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FIGHT-101, a first-in-human study of potent and selective FGFR 1–3 inhibitor pemigatinib in pan-cancer patients with *FGF/FGFR* alterations and advanced malignancies

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Abstract

Background: The phase I/II FIGHT-101 study (NCT02393248) evaluated safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of pemigatinib, a potent and selective fibroblast growth factor receptor (FGFR) 1–3 inhibitor, as monotherapy or in combination therapy, for refractory advanced malignancies, with and without fibroblast growth factor (*FGF*) and receptor (*FGFR*) gene alterations.

Patients and methods: Eligible, molecularly unselected patients with advanced malignancies were included in part 1 (dose escalation; 3 + 3 design) to determine the maximum tolerated dose. Part 2 (dose expansion) evaluated the recommended phase II dose in tumors with or where FGF/FGFR activity is relevant.

Results: Patients ($N = 128$) received pemigatinib 1–20 mg once daily intermittently (2 weeks on/1 week off; $n = 70$) or continuously ($n = 58$). No dose-limiting toxicities were reported. Doses ≥4 mg were pharmacologically active (maximum tolerated dose not reached; recommended phase II dose 13.5 mg once daily). The most common treatment-emergent adverse event (TEAE) was hyperphosphatemia (75.0%; grade ≥3, 2.3%); the most common grade ≥3 TEAE was fatigue (10.2%). Dose interruption, dose reduction, and TEAE-related treatment discontinuation occurred

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in 66 (51.6%), 14 (10.9%), and 13 (10.2%) patients, respectively. Overall, 12 partial responses were achieved, most commonly in cholangiocarcinoma ($n = 5$) as well as in a broad spectrum of tumors including head and neck, pancreatic, gallbladder, uterine, urothelial carcinoma, recurrent pilocytic astrocytoma, and non-small-cell lung cancer (each $n = 1$); median duration of response was 7.3 months [95% confidence interval (CI) 3.3–14.5 months]. Overall response rate was highest for patients with *FGFR* fusions/rearrangements [$n = 5$; 25.0% (95% CI 8.7% to 49.1%)], followed by those with *FGFR* mutations [$n = 3$; 23.1% (95% CI 5.0% to 53.8%)].

Conclusions: Pemigatinib was associated with a manageable safety profile and pharmacodynamic and clinical activity, with responses seen across tumors and driven by *FGFR* fusions/rearrangements and mutations. These results prompted a registrational study in cholangiocarcinoma and phase II/III trials in multiple tumor types demonstrating the benefit of precision therapy, even in early phase trials.

Keywords

pemigatinib; FGFR; advanced malignancies; phase I/II clinical trial; genomic profiling

INTRODUCTION

Dysregulated fibroblast growth factor receptor (FGFR) signaling, resulting from somatic *FGFR* alterations (activating mutations, amplifications, and fusions or rearrangements), has been implicated in numerous malignancies, including urothelial bladder cancer, breast cancer, cholangiocarcinoma, and lung cancer.[1–4] *FGFR* alterations occur across a wide range of tumor types,[3–5] including *FGFR3* mutations and fusions in urothelial bladder cancer[3–7] and *FGFR2* fusions or rearrangements in cholangiocarcinoma.[3–5,8] Increasing evidence for *FGFR* alterations as drivers of tumorigenesis has prompted the development of FGFR-targeted therapies in various solid tumors,[2] including urothelial carcinoma[9] and cholangiocarcinoma.[10]

Pemigatinib, a potent and selective oral inhibitor of FGFR 1–3, has shown antitumor activity in genetically defined tumor models,[11] and has demonstrated clinical benefit in patients with tumors harboring certain *FGFR* alterations.[10,12] Pemigatinib is approved in Canada, Europe, Japan, and the USA for the treatment of adults with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma with *FGFR2* fusions or other rearrangements.[13–16] The approvals were based on efficacy and safety results from the registrational phase II, FIGHT-202 study of patients with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma, with or without *FGF/FGFR* alterations (NCT02924376).[10] Patients with *FGFR2* fusions or rearrangements ($n = 108$) demonstrated an independently, centrally confirmed objective response rate (ORR) of 37.0% [95% confidence interval (CI) 27.9% to 46.9%], including four complete responses, stable disease (SD) in 45.4% of patients, median duration of response (DOR) of 8.1 months, median progression-free survival (PFS) of 7.0 months, and an estimated median overall survival (OS) of 17.5 months.[17] The initiation of FIGHT-202 was prompted by encouraging safety and efficacy results from FIGHT-101 (NCT02393248), a phase I/II, dose-escalation/dose-expansion study of pemigatinib in patients with refractory advanced malignancies. A key requirement for enrollment in the dose-expansion cohorts of FIGHT-101 is the presence of

tumor-related *FGF/FGFR* alterations. Enrollment of patients in the pemigatinib monotherapy cohorts is complete. Here, we report final results from FIGHT-101 in patients who received pemigatinib monotherapy, including safety and tolerability, the pharmacokinetic and pharmacodynamic profile of pemigatinib, and the relationship between efficacy outcomes and *FGF/FGFR* alteration status in multiple malignancies.

PATIENTS AND METHODS

Study design and treatment

FIGHT-101 (NCT02393248) enrolled patients with refractory advanced malignancies in the USA and Denmark to receive pemigatinib alone (parts 1 and 2) or in combination with other therapies (part 3). Results from part 1 (dose escalation) and part 2 (dose expansion) for pemigatinib monotherapy are reported herein (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2022.02.001). The primary objectives were to: (i) evaluate safety, tolerability, and dose-limiting toxicity (DLT); (ii) determine the pharmacologically active dose and maximum tolerated dose (MTD); and (iii) assess the pharmacodynamics of pemigatinib. Patients self-administered pemigatinib orally with water once daily (QD) either continuously or on a 2 weeks on/1 week off schedule [intermittent dosing (ID)]. One treatment cycle was defined as 21 days.

Part 1 determined the MTD of pemigatinib and doses associated with substantial pharmacological target inhibition, as demonstrated by increases in serum phosphate, see Supplementary Methods for additional details, available at https://doi.org/10.1016/j.annonc.2022.02.001. Part 2 evaluated the recommended dose of pemigatinib as monotherapy in specific cancers in which FGFR activity is relevant and that harbor amplifications, mutations, or translocations of *FGFR1*, *FGFR2*, or *FGFR3*, or alteration of *FGF1* through *FGF23*.

Patients

Patients enrolled in parts 1 and 2 were ≥18 years of age with advanced malignancies, who had experienced disease progression during prior therapy and had no further effective standard anticancer therapy available to them. Patients had life expectancy >12 weeks and Eastern Cooperative Oncology Group performance status of ≤1 for part 1 and ≤2 for part 2. Documented *FGF*/*FGFR* status was not required for enrollment in part 1. Patients enrolled in part 2 had measurable disease with documented *FGF*/*FGFR* alterations and could include those with multiple myeloma and myeloproliferative neoplasms. See Supplementary Methods for additional eligibility criteria, available at https://doi.org/10.1016/j.annonc.2022.02.001.

