporating regular tongue brushing (Togni et al., 2021) |
| | Decreased appetite | • Do some moderate physical activity each day to stimulate your appetite (which will also help with managing fatigue)<br>• Discuss your diet with your HCP or a dietician |
| | Nausea and vomiting | • Eat small meals regularly throughout the day, consisting of soft, bland foods at room temperature, and stay well hydrated (Cope, 2022)<br>• Avoid fried, fatty, spicy, and acidic foods and foods with a strong smell (Cope, 2022)<br>• Let your HCP know if you are prone to nausea |
| If symptoms occur | Inflamed and sore mouth (stomatitis/ oral mucositis) | • Seek immediate medical attention if you develop a sore or inflamed mouth; sucking on small pieces of ice may provide relief (Kommalapati et al., 2021)<br>• Bicarbonate of soda and saltwater mouth rinses (1/4 to 1/2 teaspoon of each in 1 cup of warm water) may help |
| | Diarrhea | • Although some patients may find that bland foods may help with diarrhea, this must be balanced with the need to maintain enough calories and nutrition throughout the treatment course<br>• Drink 8–10 glasses of clear, low-phosphorus fluids every day<br>• Ask your HCP about the best way to maintain and restore your electrolyte balance (Kommalapati et al., 2021; Mahipal et al., 2020) |

**Table 2. FGFR Inhibitor Adverse Event Management Strategies for Patients (cont.)**

| | | |
|---|---|---|
| *Gastrointestinal symptoms (cont.)* | | |
| If symptoms occur (cont.) | Diarrhea (cont.) | • Avoid eating cruciferous vegetables (such as broccoli, cabbage and Brussels sprouts), spicy foods, or high-fat foods (such as fried foods; Mahipal et al., 2020) |
| | Taste changes | • Increase water consumption, eat smaller meals several times a day (including cold/lukewarm food and frozen fruits), eat proteins that have mild flavors, add more seasoning to meals, and avoid bitter or metallic tasting foods or strong-smelling foods (Togni et al., 2021)<br>• Try different foods to find ones that taste appealing<br>• Ask your HCP whether zinc supplements may help, and take only the recommended amount (Spencer et al., 2021; Togni et al., 2021) |
| | Decreased appetite | • Do some moderate physical activity each day<br>• Make meals as enjoyable as possible: eat with friends, eat foods you like, and add flavors to your meals using herbs, spices, and lemon juice<br>• Eat high protein foods such as eggs and chicken (Spencer et al., 2021)<br>• Eat small, calorie-rich meals frequently (Dev et al., 2017) |
| | Constipation | • Report constipation to your HCPs early so that they can make diet and treatment recommendations to help you prevent more severe constipation (Wickham, 2017)<br>• Ask your HCP to show you or your caregiver how to carry out abdominal massage to help with self-management and relaxation (Wickham, 2017) |
| | Nausea and vomiting | • Report uncontrolled nausea or vomiting to your HCP immediately<br>• Your HCP will check whether your nausea and vomiting are caused by something other than your anticancer therapy, and can recommend the right treatment |
| *Fatigue, weakness, or lack of energy and strength* | | |
| There are differences between normal and cancer-related fatigue, and fatigue can last after treatment is finished. | | |
| Ways to prevent or postpone symptoms | | • Participate in moderate physical activity every day, prioritize sleep and nutrition, and participate in mental relaxation programs, and/or yoga (Bower et al., 2014) |
| If symptoms occur | | • Report fatigue to your HCP, who may send you to get blood tests to look for possible causes, including low levels of iron (Kommalapati et al., 2021) |
| *Symptoms related to your eyes* | | |
| Your treatment may cause symptoms such as dry eyes, blurred vision, tiny specks or dark spots that can be seen in your field of vision (visual floaters), or perceived flashes of light in the field of vision (photopsia). **Contact your HCP immediately if you experience any of these symptoms.** Your HCP may refer you to an eye specialist straight away. | | |
| Ways to prevent or postpone symptoms | | • Have a comprehensive eye exam examination before starting treatment, and at regular intervals as your HCP advises<br>• Use preservative-free artificial tears (eye drops) regularly (Mahipal et al., 2020) |
| If symptoms occur | | • If you experience visual symptoms such as floaters or blurry vision, contact your HCP, who may refer you for an eye exam examination<br>• For dry eye, continue using preservative-free artificial tears (eye drops) or try hydrating or lubricating eye gels (Incyte Corporation, 2022; Mahipal et al., 2020; Taiho Pharmaceutical Co. & Ltd., 2022) |
| *Symptoms that can affect your whole body* | | |
| While taking FGFR inhibitors, too much calcium may accumulate in your blood (hypercalcemia), or you may have increased concentrations in your blood of creatinine, or aspartate aminotransferase (a liver enzyme), or not enough red blood cells (anemia). | | |
| Ways to prevent or postpone symptoms | | • You may be asked to have regular blood tests to check that your blood levels of calcium, creatinine, aspartate aminotransferase, and red blood cells are normal. Let your HCP know all the medications and supplements that you are taking.<br>• Tell your HCP if you have any fatigue, confusion, dehydration, nausea, constipation, or abdominal pain as these may be symptoms of elevated calcium in your blood (Carroll & Schade, 2003)<br>• Tell your HCP if you have any fatigue, lethargy, shortness of breath, reduced appetite, or difficulty concentrating as these may be symptoms of anemia (Madeddu et al., 2018) |

