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ORIGINAL ARTICLE

Pemigatinib for metastatic or surgically unresectable urothelial carcinoma with *FGF/FGFR* genomic alterations: final results from FIGHT-201

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Background: Fibroblast growth factor receptor 3 (*FGFR3*) alterations are oncogenic drivers of urothelial carcinoma (UC). Pemigatinib is a selective, oral inhibitor of FGFR1-3 with antitumor activity. We report the efficacy and safety of pemigatinib in the open-label, single-arm, phase II study of previously treated, unresectable or metastatic UC with *FGFR3* alterations (FIGHT-201; NCT02872714).

Patients and methods: Patients ≥18 years old with *FGFR3* mutations or fusions/rearrangements (cohort A) and other *FGF/FGFR* alterations (cohort B) were included. Patients received pemigatinib 13.5 mg once daily continuously (CD) or intermittently (ID) until disease progression or unacceptable toxicity. The primary endpoint was centrally confirmed objective response rate (ORR) as per RECIST v1.1 in cohort A-CD. Secondary endpoints included ORR in cohorts A-ID and B, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

Results: Overall, 260 patients were enrolled and treated (A-CD, $n = 101$; A-ID, $n = 103$; B, $n = 44$; unconfirmed *FGF/FGFR* status, $n = 12$). All discontinued treatment, most commonly due to progressive disease (68.5%). ORR [95% confidence interval (CI)] in cohorts A-CD and A-ID was 17.8% (10.9% to 26.7%) and 23.3% (15.5% to 32.7%), respectively. Among patients with the most common *FGFR3* mutation (S249C; $n = 107$), ORR was similar between cohorts (A-CD, 23.9%; A-ID, 24.6%). In cohorts A-CD/A-ID, median (95% CI) DOR was 6.2 (4.1-8.3)/6.2 (4.6-8.0) months, PFS was 4.0 (3.5-4.2)/4.3 (3.9-6.1) months, and OS was 6.8 (5.3-9.1)/8.9 (7.5-15.2) months. Pemigatinib had limited clinical activity among patients in cohort B. Of 36 patients with samples available at progression, 6 patients had 8 acquired *FGFR3* secondary resistance mutations (V555M/L, $n = 3$; V553M, $n = 1$; N540K/S, $n = 2$; M528I, $n = 2$). The most common treatment-emergent adverse events overall were diarrhea (44.6%) and alopecia, stomatitis, and hyperphosphatemia (42.7% each).

Conclusions: Pemigatinib was generally well tolerated and demonstrated clinical activity in previously treated, unresectable or metastatic UC with *FGFR3* mutations or fusions/rearrangements.

Key words: metastatic urothelial carcinoma, precision medicine, FGFR, pemigatinib, targeted therapy, resistance

INTRODUCTION

First-line standard-of-care treatment of urothelial carcinoma (UC) is platinum-based chemotherapy followed by avelumab [anti-programmed death-ligand 1 (PD-L1) antibody] maintenance therapy in patients whose disease did not progress on chemotherapy; checkpoint inhibitors (CPIs) may also be indicated as first-line therapy for patients ineligible for platinum.[1-3] Available therapies in pretreated patients include vinflunine or taxane chemotherapy, CPIs, enfortumab

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vedotin, sacituzumab govitecan (in the United States), and targeted therapies.[1-3] For patients with disease progression on first-line therapy, tumor molecular profiling provides key information to guide the second-line treatment approach.[1]

Genomic and transcriptomic profiling of metastatic UC (mUC) tumors has revealed a highly heterogenous disease with high mutational burden[4] and distinct tumor subtypes with molecular features associated with differential responses to therapy.[5] Fibroblast growth factor receptor 3 (*FGFR3*) alterations have been identified as oncogenic drivers of UC.[6] *FGFR3* short variants were detected in 13.6% and 13.7% of bladder and urinary tract cancers, respectively, and *FGFR3* rearrangements occurred in 2.7% and 2.2%.[7] In the PROOF 302 study, 30% of patients with upper tract UC and 13% of patients with muscle-invasive bladder cancer had *FGFR3* alterations.[8] Moreover, tumors classified as luminal-a and luminal-b subtypes tend to exhibit high *FGFR3* expression and are enriched in *FGFR3* alterations versus other subtypes.[5] The FGF/FGFR signaling pathway is involved in many cellular processes, including proliferation and survival.[9] *FGFR3* mutations and fusions lead to ligand-independent FGFR3 activation, promoting pathway dysregulation and, consequently, tumor development.[6,9]

The pan-FGFR inhibitor erdafitinib was approved by the US Food and Drug Administration in 2019 for patients with locally advanced UC or mUC with susceptible *FGFR3* or *FGFR2* alterations with disease progression on $\geq$1 line of prior treatment, including platinum-containing chemotherapy.[10] The investigator-assessed objective response rate (ORR) in the BLC2001 trial [95% confidence interval (CI)] was 40% (30% to 49%).[11] Median (95% CI) progression-free survival (PFS) was 5.5 (4.3-6.0) months, and median (95% CI) overall survival (OS) was 11.3 (9.7-15.2) months.[11] Other FGFR inhibitors had lower ORR in UC.[12]

Pemigatinib is an oral, potent, selective FGFR1-3 inhibitor approved for previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with *FGFR2* rearrangements,[13,14] with antitumor activity in other malignant solid tumors with *FGFR* alterations.[15] Building on initial findings,[16] here we report the efficacy and safety of pemigatinib in patients with previously treated or platinum-ineligible, surgically unresectable UC or mUC in the open-label, single-arm, phase II FIGHT-201 study (NCT02872714).

PATIENTS AND METHODS

Study design

FIGHT-201 was an open-label, single-arm, multicenter, phase II study conducted at 73 academic or community-based sites across 11 countries (United States, France, Italy, Spain, Israel, Belgium, UK, Germany, Japan, Denmark, and the Netherlands). Patients were assigned to one of two cohorts based on tumor *FGF*/*FGFR* alteration status. Cohort A consisted of *FGFR3* mutations or fusions/rearrangements. Cohort B included other *FGF*/*FGFR* alterations, such as *FGF* or *FGFR* amplifications and *FGFR* variants of unknown significance. A nonexclusive list of previously reported *FGF*/*FGFR* alterations eligible for enrollment in FIGHT-201 is included in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.10.794. Enrollment and initial cohort assignment were permitted based on genomic testing results from a local laboratory. Final cohort assignment for statistical analyses was based on centrally confirmed sequencing results using the Foundation Medicine clinical trial assay (FoundationOne®, Foundation Medicine, Cambridge, MA).