Endpoints

Primary endpoints included safety and tolerability, and the pharmacodynamics of pemigatinib. Safety and tolerability were evaluated in all patients who received at least one dose of pemigatinib. Secondary endpoints included the ORR in patients with measurable disease based on investigator assessment of response, and pharmacokinetics. Exploratory

endpoints included DOR, PFS, and potential predictive biomarkers to identify patients who would benefit most from pemigatinib.

Assessments

Safety assessment.—Safety was assessed from the frequency, duration, and severity of treatment-emergent adverse events (TEAEs) according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, physical examinations, vital signs, electrocardiograms, and laboratory evaluations. Severity of hyperphosphatemia, which is not included in CTCAE version 4.03, was graded as described in the Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2022.02.001. Hyperphosphatemia was managed using dietary phosphate restriction, administration of phosphate binders, and/or dose interruption or reduction.

Pharmacokinetic, pharmacodynamic (target inhibition), and biomarker analysis.—All patients who received at least one dose of pemigatinib and provided at least one post-dose plasma sample comprised the pharmacokinetic-evaluable population. In part 1, blood samples for the determination of pemigatinib plasma concentrations were collected (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.02.001) before dosing on days 1, 2, 8, 14, 15, and 16 of cycle 1, and 0.5, 1, 2, 4, 6, 8 h after dosing on days 1 and 14 of cycle 1. See Supplementary Methods for additional details, available at https://doi.org/10.1016/j.annonc.2022.02.001.

Pharmacodynamics were evaluated in patients who received at least one dose of pemigatinib and provided at least one post-baseline blood sample for pharmacologic assessment. In an *ex vivo* pharmacodynamic analysis, phosphorylated FGFR2a was used as a surrogate pharmacodynamic marker for determining the biologic activity of pemigatinib. See Supplementary Methods for additional details of pharmacodynamic and biomarker analyses, available at https://doi.org/10.1016/j.annonc.2022.02.001.

Assessment of tumor status and genetic alterations.—Tumor status was assessed (per investigator) at screening (baseline) and every three cycles using appropriate disease-specific techniques. Solid tumors were assessed per RECIST 1.1.[18] Although computed tomography was recommended, alternative modalities compatible with RECIST 1.1 were allowed at the investigator's discretion if used consistently throughout the study.

FGF/*FGFR* alteration status in part 2 was determined with locally available techniques or by FoundationOne® (Foundation Medicine, Inc., Cambridge, MA) using next-generation sequencing.

Study conduct

The study was carried out in accordance with the Declaration of Helsinki, the protocol approved by each Institutional Review Board or Independent Ethics Committee, the US code of federal regulations for Good Clinical Practice, Good Clinical Practice guidelines of the International Council for Harmonisation, and all applicable regulatory requirements. All patients provided written informed consent.

RESULTS

Patients

As of the data cut-off (7 April 2020), 128 patients were enrolled and had received one or more doses of pemigatinib monotherapy in parts 1 or 2 of the study (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2022.02.001). Seventy patients received daily doses ranging from 1 to 20 mg on an ID schedule, and 58 received daily doses of 9, 13.5, or 20 mg continuously. Median treatment duration was 8.0 weeks (range, 0.1–160) overall and 8.0 weeks (1–105) for ID, and 8.6 weeks (0.1–160) for continuous dosing (CD). Overall, 122 patients (95.3%) discontinued treatment (ID, 100%; CD, 89.7%), most commonly for disease progression (60.9%); eight patients (6.3%) discontinued treatment due to adverse events (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.02.001). The median age of patients was 59 years (Table 1), 60.9% were women, 89.1% were white, and 76.6% had received at least three prior therapies. The most common tumor type was cholangiocarcinoma (16.4%).

Safety and tolerability

No DLTs were reported in any dose cohort, and the MTD for pemigatinib monotherapy was not reached. Among all treated patients ($N = 128$), 99.2% had a TEAE of which 90.6% were treatment-related (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.02.001). The most common any-cause TEAE was hyperphosphatemia (75.0%; ID, 68.6%; CD, 82.8%); the most common grade ≥3 TEAE of any cause was fatigue (10.2%; ID, 5.7%; CD, 15.5%) (Table 2). The most common treatment-related TEAE was hyperphosphatemia (73.4%; grade ≥3, 1.6%) (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2022.02.001). Overall, 66 (51.6%) and 14 (10.9%) patients, respectively, had dose interruptions and dose reductions; 13 (10.2%) had treatment discontinuation due to TEAEs (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.02.001). Patients receiving ID were less likely than those receiving CD to require dose interruptions (32.9% versus 74.1%), reductions (5.7% versus 17.2%), or treatment discontinuations (8.6% versus 12.1%) due to TEAEs (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.02.001). The most common TEAEs requiring dose interruption and dose reduction, respectively, were hyperphosphatemia ($n = 12$; 1 ID, 11 CD), and stomatitis ($n = 4$; all CD); the most common TEAEs requiring discontinuation were small intestinal obstruction ($n = 2$; both ID) and pneumonia ($n = 2$; both ID) (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.02.001).

Clinically notable TEAEs assessed included dry eye, eyelash changes, hyperphosphatemia, hypophosphatemia, nail toxicity, vision blurred, vitreous detachment, and serous retinal detachment [relevant (Medical Dictionary for Regulatory Activities, MedDRA) preferred terms combined; Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2022.02.001]. Clinically notable TEAEs occurred in 81.3% of treated patients (ID, 77.1%; CD, 86.2%), resulting in two treatment discontinuations. One patient discontinued pemigatinib 20 mg CD due to serious grade 3 paronychia; the other discontinued pemigatinib 13.5 mg CD due to grade 2 trichiasis. Despite the high frequency of

hyperphosphatemia, only three patients (2.3%) had grade ≥3 events. Dose reduction and dose interruption for hyperphosphatemia were required in two (1.6%) and 12 (9.4%) patients, respectively. Hypophosphatemia events occurred in 15.6% of patients (grade ≥3, 5.5%) (Table 2) and were less common for CD versus ID regimens (12.1% versus 18.6%). Two patients (1.6%) required dose interruption, and none required dose reductions due to hypophosphatemia. Overall, 32.0% of patients had nail toxicities (Table 2), most commonly onycholysis (14.8%), nail discoloration (13.3%), and paronychia (10.2%); grade ≥3 events occurred in four patients [3.1% (onycholysis, $n = 3$; paronychia, $n = 4$)]. One patient (0.8%) had dose reduction and 10 (7.8%) had dose interruption due to nail toxicities. Among all patients, TEAEs of dry eye, eyelash changes, vision blurred, and vitreous detachment occurred in 23.4%, 13.3%, 16.4%, and 1.6%, respectively. There were no TEAEs of serous retinal detachment.