**Table 2. FGFR Inhibitor Adverse Event Management Strategies for Patients (cont.)**

| | |
|---|---|
| *Symptoms that can affect your whole body (cont.)* | |
| If symptoms occur | • If blood tests or symptoms suggest that you have any of these conditions, your HCP will perform tests to find out what is causing the problem and how to treat it.<br>• You may be advised to stop eating or drinking foods that contain calcium (Zagzag et al., 2018) |
| *Stomach-area (abdominal) pain, back pain, and joint stiffness or pain* | |
| While non-specific abdominal and back pain are common presenting symptoms of CCA, particularly in the area around the liver (the right upper part of your abdomen), these symptoms are also reported during treatment with FGFR inhibitors. | |
| Ways to prevent or postpone symptoms | • Report abdominal or back pain to your healthcare team immediately to ensure prompt treatment and support |
| If symptoms occur | • Your HCP will carry out a thorough assessment of your pain to try to determine what is causing it and how best to treat it (Yoong & Poon, 2018)<br>• Ask your HCP about other supportive measures such as hypnosis, acupuncture, music therapy, mindfulness, and massage therapy (Deng, 2019) |

Hyperphosphatemia can cause soft tissue mineralization, cutaneous calcification, cutaneous calcinosis, nonuremic calciphylaxis, vascular calcification, and myocardial calcification (Incyte Corporation, 2022; Taiho Pharmaceutical Co. & Ltd., 2022; Wanat et al., 2014; Zhou et al., 2021). The median time to onset of hyperphosphatemia was 15 days (95% confidence interval: 8–47 days) in the FIGHT-202 study of pemigatinib (Abou-Alfa et al., 2020), and 5 days (range: 3–117 days) across clinical trials of futibatinib (Taiho Pharmaceutical Co. & Ltd., 2022).

Iatrogenic hypophosphatemia is most often seen in the setting of phosphate binder use, and may result from their continued use during the off-treatment week of the 3-week intermittent pemigatinib dosing schedule (Abou-Alfa et al., 2020). This would not be applicable to futibatinib treatment as this follows a continuous dosing schedule. Rarely, we have observed hypophosphatemia independent of use of phosphate binders. In the pemigatinib FIGHT-202 phase II trial, hypophosphatemia was one of the more common grade 3 TEAEs, reported by 12% of patients (Abou-Alfa et al., 2020).

Serum phosphate should be monitored regularly throughout treatment. Dietary modification is key to the management of hyperphosphatemia and hypophosphatemia (Kommalapati et al., 2021). Close collaboration with a dietician is important when feasible. Patients receiving FGFR inhibitors should be advised to monitor their intake of phosphate, which is present in an abundance of foods (Mahipal et al., 2020). A list of foods suitable for a low- or high-phosphorus diet is provided in Table 3. Plant-based and unprocessed foods tend to contain less phosphorus than animal-based and processed foods (Kommalapati et al., 2021; Mahipal et al., 2020). If serum phosphate is > 5.5 mg/dL in patients on pemigatinib, or ≥ 5.5 mg/dL in patients on futibatinib, patients should initiate a low phosphate diet (Figure 2; Incyte Corporation, 2022; Taiho Pharmaceutical Co. & Ltd., 2022). Although low phosphate diet is recommended for initial management of hyperphosphatemia, this is not always effective and adherence to a low phosphate diet is typically poor in routine clinical practice. Sevelamer is typically used for management of more severe treatment-emergent hyperphosphatemia, although treatment with sevelamer is sometimes complicated by cost, adverse reactions (particularly constipation), pill burden, and the large tablet size of sevelamer. Acetazolamide is typically reserved for patients with hyperphosphatemia refractory to initial treatment with sevelamer. If hypophosphatemia occurs, it can normally be mitigated by pausing or reducing any phosphate-lowering medications and/or reinitiating FGFR inhibitor therapy.