The study was carried out in accordance with the International Council for Harmonisation Good Clinical Practice, the principles embodied by the Declaration of Helsinki, and local regulatory requirements. The study protocol and all amendments were reviewed and approved by the institutional review board or independent ethics committee of each site before enrollment of patients. All patients provided written informed consent before screening.

Patients

Eligible patients were $\geq$18 years old with histologically or cytologically confirmed metastatic or surgically unresectable UC, life expectancy $\geq$12 weeks, and Eastern Cooperative Oncology Group performance status $\leq$2. Patients were required to have radiographically measurable disease as per RECIST v1.1, documentation of *FGF*/*FGFR* alteration status, and disease progression after $\geq$1 line of prior systemic therapy or ineligibility to receive platinum-based chemotherapy. Key exclusion criteria are listed in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2023.10.794.

Treatment

Patients self-administered pemigatinib on 21-day cycles at a starting oral dose of 13.5 mg once daily. Cohort A was divided into two dosing schedules: continuous dosing (CD) and intermittent dosing (ID; 2 weeks on/1 week off). Cohort A-ID completed enrollment before patients began enrolling in cohort A-CD. The primary objective and associated endpoints were reassigned to cohort A-CD, and efficacy endpoints in cohort A-ID became secondary endpoints due to emerging evidence that the CD regimen might offer improved responses. All patients in cohort B followed the ID schedule. Patients' dose could be escalated to 18 mg if their serum phosphate concentrations were $\leq$5.5 mg/dl, they had received pemigatinib for $\geq$1 cycle, were treatment compliant, and had no ongoing grade $\geq$2 treatment-related treatment-emergent adverse events (TEAEs). Patients continued treatment until documented radiologic disease progression, unacceptable toxicity, withdrawal of consent, or physician decision.

Endpoints and assessments

The primary endpoint was the ORR in cohort A-CD as assessed by an independent review committee (IRC). The ORR was defined as the percentage of patients who achieved complete or partial response (CR/PR) based on RECIST v1.1. Disease was assessed by computed

tomography or magnetic resonance imaging every 9 weeks for all cohorts. Patients who discontinued study treatment for reasons other than disease progression were assessed every 9 weeks during follow-up.

Secondary endpoints included IRC-confirmed ORR in cohorts A-ID and B, and for all cohorts, duration of response [DOR; time from the date of CR or PR until progressive disease (PD) or death], PFS (time from first dose to PD or death), and OS (time from first dose to death due to any cause).

Safety and tolerability were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 at screening, during treatment, at end of treatment, and during follow-up.

Plasma samples for mutational analysis of circulating tumor DNA (ctDNA) were collected at baseline and then repeatedly until end of treatment. Analysis of ctDNA for emergence of resistance mutations at end of treatment was conducted using the TruSight Oncology 500 Platform (Illumina, San Diego, CA).

Statistical analyses

Assuming an ORR of 35% for pemigatinib and 10% of patients lost to follow-up, a sample size of 100 patients each in cohorts A-CD and A-ID was calculated to provide a 95% CI with lower limit >25%. Forty patients were planned for cohort B to provide >80% probability of observing ≥6 responders, assuming an ORR of 20%. As per the prespecified statistical plan, 95% CIs were estimated using the Clopper—Pearson method for all ORR analyses. PFS, DOR, and OS were assessed using the Kaplan—Meier method, with 95% CI calculated using the Brookmeyer and Crowley method with log-log transformation. *Post hoc* analyses of ORR in subgroups based on receipt of prior immunotherapy and presence of liver metastases were carried out.

The efficacy population included all enrolled patients with centrally confirmed *FGF*/*FGFR* alteration status who received ≥1 dose of pemigatinib. The safety population included all enrolled patients who received ≥1 dose of pemigatinib.

RESULTS

Patients

From 12 January 2017 to 1 February 2022, tissues from 1834 patients were screened at baseline using Foundation Medicine Inc. testing. Of these, 324 (17.7%) had a total of 385 *FGFR3* activating gene alterations considered to be known/likely pathogenic: 61 (3.3%) fusions/rearrangements and 324 (17.7%) single nucleotide variants. Of these, 263 patients were enrolled in FIGHT-201, including 101 in cohort A-CD (*FGFR3* mutations or fusions/rearrangements), 103 in cohort A-ID, and 44 in cohort B (other *FGF*/*FGFR* alterations). Twelve patients (ID, $n = 9$; CD, $n = 3$) were excluded from efficacy evaluations because their *FGF/FGFR* status could not be centrally confirmed. Of enrolled patients, three patients did not receive pemigatinib and were therefore excluded from efficacy and safety evaluations (Figure 1).

The most frequent *FGFR3* alterations in cohort A were S249C mutations ($n = 107$, 52.5%), Y373C mutations ($n = 34$, 16.7%), and *FGFR3* fusions ($n = 28$, 13.7%). In cohort B, *FGF19* amplifications ($n = 22$, 50.0%), *FGF10* amplifications ($n = 9$, 20.5%), and *FGFR1* amplifications ($n = 6$, 13.6%) were the most common *FGF/FGFR* alterations (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.10.794). Median age of enrolled patients who received ≥1 dose of pemigatinib was 68.0 years (Table 1, Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.10.794). Most patients were men (73.8%), white (63.1%), and received prior platinum-based chemotherapy (88.1%) or immunotherapy for cancer (53.1%). The bladder was the primary tumor location in 66.5% of patients. Approximately one-third (32.7%) presented with liver metastases.

All patients discontinued treatment (Figure 1). The most common reasons for pemigatinib discontinuation across all cohorts were PD (68.5%) and adverse events (AEs) (10.0%), with PD reported less often as a reason for discontinuation among patients in cohorts A-CD versus A-ID (59.4% versus 72.8%). The median (range) duration of exposure to pemigatinib was 3.4 (0.1-40.5) months overall. Cohort A-ID had the longest pemigatinib exposure [median (range) 3.9 (0.2-26.8) months], followed by cohort A-CD [3.0 (0.2-36.4) months] and cohort B [2.2 (0.1-40.5) months].