A total of 10 patients (7.8%) died due to TEAEs, including disease progression ($n = 4$), multiple organ dysfunction syndrome, pneumonia, cerebrovascular accident, intracranial hemorrhage, acute respiratory failure, and respiratory failure (each $n = 1$). None of these deaths were considered treatment-related.

Clinical pharmacokinetics and pharmacodynamics

With multiple oral dose administration in the fasted state, pemigatinib attained peak plasma concentrations with a median time of w1–2 h after dose, followed by a biexponential decrease (Supplementary Figure S2A, available at https://doi.org/10.1016/j.annonc.2022.02.001). Steady-state plasma concentrations for doses ≥9 mg QD exceeded the *in vivo* half maximal inhibitory concentration for inhibition of FGFR2 phosphorylation over a 24-h period (Supplementary Figure S2B, available at https://doi.org/10.1016/j.annonc.2022.02.001). The steady-state geometric mean terminal-phase disposition half-life was comparable for doses ≥6 mg QD (ranging from 12.1 to 15.4 h; Supplementary Table S7 and Supplementary Figure S2B, available at https://doi.org/10.1016/j.annonc.2022.02.001). For doses of 1–20 mg QD, dose-proportional increases in pemigatinib steady-state maximum plasma drug concentration (C_{max}) and area under the plasma concentration-time curve from 0 to 24 h ($AUC_{0–24}$) were observed (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2022.02.001). Additional pharmacokinetic results including food effect (Supplementary Table S8, Supplementary Figure S2C, available at https://doi.org/10.1016/j.annonc.2022.02.001) and pharmacodynamic results including serum phosphate concentration profiles associated with ID and CD schedules (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2022.02.001), pemigatinib exposure-serum phosphate concentration relationship (Supplementary Figure S4A, available at https://doi.org/10.1016/j.annonc.2022.02.001), phosphorylated FGFR2a target inhibition (Supplementary Figure S4B and S4C, available at https://doi.org/10.1016/j.annonc.2022.02.001), and plasma FGF23 concentration profiles (Supplementary Figure S4D, available at https://doi.org/10.1016/j.annonc.2022.02.001) are provided in the Supplementary Results section, available at https://doi.org/10.1016/j.annonc.2022.02.001.

Efficacy

In part 1, 24 of 49 patients (49.0%) had available *FGF/FGFR* status assessments; in part 2, 72 of 79 patients (91.1%) had documented *FGF/FGFR* status. For most patients who lacked documented *FGF/FGFR* status in part 2, the reason was sample failure (inadequate tumor sample). Of the 96 patients enrolled in parts 1 and 2 with *FGF/FGFR* status assessments, 17 (17.7%) tested negative and 79 (82.3%) tested positive for *FGF/FGFR* alterations, including 20 patients with *FGFR* fusions or rearrangements, 13 with *FGFR* mutations, 26 with *FGFR* amplifications, and 20 with *FGF* amplifications (the 20 patients with *FGF* amplifications included 2 with *FGFR substrate 2* amplifications).

Overall, 12 patients (9.4%) achieved a partial response [PR; cholangiocarcinoma ($n = 5$), head and neck, pancreatic, gallbladder, uterine, urothelial carcinoma, recurrent pilocytic astrocytoma, and non-small-cell lung cancer (each $n = 1$)], 40 (31.3%) achieved SD, and 49 (38.3%) experienced disease progression. Four patients (3.1%) were not assessable for response, and response was not assessed or missing for 23 patients (18.0%). The ORR was highest for patients with *FGFR* fusions or rearrangements [25.0% (95% CI 8.7% to 49.1%)], followed by those with *FGFR* mutations [23.1% (95% CI 5.0% to 53.8%)] (Table 3). The median DOR was 7.3 months (95% CI 3.3–14.5 months) for all responders ($n = 12$) and 7.3 months (95% CI 2.8% to 11.3%) for those who tested positive for *FGF/FGFR* alterations ($n = 10$). A total of 40 patients (31.3%) achieved SD, including 24 (30.4%) who had *FGF/FGFR* alterations [*FGFR* fusions or rearrangements, 10/20 (50%); *FGFR* mutations, 3/13 (23.1%); *FGF* amplification, 4/20 (20%); *FGFR* amplification, 7/26 (26.9%)]. The median PFS was 2.8 months (95% CI 1.9–3.8 months) for all patients ($N = 128$) and 3.0 months (95% CI 1.8–4.1 months) for those who tested positive for *FGF/FGFR* alterations ($n = 79$); median PFS was 5.7 months (95% CI 2.8–10.0 months) and 5.0 months (95% CI 0.7–8.3 months) in patients with *FGFR* fusions or rearrangements ($n = 20$) and *FGFR* mutations ($n = 13$), respectively.

Of the 12 patients with a PR, 10 tested positive for *FGF/FGFR* alterations, including 5 with cholangiocarcinoma (*FGFR2* intron 17 rearrangement, *FGFR2-CLIP1* fusion, *FGFR2-CCDC6* fusion, *FGFR2* p.C382R mutation, and *FGF3,4,19* amplifications), and 1 each with gallbladder cancer (*FGFR2-BICC1* fusion), pancreatic cancer (*FGFR2-USP33* fusion), urothelial cancer (*FGFR3* p.S249C mutation), recurrent pilocytic astrocytoma (*FGFR1* p.N546K mutation), and uterine cancer (*FGFR1* amplification) (Figures 1 and 2). Of the 10 responders with *FGF/FGFR* alterations, 8 received pemigatinib 13.5 mg QD (ID or CD), 1 received 20 mg QD (CD), and 1 received 9 mg QD (ID) (Figure 1A–D).

The patient with pancreatic cancer and *FGFR2-USP33* fusion maintained a response for 10.7 months and then experienced disease progression; however, this patient remained on treatment because of continued clinical benefit and due to no other treatment being available to them (Figure 2A). The patient with cholangiocarcinoma and *FGFR2-CCDC6* fusion had a response duration of 11.3 months, but eventually developed multiple secondary *FGFR2* resistance mutations, including *FGFR2* p.V564I, p.N549K (two distinct mutations), and p.N549D.[19] A patient with adenoid cystic carcinoma of the head and neck achieved a PR after 6.0 months of treatment with pemigatinib 9 mg QD (CD); they subsequently experienced disease progression at 20.5 months and discontinued treatment

shortly thereafter. No *FGF/FGFR* alterations were noted for this patient and delineation of factors yielding this response requires further research. Another patient with non-small-cell lung cancer had a PR after 6.2 months of treatment with pemigatinib 9 mg QD (CD) and maintained response with continuing treatment at database lock (DOR, 29.9 months). The *FGF/FGFR* status for this patient was not known due to an inadequate tumor sample for central testing.