Phosphate lowering therapies are another approach to managing hyperphosphatemia; however, the low adherence of these therapies poses a challenge to their implementation (Kommalapati et al., 2021). If serum phosphate is > 7 mg/dL

**Table 3. Low and High Phosphorus Foods for the Management of Hyperphosphatemia and Hypophosphatemia**

| Low phosphorus foods | High phosphorus foods |
|---|---|
| • Unenriched rice milk<br>• Ice pops or frozen fruit pops<br>• Low-fat cream cheese, Swiss cheese<br>• Fresh white bread, pasta, white rice<br>• Green peas or beans, broad beans, refined grains<br>• Fruits and vegetables<br>• Olive oil, butter, sugar<br>• Meats that do not contain "phosphorous" or "phos" ingredients<br>• Ginger ale, lime soda, water<br>• Fresh-brewed coffee from beans or tea from tea bags<br>• Honey or jam, popcorn | • Dairy products, ice cream, frozen yoghurt<br>• Soft cheese (e.g., cottage cheese), hard cheese (e.g., parmesan, cheddar, pecorino)<br>• Whole grain cereal, breads, crackers<br>• Biscuits, muffins, pancakes, waffles<br>• Split peas, kidney beans, black-eyed beans, lentils<br>• Seeds, nuts<br>• Fish, shrimp, squid, salmon<br>• Processed meats containing phosphorous such as chicken nuggets<br>• Colas, and other drinks with "phosphoric acid" or "phos" ingredients<br>• Chocolate, peanut butter |

*Note.* Information from D'Alessandro et al., (2015); Kommalapati et al. (2021); Mahipal et al. (2020).

in patients on pemigatinib, or ≥ 5.5 mg/dL in patients on futibatinib, phosphate lowering therapy should be initiated (Incyte Corporation, 2022; Taiho Pharmaceutical Co. & Ltd., 2022). Patients may receive phosphate-binding therapy to decrease phosphate absorption from the gastrointestinal tract, or phosphaturic agents to increase phosphate elimination from the kidneys (Kommalapati et al., 2021; Mahipal et al., 2020). Phosphate binders used in clinical practice include magnesium hydroxide, ferric citrate, sucroferric oxyhydroxide, lanthanum carbonate, and sevelamer, and phosphaturic agents include acetazolamide, niacinamide/nicotinamide, and probenecid (Kommalapati et al., 2021; Mahipal et al., 2020). Calcium-based therapies are rarely used in clinical practice and should be avoided as they are unlikely to be very effective and may be associated with toxicities such as hypercalcemia. Magnesium-based therapies should be avoided in patients with kidney disorder (Mahipal et al., 2020). Phosphate binders may cause, or exacerbate diarrhea (Kommalapati et al., 2021), so their use should be closely monitored. Phosphate binders should be taken with or after food, as indicated, and should be held when the patient is not receiving an FGFR inhibitor (i.e., during the 7 days off therapy per cycle with pemigatinib or during dose interruptions for non-hyperphosphatemia AEs). To mitigate the possibility of hypophosphatemia, the lowest possible dose of phosphate binders should be used upon initiation, and patients' serum phosphate concentrations should be monitored.

### Dermatologic Adverse Events

Dermatologic toxicities are common, though typically not dose-limiting. Because of alteration to the patient's appearance, patient education around alopecia and nail toxicities is crucial to help set expectations.

Alopecia was a common TEAE, occurring in 49% and 34% of patients on pemigatinib or futibatinib, respectively (Abou-Alfa et al., 2020; Goyal et al., 2023). Patients should be informed that methods normally used for patients undergoing traditional chemotherapy such as scalp cooling, scalp compression, and medications, are not applicable for patients on FGFR inhibitors (Lacouture et al., 2021). Prophylactic or reactive use of topical minoxidil may be used to manage alopecia in patients treated with FGFR inhibitors (Kommalapati et al., 2021; Lacouture et al., 2021). Patients should be told that alopecia typically reverses when treatment with FGFR inhibitors is discontinued (Kommalapati et al., 2021; Lacouture et al., 2021).

Nail toxicities are another common dermatologic AE for patients on FGFR inhibitors. Patients should be informed about the potential for nail changes before treatment initiation (Lacouture et al., 2021). In the phase II FIGHT-202 study of pemigatinib, nail toxicities were reported by 42% of patients (2% grade ≥ 3) with a median time to onset of 6 months (95% confidence interval: 4.8–8.8 months); 3% and 4% of patients required dose reductions or interruptions, respectively, because of nail toxicities (Abou-Alfa et al., 2020). Paronychia was reported as a TEAE by 10 (7%)

patients, and onychoclasis by nine (6%) patients (Abou-Alfa et al., 2020). In the phase II study of futibatinib, nail toxicities were reported by 47% of patients (2% grade ≥ 3; Goyal et al., 2023). There are a range of preventative and supportive care options for paronychia and onycholysis depending on severity. Given the incidence of paronychia with FGFR inhibitors, we typically include education around paronychia management and especially vinegar soaks as part of initial chemotherapy education sessions. For paronychia, patients should keep hands and feet clean and dry, avoid trauma, irritants, and restrictive shoes, and use protective gloves and emollients (Lee & Lipner, 2022). For grade 1 paronychia, topical povidone iodine 2% to 10% should be applied twice daily, and patients should soak their nails for 15 minutes daily in water and vinegar (1:1; Lacouture et al., 2021). For grade 2 or 3 paronychia, oral antibiotics should be initiated and referral to a dermatologist is recommended (Lacouture et al., 2021). Onycholysis can be managed by trimming the nails and applying topical povidone iodine 2% to 10% under and around the nails; for subungual abscess or painful hematoma, nail avulsion may be required, and oral antibiotics should be initiated for suspected infection (Lacouture et al., 2021).