Response to treatment

Cohort A. The median (range) follow-up for efficacy-assessable patients in cohorts A-CD and A-ID was 31.7 (22.5-40.2) and 48.9 (35.0-60.2) months, respectively. The ORR (95% CI) in cohort A-CD was 17.8% (10.9% to 26.7%). No patients achieved CR, and 18 (17.8%) had PR, with median (range) time to response of 2.0 (1.4-2.9) months. The ORR (95% CI) in cohort A-ID was 23.3% (15.5% to 32.7%). Of the responders, 4 (3.9%) patients achieved CR and 20 (19.4%) had PR. The median (range) time to response was 2.0 (1.2-6.2) months. Among patients with *FGFR3* point mutations only, ORR (95% CI) was 17.9% (10.2% to 28.3%) in cohort A-CD and 24.2% (15.8% to 34.3%) in cohort A-ID. Approximately one-quarter of patients with the most common point mutation (S249C) responded; ORR (95% CI) was 23.9% (12.6% to 38.8%) in cohort A-CD and 24.6% (14.5% to 37.3%) in cohort A-ID. Among patients with the most frequently occurring *FGFR3* fusion, four (21.1%) and two (22.2%) patients in cohorts A-CD and A-ID, respectively, responded to pemigatinib. ORRs in subgroups with and without prior CPI for cancer and liver metastases are provided in Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.10.794.

The median (95% CI) DOR was 6.2 (4.1-8.3) and 6.2 (4.6-8.0) months in cohorts A-CD and A-ID, respectively (Figure 2A). The disease control rate [DCR; CR + PR + stable disease (SD)] (95% CI) was 58.4% (48.2% to 68.1%) in cohort A-CD and 61.2% (51.1% to 70.6%) in cohort A-ID. The median (range) best percentage change from baseline in sum of target lesion diameters was −20.8% (−100.0% to 87.9%)

Table 1. Patient demographics and baseline clinical characteristics in patients with *FGFR3* mutations or fusions/rearrangements (safety population)

Parameter	*FGFR3* mutations or fusions/rearrangements		Total[a] (*N* = 260)
	Cohort A-CD (*n* = 101)	Cohort A-ID (*n* = 103)	
Age, median (range), years	69.0 (42-92)	66.0 (44-92)	68.0 (38-92)
Sex, *n* (%)			
Women	23 (22.8)	29 (28.2)	68 (26.2)
Men	78 (77.2)	74 (71.8)	192 (73.8)
Race, *n* (%)			
White	63 (62.4)	64 (62.1)	164 (63.1)
Asian	12 (11.9)	1 (1.0)	16 (6.2)
Black/African American	0	0	1 (0.4)
Not reported/other	22 (21.8)	32 (31.1)	69 (26.5)
Missing	4 (4.0)	6 (5.8)	10 (3.8)
ECOG performance status, *n* (%)			
0	35 (34.7)	35 (34.0)	95 (36.5)
1	53 (52.5)	49 (47.6)	128 (49.2)
2	13 (12.9)	19 (18.4)	37 (14.2)
Number of prior systemic therapies,[b] *n* (%)			
0	3 (3.0)	5 (4.9)	9 (3.5)
1	42 (41.6)	42 (40.8)	109 (41.9)
≥2	56 (55.4)	56 (54.4)	142 (54.6)
Prior cancer surgery, *n* (%)	79 (78.2)	82 (79.6)	211 (81.2)
Prior radiation, *n* (%)	37 (36.6)	34 (33.0)	90 (34.6)
Type of prior therapy, *n* (%)			
Platinum compounds	91 (90.1)	86 (83.5)	229 (88.1)
Checkpoint inhibitors	56 (55.4)	53 (51.5)	138 (53.1)
Primary tumor location, *n* (%)			
Bladder	63 (62.4)	71 (68.9)	173 (66.5)
Renal pelvis	23 (22.8)	20 (19.4)	52 (20.0)
Ureter	18 (17.8)	18 (17.5)	42 (16.2)
Other[c]	4 (4.0)	4 (3.9)	11 (4.2)
Visceral metastasis, *n* (%)	70 (69.3)	74 (71.8)	181 (69.6)
Liver metastasis, *n* (%)	32 (31.7)	34 (33.0)	85 (32.7)

CD, continuous dose; ECOG, Eastern Cooperative Oncology Group; FGFR, fibroblast growth factor receptor; ID, intermittent dose; UC, urothelial carcinoma.
[a]Includes patients from cohort B and undetermined *FGF/FGFR* status presented in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.10.794.
[b]Defined as any oral or intravenous systemic therapy with a purpose of treatment defined as 'first line, metastatic/advanced, or palliative'. Any additional systemic therapy reported as 'adjuvant, neoadjuvant, maintenance' but administered within 12 months after the patient received systemic therapy was also counted as the prior systemic therapy for metastatic/advanced disease. If there was a 6-month gap between the same systemic therapies, these were counted as two separate prior lines of therapy.
[c]Other UC locations included pyelum left kidney; right upper pole renal; ureter and bladder; upper tract; diffusely metastatic disease of unknown primary site involving lymph nodes in chest and abdomen; bladder and other locations (muscularis propria, metastatic, and multiple lung metastases); and ureter and other locations (left and right distal ureter, kidney, and prostate/seminal vesicles).

in cohort A-CD (*n* = 86, 85.1%) and −25.0% (−100.0% to 75.0%) in cohort A-ID (*n* = 97, 94.2%; Figure 3).

Cohort B. The median (range) follow-up for efficacy-assessable patients in cohort B was 52.2 (30.4-60.1) months. The ORR (95% CI) was 6.8% (1.4% to 18.7%). All three responding patients achieved a PR, with median (range) time to response of 2.1 (2.1-4.1) months. The *FGF/FGFR* alterations confirmed in the responding patients were *FGFR2* rearrangement and *FGF3, FGF4, and FGF19* amplifications (*n* = 1); *FGF4* and *FGF19* amplifications (*n* = 1); and *FGF10* amplification (*n* = 1). The DCR (95% CI) was 27.3% (15.0% to 42.8%). The median (range) best percentage change from baseline in the sum of target lesion diameters was 6.7% (−73.0% to 65.0%) in cohort B (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.10.794).

Progression-free survival and overall survival

The median (95% CI) PFS was similar in cohorts A-CD [4.0 (3.5-4.2) months] and A-ID [4.3 (3.9-6.1) months; Figure 2B]. Kaplan–Meier estimates of PFS at 12 months were 4.0% and 10.0% for cohorts A-CD and A-ID, respectively. Median PFS in cohort B was half that in cohort A [median (95% CI) 2.0 (1.9-2.2) months]. Kaplan–Meier estimate of PFS at 12 months was 10.0% in cohort B (Supplementary Figure S3A, available at https://doi.org/10.1016/j.annonc.2023.10.794).