Best percentage change in target lesion size and duration of treatment by *FGF/FGFR* status category are shown in Figures 1 and 2 and Supplementary Figures S5 and S6, available at https://doi.org/10.1016/j.annonc.2022.02.001, respectively. Among patients with SD, those with *FGF/FGFR* alterations had best median percentage reduction in target lesion size of −8.0% (range, −27.9%−17.2%) (n = 24) versus 10.5% (range, −11.1%−18.4%) (n = 6) for those without *FGF/FGFR* alterations.

Co-occurring genomic alterations

Genomic alterations occurring with *FGFR* fusions or rearrangements and with *FGFR* mutations were predominantly *CDKN2A/B* loss-of-function alterations (fusions or rearrangements, 37%; mutations, 40%; Figure 1A and B), whereas co-occurring alterations in *TP53*, *PTEN*, *PIK3CA*, *KRAS*, or *BAP1* were less common (fusions or rearrangements, 5%, 16%, 5%, 0%, 32%; mutations, 30%, 0%, 0%, 10%, 10%). The most frequent alterations occurring with *FGFR* and *FGF* amplifications were *TP53* alterations (64% and 53%; Figure 1C and D); *CDKN2A/B* alterations occurred less frequently (18% and 13%), as did *PTEN* alterations (14% and 0%). Co-occurring oncogenic driver alterations in *KRAS* and *PIK3CA* were observed in a subset of patients with *FGFR* (14% and 14%) and *FGF* amplifications (13% and 7%). Notably, oncogenic *KRAS* (p.G12A) and *PIK3CA* (p.E545G) mutations co-occurring with *FGFR2* fusions or rearrangements were observed in two patients who achieved a PR. Of the three patients with cholangiocarcinoma and *FGFR2* fusions or rearrangements who achieved a PR, one had co-occurring alterations in both *BAP1* and *CDKN2A*. Among 46 patients with *FGF* or *FGFR* amplification, 22 (48%) had co-occurring *TP53* mutations; one of these patients, who had uterine cancer and *FGFR1* amplification, achieved a PR.

DISCUSSION

First-generation FGFR tyrosine kinase inhibitors such as ponatinib, dovitinib, lenvatinib, and nintedanib are multitarget inhibitors that target receptor kinases other than FGFRs. Consequently, effective FGFR inhibition in solid tumors could often not be achieved due to toxicity. These limitations prompted the development of selective FGFR inhibitors such as pemigatinib.[20] FIGHT-101 is a first-in-human phase I/II dose-escalation/dose-expansion study of pemigatinib in patients with advanced solid tumors, designed to find the recommended phase II dose (RP2D) for subsequent clinical trials. The study evaluated ID and CD schedules for pemigatinib alone and in combination with other common systemic cancer treatments (chemotherapy and immunotherapy). No DLTs were encountered with pemigatinib monotherapy, and the MTD was not reached in this study; as discussed below,

pemigatinib 13.5 mg QD was selected as the RP2D based on the pharmacologic and overall safety results.

Orally administered pemigatinib exhibited linear dose-dependent pharmacokinetics across the dose range. The observation that, for doses of ≥6 mg, C_{max} was reached within 1–2 h, with a dose-independent terminal half-life of 15 h supports QD dosing. Administration of a high-fat and high-calorie meal had modest effects on pemigatinib pharmacokinetics that were not considered clinically meaningful. No changes in pharmacokinetic parameters were expected for continuous administration, as steady-state concentrations were reached by approximately day 4 with QD dosing. At the 13.5-mg dose, however, the average percycle exposure of pemigatinib was increased by 50% in the CD versus the ID regimen.

From the model-predicted serum phosphate concentration versus pemigatinib exposure ($AUC_{ss,0–24}$) curve shown in Supplementary Figure S4A, available at https://doi.org/10.1016/j.annonc.2022.02.001, the EC_{50} and EC_{75} values for serum phosphate increase of 1700 and 2600 h●nM, respectively, are close to the mean $AUC_{ss,0–24}$ values resulting from pemigatinib at 9 mg QD and 13.5 mg QD dosing, respectively (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2022.02.001). Results from *ex vivo* pharmacodynamic analysis of phosphorylated FGFR2a inhibition in plasma samples from patients at steady-state pemigatinib exposure showed a ≥50% inhibition with pemigatinib at doses ≥4 mg and ≥50% inhibition at trough at doses ≥6 mg. These data suggest that sufficient target inhibition can be maintained if pemigatinib dose reduction to 9 mg or 4.5 mg QD is necessary to manage adverse events.

Overall, grade ≥3 TEAEs occurred less frequently in the ID versus the CD cohort of patients treated with pemigatinib monotherapy (50.0% versus 75.9%), including grade ≥3 fatigue (5.7% versus 15.5%) and stomatitis (1.4% versus 17.2%). In contrast, occurrence of grade ≥3 hyponatremia was similar in both groups (7.1% versus 10.3%). TEAEs leading to dose interruptions and dose reductions also were less common with ID versus CD (32.9% versus 74.1%, and 5.7% versus 17.2%, respectively), whereas frequency of TEAEs leading to treatment discontinuation were similar for ID (8.6%) versus CD (12.1%).

Hyperphosphatemia was the most common adverse event in this study (75%), consistent with findings from FIGHT-202 (60%)[10] and other selective FGFR inhibitors (55%−75%).[21] Hyperphosphatemia is an expected on-target effect of FGFR inhibition, attributable to the role of FGF23/FGFR signaling in phosphate homeostasis.[21] FGF23 released from bone regulates serum phosphate by suppressing phosphate reabsorption in the kidney via FGFR1[21]; therefore, inhibiting this action of FGF23 would be expected to increase phosphate reabsorption, resulting in hyperphosphatemia.[21] In the present study, only three patients experienced grade ≥3 hyperphosphatemia (ID, $n = 1$; CD, $n = 2$). None of the hyperphosphatemia events resulted in permanent treatment discontinuation.

Other clinically notable adverse events that have been associated with selective FGFR inhibitors include hypophosphatemia,[22,23] nail toxicities, and ocular toxicities[9,10,22–25] including serous retinal detachment.[21] Nail toxicities were common in this study (32.0%); however, only four patients had grade ≥3 events, one of which led to treatment

discontinuation (serious grade 3 paronychia). Consistent with other selective FGFR inhibitors,[21] the most common ocular toxicities in this study were dry eye and blurred vision (23.4% and 16.4%, respectively). Notably, no serous retinal detachment events were reported.

Hypophosphatemia events were observed in 15.6% of patients overall, and a minority (5.5%) of these were of grade 3 or 4 severity; two required dose interruption and none led to treatment discontinuation. Grade ≥3 hypophosphatemia has also been observed in 5%−8% of patients treated with other FGFR inhibitors.[22,23] Factors contributing to hypophosphatemia may have been the continued use of low-phosphate diet and phosphate binders during the off-treatment week in patients who received ID[21]; consistent with this, hypophosphatemia was less common in patients receiving CD versus ID regimens in this study. Hypophosphatemia may also have resulted from negative feedback regulation of FGFR23 expression via vitamin D receptor and parathyroid hormone receptor activation.[26] Although our results showed that concentrations of both phosphate and FGF23 increased after pemigatinib dosing, FGF23 concentration remained elevated during dosing holidays, whereas phosphate concentrations fell below baseline, suggesting that elevated FGF23 concentrations may be responsible for the occurrence of hypophosphatemia in some patients.