Dry skin (xerosis) occurred as a TEAE in 20% and 29% of patients on pemigatinib or futibatinib, respectively (Abou-Alfa et al., 2020; Goyal et al., 2023). Patients should be advised to use emollients both as prophylactic and supportive care (Lacouture et al., 2021). They should also avoid prolonged exposure to hot water, detergents, or any other compounds that dry the skin. Patients should be referred to a dermatologist if they have grade 2 skin toxicities that have not responded to ≥ 4 weeks of therapy or are intolerable, or have grade 3 events (Lacouture et al., 2021).

Dry mouth (xerostomia) occurred as a TEAE in 34% and 35% of patients on pemigatinib or futibatinib, respectively (Abou-Alfa et al., 2020; Goyal et al., 2023). The treatment of dry mouth can include the use of mucosal lubricants and sialagogues, intraoral topical agents, and topical and systemic salivary stimulants (Kommalapati et al., 2021; Lacouture et al., 2021).

### Gastrointestinal Adverse Events

Stomatitis (oral mucositis) was reported as a TEAE in 24% to 35% of patients in clinical trials of pemigatinib and futibatinib (Abou-Alfa et al., 2020; Goyal et al., 2023). Maintaining oral hygiene is important for prevention and supportive care of stomatitis, and a range of treatment options should be considered depending on the grade. Patients may be advised to use dexamethasone or lidocaine-based mouthwashes, or an augmented betamethasone dipropionate gel (Table 1).

Diarrhea, taste changes (dysgeusia), and decreased appetite were reported as TEAEs by 36% to 47%, 20% to 40%, and 23% to 33% of patients, respectively, in clinical trials of pemigatinib and futibatinib (Abou-Alfa et al., 2020; Goyal et al., 2023). Close collaboration with palliative care specialists is key to helping optimize patients' quality of life on treatment. Empiric prescription of anti-diarrheal medications including loperamide for use as needed with treatment-emergent diarrhea may enhance drug adherence and patient quality of life. Supportive care and treatment of diarrhea may also include diphenoxylate/atropine and increasing fluid intake (Jain & Wylie, 2022; Kommalapati et al., 2021; Mahipal et al., 2020). For dysgeusia, patients could be treated with saliva substitutes or stimulants, and should be encouraged to consume regular small meals including cold meals (Togni et al., 2021). Patients with decreased appetite should meet with a dietician to ensure they are consuming enough nutrients and be encouraged to consume calorie-rich foods (Dev et al., 2017).

### Fatigue

Fatigue was another common TEAE reported by 34% to 42% of patients across clinical trials of selective FGFR tyrosine kinase inhibitors (Abou-Alfa et al., 2020; Goyal et al., 2023). As noted for gastrointestinal adverse events, patients who experience fatigue should be in close collaboration with palliative care specialists to optimize their quality of life while on treatment. Participation in moderate physical activity, mental relaxation programs, yoga, and improving nutrition can all help with the management of fatigue in these patients (Bower et al., 2014). Patients should be referred early to a physical therapist or exercise specialist, particularly if their

fatigue interferes with daily functioning or they have comorbidities (Bower et al., 2014; Mahipal et al., 2020). Once disease- and treatment-specific morbidities have been characterized or excluded, psychostimulants such as methylphenidate may be considered and should be used cautiously; pharmacologic interventions are investigational but may improve symptoms of fatigue in some patients (National Comprehensive Cancer Network, 2022).

### Ocular Toxicities

Ocular toxicities such as RPED and dry eye may occur among patients on FGFR inhibitors. RPED may cause symptoms such as blurred vision, visual floaters, or photopsia (Incyte Corporation, 2022). The reported median time to first onset of RPED is 62 days for pemigatinib (Incyte Corporation, 2022) and 40 days for futibatinib (Taiho Pharmaceutical Co. & Ltd., 2022). Dry eye was reported as a TEAE in 25% of patients treated with pemigatinib (Abou-Alfa et al., 2020), and 21% of patients treated with futibatinib (Goyal et al., 2023). Treatment with preservative-free artificial tears is recommended as needed (Incyte Corporation, 2022; Taiho Pharmaceutical Co. & Ltd., 2022). Because ocular toxicities can sometimes be serious, we encourage patients to contact the care team right away with any ocular symptoms. Establishing relationships with ophthalmologists, and especially with ocular oncologists or retinal specialists is crucial as patients sometimes require specialized treatment to manage ocular toxicities while on therapy. Trichiasis (eyelash growth toward the eye, sometimes irritating the conjunctiva or cornea) is sometimes observed on FGFR inhibitor therapy and ophthalmology can assist with management of this.

### Other Adverse Events

Other AEs have been reported in patients taking FGFR inhibitors, including asthenia, palmar–plantar erythrodysesthesia syndrome (PPES; hand–foot syndrome), constipation, nausea, vomiting, hypercalcemia, increased creatinine, increased AST, anemia, arthralgia, and abdominal or back pain (Abou-Alfa et al., 2020; Goyal et al., 2023; Loriot et al., 2019). Strategies for the prevention and management of these AEs are reported in Tables 1 and 2.

