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Supplemental information

Clinical development and management of adverse events associated with FGFR inhibitors

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Supplementary Table 1. Overview of FGFR inhibitors

	CR/PR/SD/PD, %	Median PFS, (95% CI), mo	Median OS, (95% CI), mo
Erdafitinib, approved in the United States for metastatic or locally advanced urothelial cancer with *FGFR2* or *FGFR3* alteration, that has progressed on platinum-based chemotherapy(Janssen Oncology, 2022) IC_{50} for FGFR1, 2, 3, and 4 = 1.2, 2.5, 3.0, and 5.7 nM(Perera et al., 2017)			
Phase I			
CR100845 Open-label, multicenter, phase I, dose-escalation and confirmation study in patients with advanced or refractory solid tumors (NCT01703481)(Tabernero et al., 2015) (*N* = 65; data shown are for patients with *FGF*/*FGFR* alterations [*n* = 23])	0/22/70/9	NR	NR
Phase II			
BLC2001 Open-label, multicenter, phase II study in patients with locally advanced and unresectable or metastatic urothelial carcinoma with *FGFR* alterations (NCT02365597)(Loriot et al., 2019) (*N* = 99)	3/37/39/18	5.5 (4.2-6.0)	13.8 (9.8-NR)
Phase III			
CR108401 Open-label, randomized, multicenter study comparing erdafitinib with vinflunine or docetaxel, or pembrolizumab in patients with advanced urothelial carcinoma with selected *FGFR* aberrations (NCT03390504)(ClinicalTrials.gov, 2022) (*N* = 631 – estimated)	*Trial ongoing*	*Trial ongoing*	*Trial ongoing*
Pemigatinib, approved in the United States, Europe, Japan, China, and Canada for adults with previously treated, unresectable locally advanced or metastatic CCA with an *FGFR2* fusion or other rearrangement(Incyte Corporation, 2022) IC_{50} for FGFR1, 2, 3, and 4 = 0.4, 0.5, 1.0, and 30.0 nM(Liu et al., 2020)			
Phase I			
FIGHT-101 Open-label, phase I/II, dose-escalation study in patients with advanced solid malignancies and progression following prior therapy with no further effective standard therapy available (NCT02393248)(Subbiah et al., 2022) (*N* = 128)	0/9.4/31.3/38.3	NR	NR
FIGHT-102 Open-label, phase I, multisite study in Japanese patients with advanced malignancies (NCT03235570)(Kuboki et al., 2019) (*N* = 25)	0/6.3/56.3/37.5	NR	NR
Phase II			

FIGHT-202 Multicenter, open-label, single-arm study in patients with previously treated, locally advanced or metastatic cholangiocarcinoma with or without *FGF/FGFR* rearrangements (NCT02924376)(Abou-Alfa et al., 2020; Javle et al., 2021a) (*N* = 108 with *FGFR2* rearrangements)	0/4/36/60	7.0 (6.1-10.5)	17.5 (14.4-22.9)
FIGHT-203 Multicenter study in adult patients with MLN with *FGFR1* rearrangements (NCT03011372)(Gotlib et al., 2021) (*N* = 34)	77.4/NR/NR/NR	NR	NR
Phase III			
FIGHT-302 Open-label, randomized, active-controlled, multicenter, global study comparing the efficacy and safety of first-line pemigatinib with gemcitabine-cisplatin in patients with advanced CCA with *FGFR2* rearrangements (NCT03656536)(Bekaii-Saab et al., 2020) (*N* = 432 – target enrollment)	*Trial ongoing*	*Trial ongoing*	*Trial ongoing*
Futibatinib, approved in the United States for previously treated, unresectable locally advanced or metastatic iCCA with *FGFR2* gene fusions or other rearrangements(Taiho Oncology, 2022) IC_{50} for FGFR1, 2, 3, and 4 = 1.8, 1.4, 1.6, and 3.7.nM(Sootome et al., 2020)			
Phase I/II			
FOENIX-CCA2 First-in-human, phase I/II, dose-escalation and expansion study in patients with advanced solid tumors harboring *FGF*/*FGFR* aberrations (NCT02052778)(Goyal et al., 2023; Meric-Bernstam et al., 2021) (*N* = 201; 83 with CCA)	Overall: 0/13.7/37.6/48.7	NR	NR
Phase III			
FOENIX-CCA3 Phase III, randomized, open-label, multicenter study comparing futibatinib with gemcitabine plus cisplatin as first-line therapy in patients with advanced, metastatic or unresectable intrahepatic cholangiocarcinoma harboring *FGFR2* rearrangements (NCT04093362)(Borad et al., 2020) (*N* = 216 – estimated)	*Trial ongoing*	*Trial ongoing*	*Trial ongoing*
Derazantinib, not yet approved IC_{50} for FGFR1, 2, 3, and 4 = 4.5, 1.8, 4.5, 34 nM(Hall et al., 2016)			
Phase I			
ARQ 087-101 Multicenter, phase I/II, open-label study of derazantinib in patients with advanced solid tumors with *FGFR* genetic alterations, including iCCA with *FGFR2* fusion (NCT01752920)(Mazzaferro et al., 2019)	0/20.7/62.1/17.2	5.7 (4.0-9.2)	NR