The observation that three of the 12 patients who achieved a PR and eight of the 40 patients who achieved SD did so at doses less than the RP2D of 13.5 mg QD is consistent with the finding that the percent inhibition of phosphorylated *FGFR2* by doses <13.5 mg QD exceeded the target coverage required for maximal efficacy (Supplementary Figure S4C, available at https://doi.org/10.1016/j.annonc.2022.02.001). This provides another indication that sufficient target inhibition can be maintained if dose reduction is necessary to manage adverse events.

The percentage of patients with SD was similar for all patients compared with those with *FGF*/*FGFR* alterations (31.3% versus 30.4%). Moreover, patients with *FGFR* fusions or rearrangements had a higher SD achievement rate (50%) compared with patients who had other *FGF*/*FGFR* alterations (20.0%−26.9%). Among patients with SD, those with *FGF*/*FGFR* alterations experienced a greater median percentage reduction in target lesion size compared with those without *FGF*/*FGFR* alterations [−8.0% (range, −27.9% to 17.2%) versus 10.5% (−11.1% to 18.4%)]. A previously published case study[27] described a patient enrolled in FIGHT-101 with myeloid/lymphoid neoplasm (designated myeloproliferative neoplasm in Figure 2) and *FGFR1-CEP110* fusion who achieved a rapid response with complete resolution of eosinophilia, complete hematologic and cytogenetic remission, and complete molecular remission with undetectable *FGFR1-CEP110* fusion. This patient, however, discontinued treatment at 3.9 months for disease progression, was not evaluable for change in target lesion size, and did not qualify for a response per RECIST 1.1.

Overall, the most encouraging clinical activity of pemigatinib was apparent in patients with cholangiocarcinoma harboring *FGFR2* fusions or rearrangements. Among these 13 patients, three (23.1%) achieved a PR and eight (61.5%) achieved SD. In addition, PR was observed in one patient with cholangiocarcinoma harboring an *FGFR2* p.C382R mutation. This result

supports the efficacy findings of FIGHT-202, in which patients with previously treated advanced cholangiocarcinoma with *FGFR2* fusions or rearrangements achieved an ORR of 35.5% and a disease control rate of 82%, whereas patients with other and no *FGF*/*FGFR* alterations had no responses and a disease control rate of 40% and 22%, respectively.[10] Thus, molecular screening for *FGFR* alterations using multigene panel testing to assess these co-occurring alterations is strongly recommended. This type of screening may also expand potential benefits of FGFR inhibitor therapy across cancer types and may facilitate identification of on- and off-target resistance mechanisms to aid the rational design of next-generation FGFR inhibitors and combination therapies.

A recent genomic profiling analysis of patients with cholangiocarcinoma harboring *FGFR2* fusions or rearrangements enrolled in FIGHT-202 showed that co-occurring *TP53* or *CDNK2A/B* alterations were both associated with significantly shortened PFS.[8] *BAP1* alterations also had a negative effect on PFS, but the magnitude of this effect was not statistically significant.[8] Elsewhere, an analysis of co-alterations in 95 patients with cholangiocarcinoma and *FGFR2* alterations found no prognostic effect for *BAP1* mutation, whereas *TP53* and *CDKN2A/B* alterations were associated with significantly shorter OS.[28] Given the heterogeneity of the FIGHT-101 study population, it is difficult to draw firm conclusions from these data regarding the significance of specific co-alterations for the observed response patterns in patients with various *FGF/FGFR* alterations. Nevertheless, the observation that one of the three patients with cholangiocarcinoma harboring *FGFR2* fusions or rearrangements who achieved a PR had co-alterations in both *BAP1* and *CDKN2A/B*, suggests that *BAP1* and *CDKN2A/B* co-alterations may not prevent response to pemigatinib treatment. The common co-occurrence of *TP53* mutations in tumors with *FGF* or *FGFR* amplifications observed in this study may also, in part, explain why patients harboring these amplifications were less likely to respond to pemigatinib than patients with *FGFR* fusions or rearrangements. The likelihood of response may, however, depend on the degree of *FGF* or *FGFR* amplification; the significance of *FGF* amplifications as actionable oncogenic drivers remains to be resolved. Post-progression analysis of plasma circulating tumor DNA in patients with cholangiocarcinoma harboring *FGFR2* fusions identified multiple previously described resistance mutations,[8,29] adding to accruing evidence for acquired resistance to FGFR inhibitors.