## DOSE REDUCTION OR INTERRUPTION

Dose reduction or interruption may be required for the management of specific AEs. In the phase II trial of pemigatinib ($N$ = 146), dose interruptions due to AEs occurred in 42% of patients, most frequently due to stomatitis, PPES, arthralgia, fatigue, and abdominal pain (Abou-Alfa et al., 2020). Dose reductions due to AEs occurred in 14% of patients who received pemigatinib, most frequently for stomatitis, PPES, arthralgia, asthenia, and onychomadesis (Abou-Alfa et al., 2020). Permanent discontinuation of pemigatinib due to an AE occurred in 9% of patients, most frequently (at least two patients) for intestinal obstruction and acute kidney injury (Abou-Alfa et al., 2020). For futibatinib, dose interruptions due to AEs occurred in 66% of patients, most frequently due to hyperphosphatemia, PPES, increased ALT, increased AST, and fatigue (Taiho Pharmaceutical Co. & Ltd., 2022). Dose reductions due to AEs occurred in 58% of patients who received futibatinib, most frequently for hyperphosphatemia, PPES, fatigue, increased ALT, increased AST, nail toxicity, and stomatitis (Taiho Pharmaceutical Co. & Ltd., 2022). Permanent discontinuation of futibatinib due to an AE was reported in 5% of patients, with one patient each discontinuing due to esophagitis, oral dysesthesia, bile duct obstruction, dizziness, and anemia (Taiho Pharmaceutical Co. & Ltd., 2022).

In the case of hyperphosphatemia, pemigatinib should be withheld if serum phosphate is > 10 mg/dL 1 week after starting phosphate lowering therapy or > 7 mg/dL 2 weeks after starting phosphate lowering therapy (Incyte Corporation, 2022). Pemigatinib can be resumed at the same dose once phosphate concentrations are < 7 mg/dL following the first occurrence of hyperphosphatemia, and at a reduced dose in subsequent occurrences or if serum phosphate concentration was > 10 mg/dL before treatment (Figure 2A; Incyte Corporation, 2022). If serum phosphate > 10 mg/dL recurs following two dose reductions, pemigatinib should be permanently discontinued (Incyte Corporation, 2022). In patients taking futibatinib with serum phosphate > 7 mg/dL and ≤ 10 mg/dL, futibatinib should be reduced to the next lower dose (Figure 2B; Taiho Pharmaceutical Co. & Ltd., 2022). If serum

phosphate is > 7 mg/dL after 2 weeks, a further dose reduction of futibatinib should occur, and if serum phosphate is > 7 mg/dL within 2 weeks of the second dose reduction, the dose should be held until serum phosphate is ≤ 7 mg/dL and then resumed at the previously tolerated dose (Taiho Pharmaceutical Co. & Ltd., 2022). If serum phosphate is > 10 mg/dL, the futibatinib dose should be held until serum phosphate is ≤ 7 mg/dL, and then resumed at a reduced dose (Taiho Pharmaceutical Co. & Ltd., 2022). Futibatinib should be permanently discontinued if serum phosphate is > 7 mg/dL 2 weeks following two dose interruptions and reductions (Taiho Pharmaceutical Co. & Ltd., 2022).

Dose interruption or reduction of FGFR inhibitors may be required for diarrhea, fatigue, and stomatitis, depending on their severity (Kommalapati et al., 2021; Mahipal et al., 2020). If grade 2 diarrhea persists for > 2 days despite maximal supportive care (such as antidiarrheal agents), dose interruption is recommended; if it persists for > 14 days, dose reduction is recommended (Mahipal et al., 2020).

## RESOURCES FOR HEALTH-CARE PROFESSIONALS AND PATIENTS

An extensive range of supportive care resources are available for advanced practice providers and their patients with CCA who are being treated with FGFR inhibitors (Table 4), including the Cholangiocarcinoma Foundation, and the Alan Morement Memorial Fund (AMMF; a cholangiocarcinoma charity in the United Kingdom). Other online resources are also available for patients such as the Oral Chemotherapy Education medication sheets, and mobile applications for monitoring symptoms (Warrington et al., 2019). The National Comprehensive Cancer Network (NCCN) has specific guidelines for patients, including useful information and links for further information about various AEs. On the Cancer.net site, the American Society of Clinical Oncology (ASCO) provides a range of fact sheets on side effects, including appetite loss, diarrhea, and fatigue. Financial assistance resources may also be available to patients based on their level of health coverage and subject to funding availability.

## DISCUSSION

Selective FGFR inhibitors for CCA with *FGFR* fusions or rearrangements such as pemigatinib and futibatinib have generally similar AE profiles. Management of AEs by a multidisciplinary care team including specialists such as dieticians, ophthalmologists, and dermatologists is important for improving patient outcomes. Advanced practice providers are on the front lines of treatment and are best positioned to relate directly with the patients and help them mitigate or manage their AEs, which will importantly reduce the need for dose reduction or discontinuation (see Appendices A and B for fictional scenarios illustrating the management of patients with CCA).