As of the data cut-off date, 19 patients (18.8%) were alive and censored for OS in cohort A-CD (Figure 2C). Median (95% CI) OS was 6.8 (5.3-9.1) months, with a Kaplan–Meier estimate (95% CI) of 12-month survival of 34.6% (25.3% to 44.1%). In cohort A-ID, 15 patients (14.6%) were alive and censored for OS. OS was ∼2 months longer in cohort A-ID [median (95% CI) 8.9 (7.5-15.2) months], with a Kaplan–Meier estimate (95% CI) of 12-month survival of 44.7% (34.9% to 53.9%). Five (11.4%) patients in cohort B were alive and censored for OS as of the data cut-off date (Supplementary Figure S3B, available at https://doi.org/10.1016/j.annonc.2023.10.794). Median (95% CI) OS was 9.1 (5.5-17.1) months; the Kaplan–Meier estimate (95% CI) of 12-month survival was 43.1% (28.0% to 57.3%).

Molecular characterization

Among efficacy-assessable patients in cohort A, the most frequently detected co-altered genes were *TERT* (72%) and *CDKN2A* (60%) (Supplementary Figure S4, available at

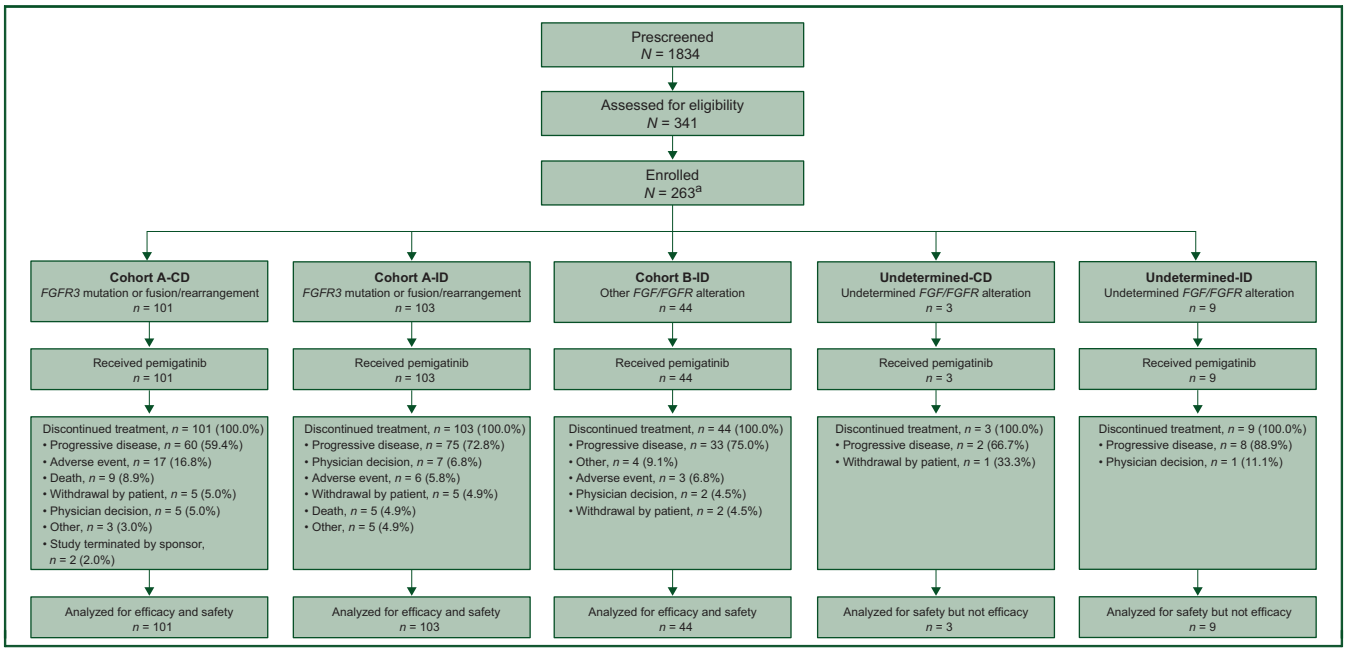

Figure 1. Patient disposition.
Patients were assigned to one of two cohorts based on *FGF/FGFR* alteration status. Cohort A was further divided into CD and ID schedules. Patients whose tumor samples could not be analyzed for *FGF/FGFR* status by the central laboratory (FoundationOne®, Foundation Medicine) were assigned 'Undetermined' and were not included in the efficacy analyses. [a]Three patients were enrolled but did not receive the study drug and were therefore not included in any cohort.
CD, continuous dose; FGF, fibroblast growth factor; FGFR, FGF receptor; ID, intermittent dose.

https://doi.org/10.1016/j.annonc.2023.10.794). Analysis of covariant genes grouped by functional pathways indicated that PI3K pathway (*PIK3CA, PTEN, TSC1*) genes were significantly more frequently altered in nonresponding tumors (corrected $P = 0.043$; Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2023.10.794); only *TSC1,* a tumor suppressor in the mammalian target of rapamycin pathway, was individually identified as a negative predictor of response (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2023.10.794). TP53 pathway co-alterations occurred in 37.1% and 52.2% of patients who did and did not respond to pemigatinib, respectively, but this difference was not statistically significant (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2023.10.794). Of the 36 patients with longitudinal ctDNA samples, 6 patients (PR, $n = 2$; SD, $n = 4$) acquired secondary mutations in *FGFR3* by the end of treatment, reflecting acquired resistance to pemigatinib. The mutations included 'gatekeeper residue' mutations in V555M/L ($n = 3$) and V553M ($n = 1$), and 'molecular brake' mutations in N540K/S ($n = 2$) and M528I ($n = 2$; Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2023.10.794).

Safety

Overall, 259 (99.6%) patients experienced ≥1 TEAE, and 189 (72.7%) had ≥1 grade ≥3 TEAE (Table 2, Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2023.10.794). The most common any-grade TEAEs were diarrhea (44.6%) and alopecia, stomatitis, and hyperphosphatemia (42.7% each); the most common grade ≥3 TEAEs were stomatitis (8.8%), anemia (8.1%), and urinary tract infection (7.3%; Table 3, Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2023.10.794). Sponsor-defined clinically notable TEAEs (CNAEs) are TEAEs for which there is a clinical interest in connection with pemigatinib. CNAEs were collected as Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and aggregated into categories (e.g. 'nail toxicity' includes fungal paronychia, nail bed bleeding, nail discoloration, nail discomfort, nail disorder, nail dystrophy, nail infection, nail ridging, nail toxicity, onychalgia, onycholysis, onychomadesis, onychomycosis, and paronychia). The most frequently reported CNAEs were hyperphosphatemia (53.5%), nail toxicity (40.0%), dry eye (26.9%), serous retinal detachment (13.1%), vision blurred (12.7%), eyelash changes (8.8%), hypophosphatemia (8.5%), and vitreous detachment (2.3%). Pemigatinib discontinuations due to specific CNAEs were attributed to dry eye (grade 2 keratitis, $n = 1$), hyperphosphatemia ($n = 1$), serous retinal detachment (chorioretinopathy, $n = 1$), and vision blurred (visual acuity reduced, $n = 1$).