In summary, FIGHT-101 (parts 1 and 2) characterized the pharmacokinetics and pharmacodynamics of pemigatinib QD monotherapy in patients with advanced solid tumors and established 13.5 mg QD as the recommended dose for further studies. Phase II studies of pemigatinib monotherapy are ongoing in multiple tumor types, including a study in patients with myeloid/lymphoid neoplasms with *FGFR1* rearrangements (FIGHT-203; NCT03011372). In addition, a randomized phase III study (FIGHT-302; NCT03656536) is underway to evaluate the efficacy and safety of pemigatinib versus gemcitabine plus cisplatin as first-line therapy for patients with advanced cholangiocarcinoma harboring *FGFR2* rearrangements.[30]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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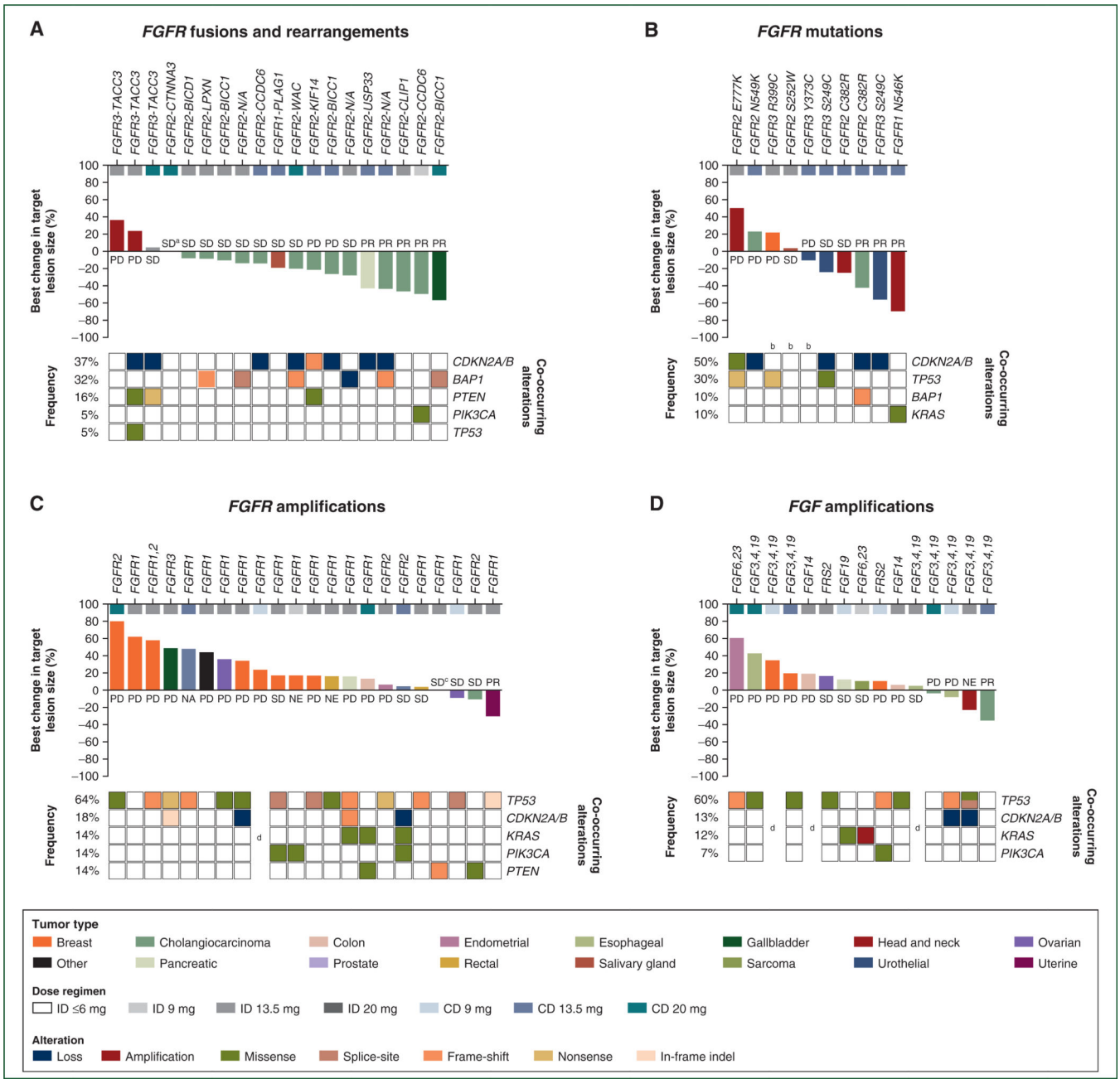

Figure 1. Best percentage change in target lesion size and genomic alterations occurring with (A) *FGFR* fusions or rearrangements, (B) *FGFR* mutations, (C) *FGFR* amplifications, and (D) *FGF* amplifications in individual patients.

Bar plots show percentage change in target lesion size in assessable patients, with colors indicating tumor type. Corresponding best overall responses per RECIST v1.1 are also shown.

CD, continuous dosing; *FGF*, fibroblast growth factor; *FGFR*, fibroblast growth factor receptor; ID, intermittent dosing; MDACC, MD Anderson Cancer Center; NA, not assessed; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Patient had cholangiocarcinoma with best change in target lesion size of 1.1%.

[b]By MDACC solid tumor assay.

[c]Patient had breast cancer with best change in target lesion size of 0%.

[d]Full report not available (these patients were included in denominators for calculation of co-occurring frequency).

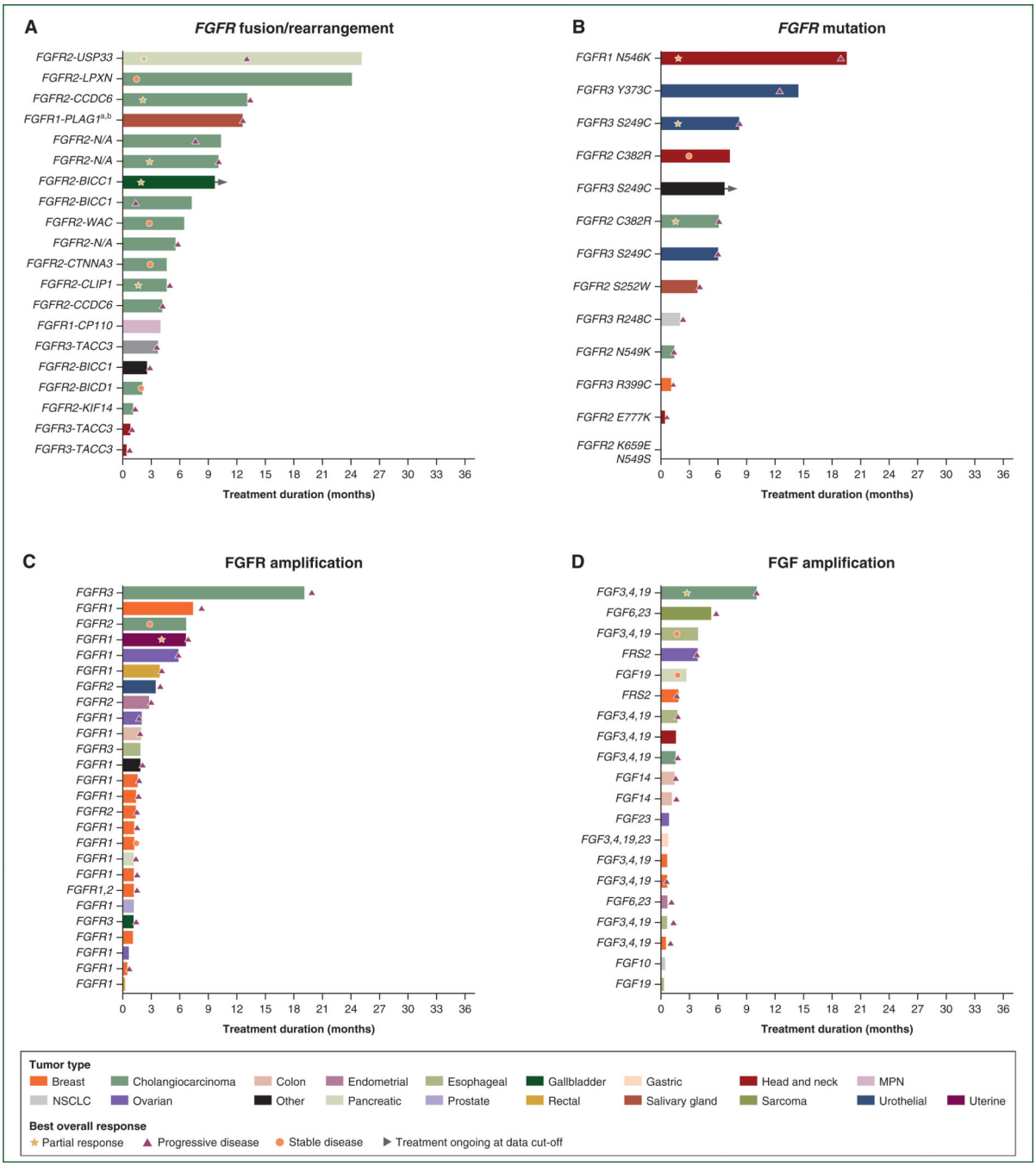

Figure 2. Treatment duration and duration of response for individual patients harboring (A) *FGFR* fusions or rearrangements, (B) *FGFR* mutations, (C) *FGFR* amplifications, and (D) *FGF* amplifications.