Before initiating treatment with selective FGFR inhibitors, patients and their caregivers should be well informed about the AEs they may expect during treatment, and that these AEs are generally manageable with appropriate prophylaxis, proactive monitoring, and timely treatment. Implementing patient-reported outcomes questionnaires could be considered to assess health-related quality of life, which is a valuable measure for reducing treatment discontinuation and optimizing treatment outcomes in these patients. Advanced practice providers can also use tools such as the ECOG performance status scale to monitor patients' level of functioning, to provide more individualized support with AE management. For example, for the management of fatigue, participation in moderate physical activity or yoga may be affected by a patient's physical ability; therefore, in some cases, individualized support such as recommending mental relaxation programs for the management of fatigue would be more beneficial to the patient.

Overall, advanced practice providers play an essential role in the management of AEs associated with selective FGFR inhibitors, which may optimize treatment adherence and improve quality of life in patients receiving these therapies.

### Acknowledgment

This review was funded by Incyte Corporation (Wilmington, DE, USA). Medical writing assistance was provided by Ciara Duffy, PhD, CMPP (Envision Pharma Group, Fairfield, CT) and funded by Incyte Corporation.

**Table 4. Supportive Care Resources for the Management of Adverse Events Relevant to Patients With CCA Receiving Selective FGFR Inhibitors**

| Organization | URL |
|---|---|
| *All adverse events* | |
| OCE | http://www.oralchemoedsheets.com/sheets/Pemigatinib_Patient_Education.pdf |
| CCF | https://cholangiocarcinoma.org/publications/ |
| *Abdominal pain, back pain, or arthralgia* | |
| ACS | https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/pain.html |
| ASCO | https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/joint-pain |
| ESMO | http://interactiveguidelines.esmo.org/esmo-web-app/gl_toc/index.php?GL_id=50&interactive_tool=82 |
| NCI/NIH | https://www.cancer.gov/about-cancer/treatment/side-effects/pain |
| ONS | https://www.ons.org/pep/acute-pain; https://www.ons.org/pep/breakthrough-pain; https://www.ons.org/pep/chronic-pain |
| *Alopecia* | |
| ACS | https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/hair-loss.html |
| ASCO | https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/hair-loss-or-alopecia |
| NCI/NIH | https://www.cancer.gov/about-cancer/treatment/side-effects/hair-loss |
| *Anemia* | |
| ACS | https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/low-blood-counts/anemia.html |
| ASCO | https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/anemia |
| ESMO | http://interactiveguidelines.esmo.org/esmo-web-app/gl_toc/index.php?GL_id=65 |
| NCCN | https://www.nccn.org/patients/guidelines/content/PDF/anemia-patient-guideline.pdf |
| NCI/NIH | https://www.cancer.gov/about-cancer/treatment/side-effects/anemia |
| *Constipation* | |
| ACS | https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/stool-or-urine-changes/constipation.html |
| ASCO | https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/constipation |
| NCI/NIH | https://www.cancer.gov/about-cancer/treatment/side-effects/constipation |
| ONS | https://www.ons.org/pep/constipation |
| *Diarrhea* | |
| ACS | https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/stool-or-urine-changes/diarrhea.html |
| ASCO | https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/diarrhea |
| ESMO | http://interactiveguidelines.esmo.org/esmo-web-app/gl_toc/index.php?GL_id=64 |
| NCI/NIH | https://www.cancer.gov/about-cancer/treatment/side-effects/diarrhea |
| ONS | https://www.ons.org/pep/chemotherapy-induced-diarrhea |

*Note.* ACS = American Cancer Society; AE = adverse event; AMMF = Alan Morement Memorial Fund; ASCO = American Society of Clinical Oncology; CCA = cholangiocarcinoma; CCF = Cholangiocarcinoma Foundation; ESMO = European Society of Medical Oncology; FGFR = fibroblast growth factor receptor; MASCC = Multinational Association of Supportive Care in Cancer; NCCN = National Comprehensive Cancer Network; NCI/NIH = National Cancer Institute/National Institutes of Health; OCE = Oral Chemotherapy Education; ONS = Oncology Nursing Society.