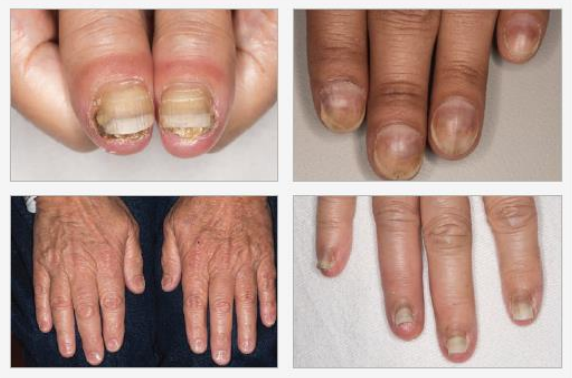
(*N* = 29 [patients with iCCA and *FGFR2* gene fusion only])			
FIDES-02 Multicohort, open-label, phase Ib/II study of derazantinib plus atezolizumab in patients with advanced solid tumors (NCT04045613)(Abdul-Karim et al., 2021) (*N* = 26; *n* = 10 evaluable for response)	0/0/40/60	NR	NR
Phase II			
FIDES-01 Pivotal, open-label, single-arm phase II study of derazantinib in previously treated patients with inoperable or advanced iCCA and *FGFR2* gene fusions, mutations, or amplifications (NCT03230318)(ClinicalTrials.gov, 2021; Droz Dit Busset et al., 2021; Javle et al., 2020) (*N* = 103)	0/21/54/25	7.8 (5.5-8.2)	15.5 (11.8-21.9)
Rogaratinib, not yet approved IC_{50} for FGFR1, 2, 3, and 4 = 1.8, <1, 9.2, 1.2 nM(Grunewald et al., 2019)			
Phase I			
16443 Phase I, dose-escalation and expansion study of rogaratinib in patients with advanced solid tumors (NCT01976741)(Schuler et al., 2019) (*n* = 126; *n* = 100 evaluable for response)	1/14/56/29	3.1 (2.0-3.4)	NR
FORT-2 Phase Ib/2 study of rogaratinib plus atezolizumab in patients with first-line cisplatin-ineligible advanced/metastatic urothelial carcinoma with *FGFR1/3* overexpression (NCT03473756)(Rosenberg et al., 2021) (*N* = 26)	13/42/29/17	NR	NR
Phase II/III			
FORT-1 Phase II/III, randomized, open-label study comparing rogaratinib with chemotherapy in patients with advanced or metastatic urothelial carcinoma with *FGFR1/3* overexpression (NCT03410693)(Quinn et al., 2020) (*N* = 87 treated with rogaratinib, 88 treated with chemotherapy)	NR	2.7 (1.6-4.2) (rogaratinib) versus 2.9 (2.6-4.2) (chemotherapy)	NR