Corresponding best overall responses per RECIST v1.1 are also shown.

FGF, fibroblast growth factor; *FGFR*, fibroblast growth factor receptor; FISH, fluorescence in situ hybridization; MPN, myeloproliferative neoplasm; NSCLC, non-small-cell lung cancer; RECIST, per Response Evaluation Criteria in Solid Tumors.

[a]This patient had salivary gland cancer harboring both *FGFR1-PALG1* fusion and *FGFR2* p.C382R mutation and was grouped under *FGFR* fusion/rearrangements owing to perceived importance.

[b]FISH assay.

Table 1.

Demographic and clinical characteristics

Characteristic	ID (*n* = 70)	CD (*n* = 58)	All treated patients (*N* = 128)
Age, median (range), years	57.5 (21–77)	61 (21–83)	59 (21–83)
≥65 years, *n* (%)	18 (25.7)	23 (39.7)	41 (32.0)
Female, *n* (%)	42 (60.0)	36 (62.1)	78 (60.9)
Race, *n* (%)			
White	60 (85.7)	54 (93.1)	114 (89.1)
Black	9 (12.9)	0	9 (7.0)
Asian	0	3 (5.2)	3 (2.3)
Other	1 (1.4)	1 (1.7)	2 (1.6)
ECOG PS, *n* (%)			
0	16 (22.9)	9 (15.5)	25 (19.5)
1	54 (77.1)	47 (81.0)	101 (78.9)
≥2	0	2 (3.4)	2 (1.6)
Number of prior therapies, *n* (%)			
0	3 (4.3)	1 (1.7)	4 (3.1)
1	5 (7.1)	6 (10.3)	11 (8.6)
2	12 (17.1)	3 (5.2)	15 (11.7)
≥3	50 (71.4)	48 (82.8)	98 (76.6)
Tumor type, *n* (%)			
Cholangiocarcinoma	11 (15.7)	10 (17.2)	21 (16.4)
Breast cancer	12 (17.1)	6 (10.3)	18 (14.1)
Colon cancer	5 (7.1)	5 (8.6)	10 (7.8)
Non-small-cell lung cancer	4 (5.7)	6 (10.3)	10 (7.8)
Head and neck cancer	5 (7.1)	4 (6.9)	9 (7.0)
Esophageal cancer	5 (7.1)	2 (3.4)	7 (5.5)
Ovarian cancer	4 (5.7)	3 (5.2)	7 (5.5)
Urothelial tract/bladder cancer	1 (1.4)	5 (8.6)	6 (4.7)
Rectal cancer	4 (5.7)	1 (1.7)	5 (3.9)
Pancreatic cancer	2 (2.9)	2 (3.4)	4 (3.1)

Characteristic	ID (*n* = 70)	CD (*n* = 58)	All treated patients (*N* = 128)
Other	17 (24.3)	14 (24.1)	31 (24.2)

Data represent patients who had received at least one dose of pemigatinib.

CD, continuous dosing; ECOG PS, Eastern Cooperative Oncology Group performance status; ID, intermittent dosing.

Table 2.

Most common TEAEs and clinically notable TEAEs

Grade	ID								CD						All treated patients (*N* = 128)	
	1, 2, 4, or 6 mg (*n* = 7)		9 or 13.5 mg (*n* = 57)		20 mg (*n* = 6)		All ID (*n* = 70)		9 or 13.5 mg (*n* = 43)		20 mg (*n* = 15)		All CD (*n* = 58)			
	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3
TEAEs (preferred term) in ≥15% of all patients,[a] *n* (%)																
Hyperphosphatemia	1 (14.3)	0	43 (75.4)	1 (1.8)	4 (66.7)	0	48 (68.6)	1 (1.4)	35 (81.4)	2 (4.7)	13 (86.7)	0	48 (82.8)	2 (3.4)	96 (75.0)	3 (2.3)
Fatigue	2 (28.6)	0	23 (40.4)	3 (5.3)	2 (33.3)	1 (16.7)	27 (38.6)	4 (5.7)	18 (41.9)	6 (14.0)	5 (33.3)	3 (20.0)	23 (39.7)	9 (15.5)	50 (39.1)	13 (10.2)
Dry mouth	1 (14.3)	0	20 (35.1)	0	2 (33.3)	0	23 (32.9)	0	18 (41.9)	0	8 (53.3)	0	26 (44.8)	0	49 (38.3)	0
Stomatitis	0	0	13 (22.8)	1 (1.8)	3 (50.0)	0	16 (22.9)	1 (1.4)	21 (48.8)	8 (18.6)	7 (46.7)	2 (13.3)	28 (48.3)	10 (17.2)	44 (34.4)	11 (8.6)
Diarrhea	1 (14.3)	0	13 (22.8)	0	2 (33.3)	0	16 (22.9)	0	16 (37.2)	0	9 (60.0)	2 (13.3)	25 (43.1)	2 (3.4)	41 (32.0)	2 (1.6)
Alopecia	0	0	18 (31.6)	0	1 (16.7)	0	19 (27.1)	0	16 (37.2)	0	5 (33.3)	0	21 (36.2)	0	40 (31.3)	0
Constipation	0	0	16 (28.1)	1 (1.8)	2 (33.3)	0	18 (25.7)	1 (1.4)	15 (34.9)	0	4 (26.7)	1 (6.7)	19 (32.8)	1 (1.7)	37 (28.9)	2 (1.6)
Nausea	2 (28.6)	0	9 (15.8)	0	2 (33.3)	0	13 (18.6)	0	19 (44.2)	0	5 (33.3)	1 (6.7)	24 (41.4)	1 (1.7)	37 (28.9)	1 (0.8)
Dysgeusia	1 (14.3)	0	10 (17.5)	0	2 (33.3)	0	13 (18.6)	0	15 (34.9)	0	6 (40.0)	0	21 (36.2)	0	34 (26.6)	0
Decreased appetite	2 (28.6)	0	13 (22.8)	0	1 (16.7)	0	16 (22.9)	0	11 (25.6)	0	5 (33.3)	1 (6.7)	16 (27.6)	1 (1.7)	32 (25.0)	1 (0.8)
Anemia	1 (14.3)	0	12 (21.1)	2 (3.5)	2 (33.3)	0	15 (21.4)	2 (2.9)	10 (23.3)	3 (7.0)	5 (33.3)	4 (26.7)	15 (25.9)	7 (12.1)	30 (23.4)	9 (7.0)
Vomiting	1 (14.3)	0	9 (15.8)	1 (1.8)	1 (16.7)	0	11 (15.7)	1 (1.4)	12 (27.9)	0	4 (26.7)	1 (6.7)	16 (27.6)	1 (1.7)	27 (21.1)	2 (1.6)
Dry eye	0	0	8 (14.0)	0	1 (16.7)	0	9 (12.9)	0	13 (30.2)	1 (2.3)	4 (26.7)	0	17 (29.3)	1 (1.7)	26 (20.3)	1 (0.8)
Abdominal pain	0	0	12 (21.1)	2 (3.5)	1 (16.7)	0	13 (18.6)	2 (2.9)	8 (18.6)	1 (2.3)	3 (20.0)	1 (6.7)	11 (19.0)	2 (3.4)	24 (18.8)	4 (3.1)