Treatment-related AEs (TRAEs) occurred in 94.2% of patients, and 41.9% experienced grade ≥3 TRAEs (Supplementary Table S9, available at https://doi.org/10.1016/j.annonc.2023.10.794). Overall, the most common TRAEs were hyperphosphatemia (41.2%), stomatitis (40.4%), and alopecia (38.8%). Stomatitis (8.8%), hyponatremia (4.2%), and fatigue and palmar-plantar erythrodysesthesia syndrome (3.8% each) were the most frequently reported grade ≥3 TRAEs.

Serious AEs (SAEs) occurred in 47.3% of patients overall. The most common SAEs included urinary tract infection (5.8%), general physical health deterioration (4.6%), and

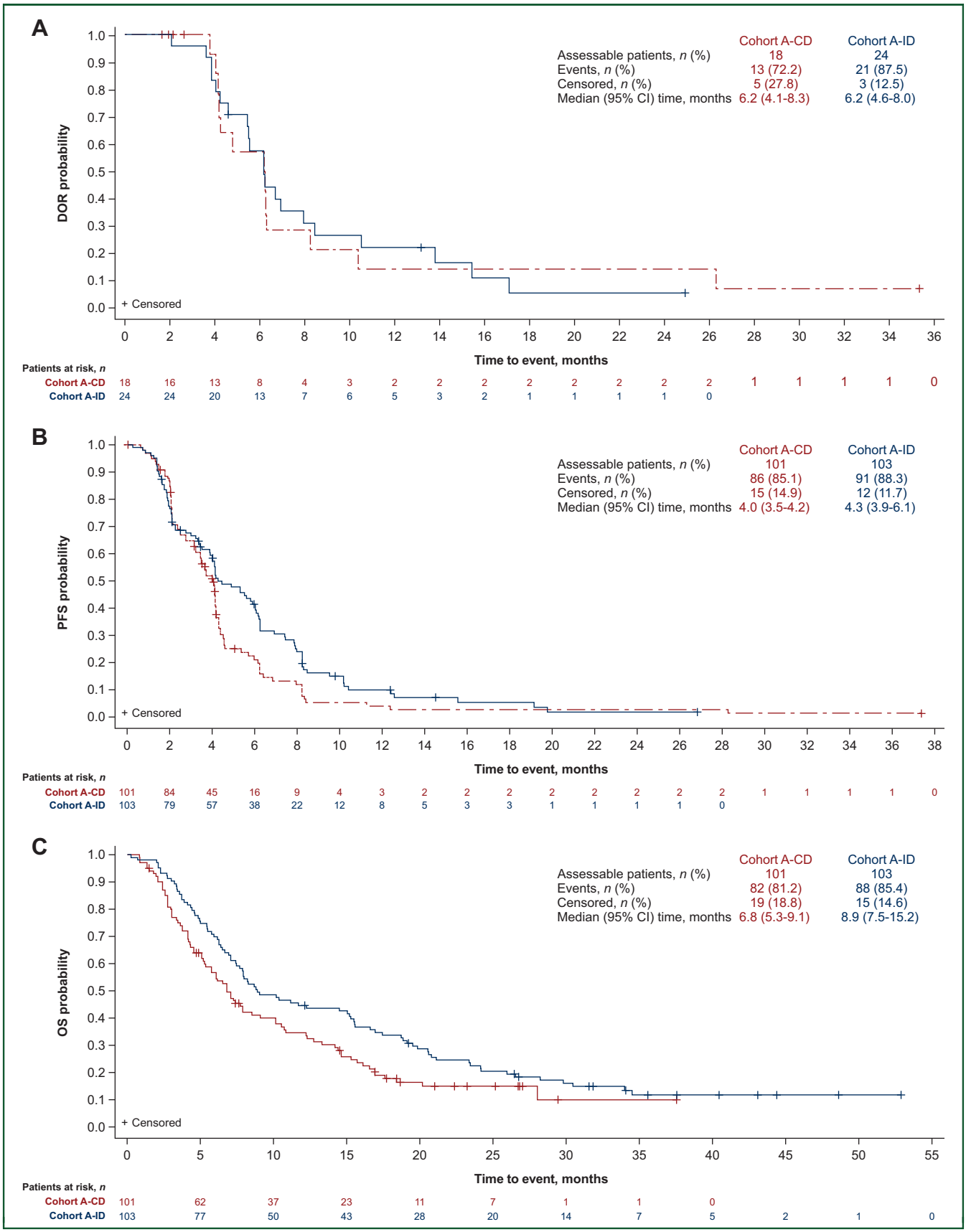

Figure 2. Kaplan–Meier estimates.
(A) DOR based on IRC assessment, (B) PFS based on IRC assessment, and (C) OS in cohort A (FGFR3 mutations or fusions/ rearrangements) stratified by dosing schedule (efficacy-assessable population).
CD, continuous dose; DOR, duration of response; FGFR, fibroblast growth factor receptor; ID, intermittent dose; IRC, independent review committee; OS, overall survival; PFS, progression-free survival.