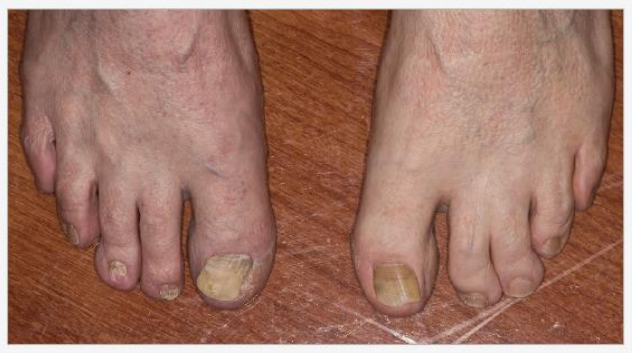
CCA, cholangiocarcinoma; CI, confidence interval; CR, complete response; FDA, US Food and Drug Administration; IC_{50}, half maximal concentration; iCCA, intrahepatic cholangiocarcinoma; MLN, myeloid/lymphoid neoplasm; NR, not reported; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Supplementary Table 2. High- and low-phosphate foods

High-phosphate food	Low-phosphate food
Milk, pudding, yogurt (from animals and from many soy varieties)	Rice milk (unfortified), nondairy creamer (if no ingredients with the letters “phos” in their name)
Hard cheese, ricotta, cottage cheese, fat-free cream cheese	Regular and low-fat cream cheese
Ice cream or frozen yogurt	Sherbet or frozen fruit pops
Soups made with higher-phosphate ingredients (milk, dried peas, beans, lentils)	Soups made with lower phosphate ingredients (broth- or water-based with other lower phosphate ingredients)
Whole grains, including whole grain breads, crackers, cereal, rice, and pasta	Refined grains including white bread, crackers, cereals, rice, and pasta
Quick breads, biscuits, cornbread, muffins, pancakes, or waffles	Homemade refined (white) dinner rolls, bagels, or English muffins
Dried peas (split, black-eyed), beans (black, garbanzo, lima, kidney, navy, pinto), or lentils	Green peas (canned, frozen), green beans, or wax beans
Organ meats, walleye, pollock, or sardines	Lean beef, pork, lamb, poultry, or other fish
Nuts and seeds	Popcorn
Peanut butter and other nut butters	Jam, jelly, or honey
Chocolate including chocolate drinks	Carob candy, hard candy, or gumdrops
Colas and pepper-type sodas, flavored waters, bottled teas (with ingredients whose names contain the letters “phos”)	Lemon-lime soda, ginger ale or root beer, plain water

Supplementary Figure 1. Representative images of adverse events commonly found with fibroblast growth factor receptor inhibitors. (A) Hand nail changes; (B) foot nail changes; (C) axillary calcification; (D) leg calcification.





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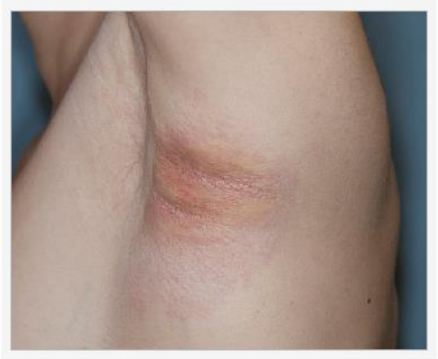

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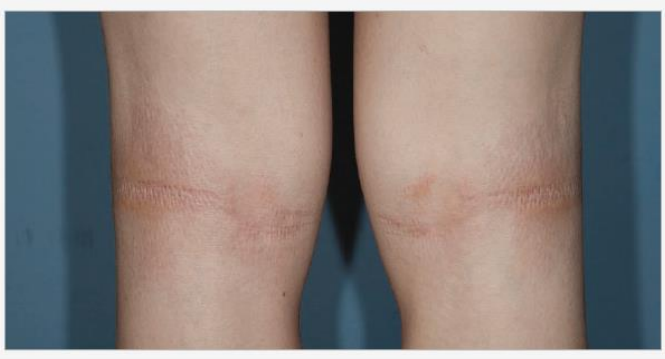

Supplementary Figure 2. Interpretive diagram of 40 eyes of 20 patients showing the location, size, and configuration of each fluid focus: blue = dome, yellow = splitting. Number represents patient number and circle designates patient had visual symptoms. Reproduced with permission from Francis et al. 2021.(Francis et al., 2021)