**Table 4. Supportive Care Resources for Management of AEs Relevant to Patients With CCA Receiving Selective FGFR Inhibitors (cont.)**

| Organization | URL |
|---|---|
| *Dry mouth* | |
| ACS | https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/mouth-problems/dry-mouth.html |
| ASCO | https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/dental-and-oral-health; https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/dry-mouth-or-xerostomia |
| NCI/NIH | https://www.cancer.gov/about-cancer/treatment/side-effects/mouth-throat |
| *Fatigue and weakness* | |
| ACS | https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/fatigue.html |
| ASCO | https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/fatigue |
| CCF | https://cholangiocarcinoma.org/wp-content/uploads/2015/01/NAB-Fatigue.pdf |
| ESMO | http://interactiveguidelines.esmo.org/esmo-web-app/gl_toc/index.php?GL_id=76 |
| NCCN | https://www.nccn.org/guidelines/guidelines-detail?category=3&id=1424 |
| NCI/NIH | https://www.cancer.gov/about-cancer/treatment/side-effects/fatigue |
| ONS | https://www.ons.org/pep/fatigue |
| *Palmar–plantar erythrodysesthesia* | |
| ASCO | https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/hand-foot-syndrome-or-palmar-plantar-erythrodysesthesia |
| *Hypercalcemia* | |
| ASCO | https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/high-calcium-levels-or-hypercalcemia |
| *Anorexia* | |
| ACS | https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/eating-problems/poor-appetite.html |
| AMMF | https://ammf.org.uk/nutrition/ |
| ASCO | https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/appetite-loss |
| ESMO | http://interactiveguidelines.esmo.org/esmo-web-app/gl_toc/index.php?GL_id=76 |
| NCI/NIH | https://www.cancer.gov/about-cancer/treatment/side-effects/appetite-loss |
| ONS | https://www.ons.org/pep/anorexia |
| *Nail changes* | |
| ACS | https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/nail-changes.html |
| NCI/NIH | https://www.cancer.gov/about-cancer/treatment/side-effects/skin-nail-changes |
| *Nausea and vomiting* | |
| ACS | https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/nausea-and-vomiting.html |

*Note.* ACS = American Cancer Society; AE = adverse event; AMMF = Alan Morement Memorial Fund; ASCO = American Society of Clinical Oncology; CCA = cholangiocarcinoma; CCF = Cholangiocarcinoma Foundation; ESMO = European Society of Medical Oncology; FGFR = fibroblast growth factor receptor; MASCC = Multinational Association of Supportive Care in Cancer; NCCN = National Comprehensive Cancer Network; NCI/NIH = National Cancer Institute/National Institutes of Health; OCE = Oral Chemotherapy Education; ONS = Oncology Nursing Society.

**Table 4. Supportive Care Resources for Management of AEs Relevant to Patients With CCA Receiving Selective FGFR Inhibitors (cont.)**

| Organization | URL |
|---|---|
| *Nausea and vomiting (cont.)* | |
| ASCO | https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/nausea-and-vomiting |
| ESMO | http://interactiveguidelines.esmo.org/esmo-web-app/gl_toc/index.php?GL_id=27 |
| NCCN | https://www.nccn.org/patients/guidelines/content/PDF/nausea-patient.pdf |
| NCI/NIH | https://www.cancer.gov/about-cancer/treatment/side-effects/nausea-vomiting |
| ONS | https://www.ons.org/pep/chemotherapy-induced-nausea-and-vomiting-adult |
| *Skin problems or toxicities* | |
| ACS | https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/skin-problems.html |
| ASCO | https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/skin-reactions-targeted-therapy-and-immunotherapy |
| ONS | https://www.ons.org/pep/skin-reactions |
| NCI/NIH | https://www.cancer.gov/about-cancer/treatment/side-effects/skin-nail-changes |
| *Stomatitis (oral mucositis)* | |
| ACS | https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/mouth-problems/mouth-sores.html |
| ASCO | https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/mouth-sores-or-mucositis |
| ONS | https://www.ons.org/pep/mucositis |
| ESMO | http://interactiveguidelines.esmo.org/esmo-web-app/gl_toc/index.php?GL_id=22 |
| MASCC | https://acsjournals.onlinelibrary.wiley.com/doi/epdf/10.1002/cncr.33100 |
| *Taste and smell changes* | |
| ACS | https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/eating-problems/taste-smell-changes.html |
| ASCO | https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/taste-changes |

*Note.* ACS = American Cancer Society; AE = adverse event; AMMF = Alan Morement Memorial Fund; ASCO = American Society of Clinical Oncology; CCA = cholangiocarcinoma; CCF = Cholangiocarcinoma Foundation; ESMO = European Society of Medical Oncology; FGFR = fibroblast growth factor receptor; MASCC = Multinational Association of Supportive Care in Cancer; NCCN = National Comprehensive Cancer Network; NCI/NIH = National Cancer Institute/National Institutes of Health; OCE = Oral Chemotherapy Education; ONS = Oncology Nursing Society.

## Disclosure

Ms. Schwartz has served as a consultant for AstraZeneca and on speakers bureaus for AstraZeneca, Eisai, Exelixis, and Incyte, and has stock in Sutro Biopharmaceuticals. Dr. Darling has no conflicts of interest to disclose.

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## Appendix A. Patient Scenario 1

A 77-year-old female with a history of intrahepatic cholangiocarcinoma, hypertension, and stage IV kidney disease with an estimated glomerular filtration rate (eGFR) of 22 who was diagnosed after routine laboratory examinations showed elevated alkaline phosphatase and total bilirubin 3.4 mg/dL. Carbohydrate antigen 19-9 was not elevated at baseline.