https://doi.org/10.1016/j.annonc.2023.10.794

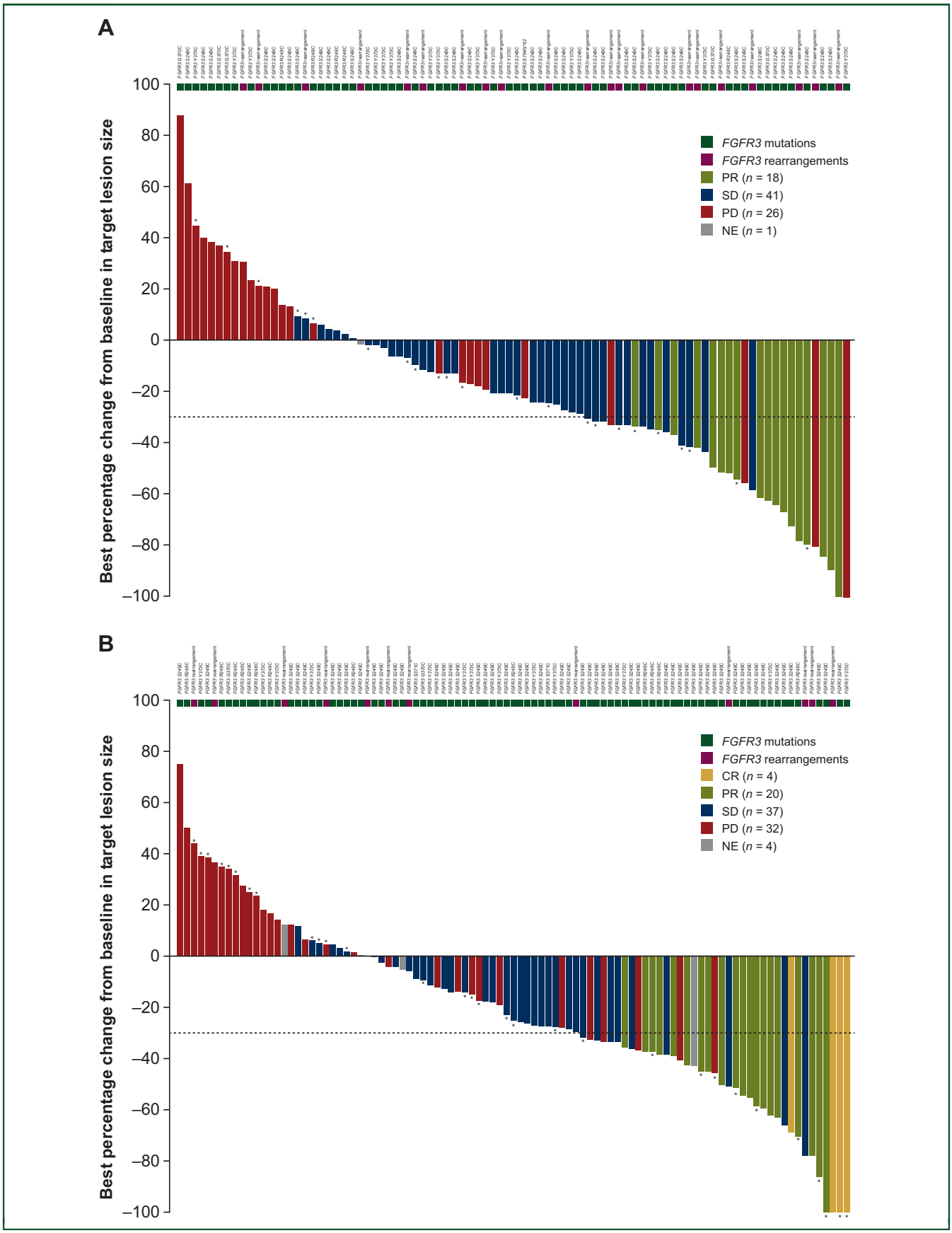

Figure 3. Best percentage change from baseline in target lesion size.
Best percentage change from baseline in target lesion size based on IRC assessment among efficacy-assessable patients in cohort A (*FGFR3* mutations or fusions/rearrangements) stratified by (A) continuous and (B) intermittent dosing schedules. The dashed line indicates one of the criteria for partial response (≥30% decrease in sum of target lesion diameters). Bars are color coded by BOR. *FGF/FGFR* alteration for each patient is shown above response. Asterisks indicate the presence of liver metastases. BOR, best overall response; CR, complete response; FGF, fibroblast growth factor; FGFR, FGF receptor; IRC, independent review committee; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Table 2. Summary of TEAEs overall and in cohort A (*FGFR3* mutations or fusions/rearrangements) (safety population)

Parameter, *n* (%)	*FGFR3* mutations or fusions/rearrangements		Total[a] (*N* = 260)
	Cohort A-CD (*n* = 101)	Cohort A-ID (*n* = 103)	
Patients with a TEAE	100 (99.0)	103 (100.0)	259 (99.6)
Patients with a serious TEAE	48 (47.5)	45 (43.7)	123 (47.3)
Patients with a grade ≥3 TEAE	79 (78.2)	67 (65.0)	189 (72.7)
Patients with a fatal TEAE	16 (15.8)	14 (13.6)	36 (13.8)[b]
Patients with a TEAE leading to pemigatinib			
Discontinuation	18 (17.8)	8 (7.8)	32 (12.3)
Interruption	71 (70.3)	51 (49.5)	143 (55.0)
Dose reduction	31 (30.7)	26 (25.2)	67 (25.8)

CD, continuous dose; FGFR, fibroblast growth factor receptor; ID, intermittent dose; TEAE, treatment-emergent adverse event.
[a]Includes patients from cohort B and undetermined *FGF/FGFR* status presented in Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2023.10.794.
[b]Three fatal TEAEs (cerebrovascular accident, blood creatinine increased, sudden death) were considered by investigators to be related to pemigatinib; however, the sponsor concluded upon further review that there was no reasonable possibility that the TEAEs were related to pemigatinib, as patients had underlying conditions, medical history, and concomitant use of other medication that confounded the assessment of causality.

acute kidney injury (3.5%). Fatal TEAEs were reported in 36 patients (13.8%). Fatal TEAEs that occurred in >1 patient were general physical health deterioration (4.2%), disease progression (1.5%), and sepsis (0.8%). Investigators considered, but did not conclusively link, three (1.2%) fatal TEAEs to be related to pemigatinib. One patient who experienced a fatal cerebrovascular accident also had concurrent cardiovascular conditions, obesity, and hypothyroidism. The patient with a fatal TEAE of increased blood creatinine was also prescribed etoricoxib, which is associated with impaired renal function and increased creatinine. One patient who died suddenly had underlying disease and a medical history of pulmonary embolism. Upon review, the fatal TEAEs were deemed unrelated to pemigatinib.

TEAEs led to pemigatinib dose interruptions, dose reductions, and discontinuations in 55.0%, 25.8%, and 12.3% of patients, respectively. The most frequent TEAEs leading to dose interruptions were palmar-plantar erythrodysesthesia syndrome (7.3%), stomatitis (6.9%), and hyperphosphatemia (5.8%). The most common TEAEs leading to dose reductions were stomatitis (3.8%), fatigue and hyperphosphatemia (2.3% each), and diarrhea and asthenia (1.9% each). The TEAEs leading to pemigatinib discontinuation in >1 patient were general physical health deterioration (1.5%), and anemia, hyponatremia, and disease progression (0.8% each).