Grade	ID								CD						All treated patients (N = 128)	
	1, 2, 4, or 6 mg (n = 7)		9 or 13.5 mg (n = 57)		20 mg (n = 6)		All ID (n = 70)		9 or 13.5 mg (n = 43)		20 mg (n = 15)		All CD (n = 58)			
	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3
AST increased	1 (14.3)	1 (14.3)	8 (14.0)	1 (1.8)	0	0	9 (12.9)	2 (2.9)	11 (25.6)	3 (7.0)	3 (20.0)	0	14 (24.1)	3 (5.2)	23 (18.0)	5 (3.9)
Hypercalcemia	1 (14.3)	1 (14.3)	6 (10.5)	0	0	0	7 (10.0)	1 (1.4)	10 (23.3)	0	4 (26.7)	1 (6.7)	14 (24.1)	1 (1.7)	21 (16.4)	2 (1.6)
ALT increased	1 (14.3)	1 (14.3)	5 (8.8)	0	0	0	6 (8.6)	1 (1.4)	12 (27.9)	3 (7.0)	2 (13.3)	0	14 (24.1)	3 (5.2)	20 (15.6)	4 (3.1)
Dehydration	2 (28.6)	0	7 (12.3)	0	1 (16.7)	0	10 (14.3)	0	6 (14.0)	1 (2.3)	4 (26.7)	0	10 (17.2)	1 (1.7)	20 (15.6)	1 (0.8)
Hypophosphatemia	0	0	12 (21.1)	4 (7.0)	1 (16.7)	0	13 (18.6)	4 (5.7)	5 (11.6)	1 (2.3)	2 (13.3)	2 (13.3)	7 (12.1)	3 (5.2)	20 (15.6)	7 (5.5)
Pain in extremity	1 (14.3)	0	5 (8.8)	0	1 (16.7)	0	7 (10.0)	0	10 (23.3)	2 (4.7)	3 (20.0)	0	13 (22.4)	2 (3.4)	20 (15.6)	2 (1.6)
Clinically notable TEAEs (category),[b] n (%)																
Hyperphosphatemia	1 (14.3)	0	43 (75.4)	1 (1.8)	4 (66.7)	0	48 (68.6)	1 (1.4)	35 (81.4)	2 (4.7)	13 (86.7)	0	48 (82.8)	2 (3.4)	96 (75.0)	3 (2.3)
Nail toxicity	0	0	12 (21.1)	1 (1.8)	3 (50.0)	0	15 (21.4)	1 (1.4)	20 (46.5)	2 (4.7)	6 (40.0)	1 (6.7)	26 (44.8)	3 (5.2)	41 (32.0)	4 (3.1)
Dry eye	0	0	9 (15.8)	0	2 (33.3)	0	11 (15.7)	0	15 (34.9)	1 (2.3)	4 (26.7)	0	19 (32.8)	1 (1.7)	30 (23.4)	1 (0.8)
Vision blurred	2 (28.6)	0	7 (12.3)	0	3 (50.0)	0	12 (17.1)	0	6 (14.0)	1 (2.3)	3 (20.0)	1 (6.7)	9 (15.5)	2 (3.4)	21 (16.4)	2 (1.6)
Hypophosphatemia	0	0	12 (21.1)	4 (7.0)	1 (16.7)	0	13 (18.6)	4 (5.7)	5 (11.6)	1 (2.3)	2 (13.3)	2 (13.3)	7 (12.1)	3 (5.2)	20 (15.6)	7 (5.5)
Eyelash changes	0	0	7 (12.3)	0	0	0	7 (10.0)	0	8 (18.6)	1 (2.3)	2 (13.3)	0	10 (17.2)	1 (1.7)	17 (13.3)	1 (0.8)
Vitreous detachment	0	0	0	0	0	0	0	0	2 (4.7)	0	0	0	2 (3.4)	0	2 (1.6)	0
Serous retinal detachment	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CD, continuous dosing; ID, intermittent dosing; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

[a] TEAEs are ordered by decreasing frequency in all treated patients.

[b] Relevant MedDRA preferred terms combined (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.02.001)

Table 3.

Summary of BOR

	***FGF/FGFR* alterations**							**Total (*N* = 128)**
	FGFR RE (*n* = 20)	**FGFR MUT (*n* = 13)**	**FGF AMP (*n* = 20)**	**FGFR AMP (*n* = 26)**	**Positive (*n* = 79)**	**Negative (*n* = 17)**	**Unknown (*n* = 32)**	
BOR, *n* (%)								
CR	0	0	0	0	0	0	0	0
PR	5 (25.0)	3 (23.1)	1 (5.0)	1 (3.8)	10 (12.7)	1 (5.9)	1 (3.1)	12 (9.4)
SD	10 (50.0)	3 (23.1)	4 (20.0)	7 (26.9)	24 (30.4)	6 (35.3)	10 (31.3)	40 (31.3)
PD	4 (20.0)	5 (38.5)	9 (45.0)	13 (50.0)	31 (39.2)	4 (23.5)	14 (43.8)	49 (38.3)
NE	0	0	1 (5.0)	2 (7.7)	3 (3.8)	1 (5.9)	0	4 (3.1)
NA	0	0	0	1 (3.8)	1 (1.3)	0	0	1 (0.8)
Missing	1 (5.0)	2 (15.4)	5 (25.0)	2 (7.7)	10 (12.7)	5 (29.4)	7 (21.9)	22 (17.2)
Best ORR, *n* (%) (95% CI)	5 (25.0) (8.7–49.1)	3 (23.1) (5.0–53.8)	1 (5.0) (0.1–24.9)	1 (3.8) (0.1–19.6)	10 (12.7) (6.2–22.0)	1 (5.9) (0.1–28.7)	1 (3.1) (0.1–16.2)	12 (9.4) (4.9–15.8)

AMP, amplification; BOR, best overall response; CI, confidence interval; CR, complete response; MUT, mutation; NA, not assessed; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RE, rearrangement; SD, stable disease.