Baseline imaging showed a large and partially obstructing mass at segment IV thought to arise from the bile duct along with moderate biliary dilatation and osseous metastases at L4 and the left fifth rib.

After discussion with colleagues, the patient was sent for endoscopic retrograde cholangiopancreatography for brushings. A plastic stent was placed given high risk for biliary obstruction. The brushings demonstrated adenocarcinoma combined with pancreaticobiliary origin but with scant cellularity in the sample collected. The brushings were insufficient for next generation sequencing.

Next-generation sequencing by a circulating free tumor DNA assay showed an FGFR2-AHCYL2 fusion.

The patient initiated therapy with gemcitabine and carboplatin (carboplatin substituted for cisplatin owing to her renal disease) with empiric dose reduction and had progression at time of first restaging.

The patient later started pemigatinib with dose reduction to 9 mg daily as per the label for patients with severe renal disease.

The patient developed grade 2 hyperphosphatemia 7 days after initiation of therapy, which required initiation on the maximal dose of sevelamer with improvement to grade 1 on laboratory recheck 3 days after initiating sevelamer.

After 1 month on treatment, the patient called the clinic with reports of worsening diarrhea to about three times per day over baseline. Despite treatment with loperamide, the patient developed worsening diarrhea to about eight times daily over baseline with concurrent worsening of the renal function to eGFR of 10. The patient was instructed to stop sevelamer, and IV hydration as an outpatient was associated with improved renal function on post-hydration laboratory examinations, consistent with prerenal kidney injury. The patient continued to receive daily IV hydration in the clinic with resolution of diarrhea within about 3 days of stopping pemigatinib and with improvement of her renal function to her baseline. After 1 week, the patient restarted pemigatinib with further dose reduction to 4.5 mg daily. The patient was able to continue treatment with only grade 1 intermittent diarrhea, which was managed with diet alone and without recurrence of renal function changes. The patient stopped sevelamer during her 1-week dose hold but then restarted sevelamer at maximal dose with reinitiation of therapy and with continued control of her hyperphosphatemia for the duration of her therapy.

Restaging after 10 weeks on treatment showed stable disease. The patient continued treatment with pemigatinib for 8 months before imaging showed progression of disease.

*Note.* This is a fictional scenario written by the authors.

**Appendix B. Patient Scenario 2**

A 49-year-old male with a history of intrahepatic cholangiocarcinoma was diagnosed on CT imaging after presenting to the emergency department with cholangitis. The baseline carbohydrate antigen 19-9 (CA 19-9) was 512 U/mL.

He had R0 resection of 3.2 cm cholangiocarcinoma (Stage Ia: pT1aN0M0), followed by a course of adjuvant GemCis per ABC-02 (NCT00262769). His nadir CA 19-9 was at C6 with CA 19-9 of 42 U/mL, but he experienced steady increase of CA 19-9 though without apparent disease recurrence on multiphase CT imaging conducted shortly after completion of his eighth cycle of adjuvant therapy. With further increase of CA 19-9, a magnetic resonance angiography/pancreatography was conducted 2 months following completion of therapy, which showed new enhancing lesions in segments IVa and V.

Tumor tissue-based next generation sequencing showed an FGFR2-KRT23 fusion as well as a *BRCA1* mutation. He starts treatment with futibatinib at a dose of 20 mg orally daily.

Grade 1 hyperphosphatemia was noted on routine laboratory tests 1 week after starting therapy. The patient started a low phosphate diet; however, his hyperphosphatemia progressed to grade 2 two weeks after start of therapy and prompting initiation of sevelamer. His hyperphosphatemia improved to grade 1 on repeat laboratory tests one week after starting sevelamer.

Restaging after 2 months on therapy showed partial response, with reduced size of both intrahepatic lesions.

Baseline ophthalmic examination showed no abnormalities though examination 2 months after starting therapy showed asymptomatic retinal pigment epithelial detachment (RPED) of the left eye on optical coherence tomography (OCT). The RPED did not resolve within 14 days and the patient developed darkening of the central portion of the left visual field.

The patient was instructed to stop taking futibatinib and phosphate binders and urgent ophthalmic examination showed increased RPED of the left eye with also new RPED on the right eye. The patient experienced improvement in visual symptoms within about 2 days of stopping treatment and reported resolution of visual changes about 10 days after stopping futibatinib therapy. Repeat ophthalmic examination showed resolution of the RPED of the right eye with improvement of the RPED of the left eye. As the RPED of the left eye was resolving, treatment was resumed at a reduced dose of 16 mg once daily.

When futibatinib was restarted with dose reduction, sevelamer was also restarted. The patient developed grade 1 hypophosphatemia which resolved after stopping sevelamer.

The patient was able to continue therapy without recurrent RPED. Restaging imaging after 10 months on treatment demonstrated progression of disease, resulting in switch off futibatinib to FOLFOX per ABC-06 (NCT01926236).

*Note.* This is a fictional scenario written by the authors.