Treatment after pemigatinib discontinuation

All patients discontinued pemigatinib, and 104 (40.0%) received treatment after discontinuation. The most common post-pemigatinib therapies were monoclonal antibodies (*n* = 54, 20.8%), including the following administered to ≥2 patients: pembrolizumab (*n* = 30, 11.5%), durvalumab (*n* = 8, 3.1%), atezolizumab (*n* = 6, 2.3%), nivolumab (*n* = 5, 1.9%), and ramucirumab (*n* = 2, 0.8%). Patients also received antibody-drug conjugates including

Table 3. Summary of TEAEs in ≥20% of patients overall and in cohort A (*FGFR3* mutations or fusions/rearrangements) by MedDRA preferred term (safety population)

Events,[a] *n* (%)	*FGFR3* mutations or fusions/rearrangements				Total[b] (*N* = 260)	
	Cohort A-CD (*n* = 101)		Cohort A-ID (*n* = 103)			
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhea	34 (33.7)	4 (4.0)	55 (53.4)	3 (2.9)	116 (44.6)	10 (3.8)
Alopecia	38 (37.6)	0	49 (47.6)	0	111 (42.7)	1 (0.4)
Stomatitis	46 (45.5)	11 (10.9)	48 (46.6)	7 (6.8)	111 (42.7)	23 (8.8)
Hyperphosphatemia	56 (55.4)	0	36 (35.0)	1 (1.0)	111 (42.7)	2 (0.8)
Dry mouth	39 (38.6)	0	33 (32.0)	1 (1.0)	93 (35.8)	1 (0.4)
Constipation	33 (32.7)	0	36 (35.0)	1 (1.0)	88 (33.8)	1 (0.4)
Fatigue	29 (28.7)	3 (3.0)	37 (35.9)	7 (6.8)	86 (33.1)	13 (5.0)
Dysgeusia	31 (30.7)	—	32 (31.1)	—	79 (30.4)	—
Decreased appetite	30 (29.7)	5 (5.0)	33 (32.0)	1 (1.0)	79 (30.4)	9 (3.5)
Asthenia	33 (32.7)	7 (6.9)	28 (27.2)	2 (1.9)	72 (27.7)	12 (4.6)
Nausea	18 (17.8)	0	29 (28.2)	0	64 (24.6)	2 (0.8)
Urinary tract infection	17 (16.8)	8 (7.9)	28 (27.2)	10 (9.7)	56 (21.5)	19 (7.3)
Dry skin	22 (21.8)	1 (1.0)	21 (20.4)	0	55 (21.2)	1 (0.4)
Dry eye	19 (18.8)	1 (1.0)	21 (20.4)	0	52 (20.0)	1 (0.4)

CD, continuous dose; FGFR, fibroblast growth factor receptor; ID, intermittent dose; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; TEAE, treatment-emergent adverse event.
[a]Patients were counted once under each MedDRA PT.
[b]All any-grade TEAEs occurring in ≥20% of the total population are shown.

sacituzumab govitecan ($n = 2$, 0.8%) and enfortumab vedotin ($n = 2$, 0.8%), taxanes ($n = 38$, 14.6%), and platinum compounds ($n = 23$, 8.8%).

DISCUSSION

Consistent with the efficacy of pemigatinib in advanced cholangiocarcinoma with *FGFR2* fusions or rearrangements[14] and other solid tumors with *FGF/FGFR* alterations,[15] this phase II study demonstrated that pemigatinib had antitumor activity in patients with previously treated, unresectable UC or mUC with *FGFR3* mutations or fusions/rearrangements.

The ORR values in this study (17.8% and 23.3% in cohorts A-CD and A-ID, respectively) did not reach the clinically meaningful level of 35% defined in the protocol. Additionally some stabilization of disease was observed (DCR was 58.4% and 61.2% in the A-CD and A-ID cohorts, respectively). In the absence of head-to-head studies, conclusive inferences cannot be made by comparing results across clinical trials. However, ORRs >40% have been observed for the FGFR inhibitor erdafitinib[11] and the antibody-drug conjugate enfortumab vedotin in the post-CPI setting[17] and, although the IRC-confirmed ORR of pemigatinib was lower than the investigator-assessed ORR of erdafitinib (40%) reported for the BLC2001 phase II study, median PFS was similar between the studies (erdafitinib, 5.5 months versus pemigatinib, 4.0 and 4.3 months).[11] The phase III THOR study of erdafitinib versus investigators' choice of chemotherapy in 266 patients with mUC who progressed after one or two prior therapies gave an ORR of 46% for erdafitinib, a median PFS (mPFS) of 5.6 months, and a median OS of 12.1 months.[18] The phase II NORSE study of 87 cisplatin-ineligible patients with first-line mUC gave an ORR for erdafitinib of 44.2% and an mPFS of 5.6 months.[19] The ORR for erdafitinib combined with cetrelimab was 54.5%.[19] The combination of pemigatinib with immunotherapy may be a possibility for future development, given the safety profile of pemigatinib. Potency may not explain the difference in ORR values between pemigatinib and erdafitinib; both drugs inhibit FGFR3 with similar IC_{50} values (1 nM and 3 nM, respectively).[20,21] Notably, the reported FGFR3/FGFR1 potencies are essentially identical for pemigatinib and erdafitinib (both a ratio of 2.5).[20,21] However, the discrepancy in the types of alterations in patients recruited to the pemigatinib and erdafitinib studies may play a role in the differences in ORR. Similar to pemigatinib, ORR to infigratinib, another pan-FGFR antagonist, was 25.6% in patients with platinum-ineligible, advanced UC or mUC; mPFS was 3.8 months.[22] Other agents have provided promising signals in this space in early-phase studies.[23,24] The development of inhibitors with greater FGFR3 selectivity, such as LOXO-435, KIN-3248, and TYRA-300, currently in phase I trials, may afford improvements in therapeutic index.[25-27] Additionally, intravesical delivery may improve response rates to established FGFR inhibitors, such as erdafitinib.[28]

Our study provided some insights into mechanisms of acquired resistance to pemigatinib. Analysis of ctDNA samples at the time of progression for 36 cohort A patients identified 8 *FGFR3* secondary resistance mutations in the FGFR3 kinase domain. These mutations affect known resistance mechanisms, impacting the FGFR3 V555 gatekeeper residue and disrupting the molecular brake of FGFR3 through mutation of N540, suggesting that development of resistance mutations may have contributed to disease progression.[29,30]

Together with genomic data from multiple solid tumors in the Foundation Medicine database,[7] our findings provide some insight on the impact of specific *FGFR3* alterations and co-alterations on tumor response. Notably, among the most prevalent *FGFR3* mutations, ORR to pemigatinib varied. The combined ORRs for cohorts A-CD and A-ID for S249C, R248C, and G370C were 23%, 29%, and 29%, respectively, whereas response among patients with the Y373C alteration was only 9%. Similarly, ORR among tumors with *FGFR3* rearrangements only was 17%, suggesting that pemigatinib may be more effective for specific *FGFR3* mutations like S249C, R248C, and G370C than other *FGFR3* alterations. Analysis of genomic prescreening data found a relatively high rate of *CDKN2A* alterations (60%) and relatively low rates of *TP53* mutations (25%) in cohort A; similar frequencies have been observed in patients with *FGFR3* aberrations in the Foundation Medicine database.[7] In our study, co-alterations in the tumor suppressor *TSC1* were associated with SD and PD. Beyond *TSC1,* co-alterations in a larger set of PI3K pathway genes occurred significantly more often in tumors of patients who did not respond to pemigatinib treatment. Notably, although PFS in patients with *FGFR2*-altered cholangiocarcinoma treated with pemigatinib was previously found to be significantly lower in patients with co-occurring *TP53* alterations versus those without,[31] no significant difference in response rate between patients with and without *TP53* alterations was observed in UC. Our results suggest that combination therapies designed to overcome *FGFR3* resistance mutations or address clinically significant co-alterations may be a viable approach. Although FGFR and PIK3CA co-inhibition in patients with advanced solid tumors with *PIK3CA* alterations failed in an early study, additional data are needed to explore combination therapies as a therapeutic strategy for mUC, particularly in *FGFR3*-altered tumors.[32]

Molecular profiling of mUC tumors is critical to determine appropriate second-line therapies and timely treatment.[1] Historically, clinical outcomes for patients with mUC who receive second-line therapies have been poor,[33] further emphasizing the importance of choosing second-line therapies tailored to the patient. Differential response to the CPIs atezolizumab (anti-PD-L1) and nivolumab (anti-programmed cell death protein 1) following platinum-based chemotherapy in patients with mUC has been observed.[34,35] Luminal papillary subtypes of muscle-invasive mUC tend to be enriched in *FGFR3* alterations.[36] Because responders to atezolizumab treatment were enriched in other luminal and neuroendocrine transcriptomic subtypes

but not the luminal papillary subtype,[36] patients with *FGFR3* alterations may be poor candidates for CPI therapy alone.[37]

No new safety concerns were identified in FIGHT-201. The most common TEAEs overall were diarrhea, alopecia, stomatitis, and hyperphosphatemia. When analyzed by dose regimen, the incidence of diarrhea and alopecia was higher in cohort A-ID compared with A-CD. Hyperphosphatemia was higher in A-CD versus A-ID, whereas stomatitis incidence did not differ by regimen. Rates of dose adjustment due to TEAEs were higher in cohort A-CD versus A-ID (discontinuation, 17.8% versus 7.8%; dose reduction, 30.7% versus 25.2%; treatment interruption, 70.3% versus 49.5%). Both regimens were efficacious and tolerable and can therefore be used with appropriate management of toxicities.

One limitation of this study was the single-arm, open-label design with no comparator. Other possible limitations are selection bias and residual confounding. In this analysis of final data from FIGHT-201, pemigatinib demonstrated clinical activity and manageable AEs in patients with previously treated unresectable UC or mUC and *FGFR3* alterations irrespective of dosing regimen. Nonresponding tumors tended to harbor co-alterations in genes belonging to the PI3K pathway, with co-alterations in *TSC1* negatively predicting response to pemigatinib. These results further highlight the need for molecular testing in patients with UC and emphasize the need to refine the biomarkers best suited for identification of targeted therapies against *FGFR* genomic alterations.

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AN received honoraria from Astellas, AstraZeneca, BMS, Foundation Medicine, Janssen, MSD, and Roche; served as a consultant and/or advisor to AstraZeneca, Basilea Pharmaceutica, Bayer, Bicycle Therapeutics, BMS, Catalym, Clovis Oncology, GlaxoSmithKline, Incyte, Janssen, MSD, Rainier Therapeutics, Roche, and Seattle Genetics/Astellas; received research funding paid to the institution from AstraZeneca, Gilead, Ipsen, and MSD; received payments for travel and accommodations from AstraZeneca, Janssen, MSD, Pfizer, Rainer Therapeutics, and Roche; and reports that his spouse is an employee and shareholder of Bayer. DP received research grants paid to his institution from AstraZeneca, BMS, Merck Sharp & Dohme, Roche, and Seattle Genetics; received honoraria from AstraZeneca, Astellas Pharma, BMS, Ipsen, MSD Oncology, and Pfizer/Astellas; served as a consultant for Astellas Pharma, BMS/Medarex, Merck, MSD Oncology, and Pfizer; and received payments for travel and accommodations from AstraZeneca and Pfizer. RL received honoraria from AstraZeneca, Bayer, BMS, Isotopia, Janssen, MSD, Pfizer, and Roche; served as a consultant and/or advisor for Astellas Medivation, AstraZeneca, Bayer, Immunai, Kamada, NeoPharm, Oncohost, Pfizer, and Sanofi; received travel support from Janssen and Pfizer; and served as a principal investigator on studies from BMS, Eisai, Incyte, Janssen, MSD, and Pfizer. SG received research funding from Acrotech, Astellas, AstraZeneca, BMS, Clovis Oncology, Daiichi Sankyo/Lilly, Five Prime Therapeutics, Hoosier Cancer Research Network, Immunocore, Incyte, LSK BioPharma, MedImmune, Merck, Mirati Therapeutics, Novartis, Pfizer, QED Therapeutics, Rexahn Pharmaceuticals, Seattle Genetics, and Viralytics. AF received honoraria from Astellas, Janssen, Merck, MSD, Pfizer, and Seagen. JGD received researching funding from Astellas, BMS, GSK, Ipsen, Janssen, Pfizer, Roche, and Sanofi and honoraria for serving as a speaker for AstraZeneca, BMS, Janssen, and Roche. MAB has acted as a paid consultant for and/or as a member of the advisory boards of AstraZeneca, Bayer, BMS, Calithera Biosciences, Eisai, EMD Serono, Exelixis, Genomic Health, Janssen, Nektar, Pfizer, Sanofi, and SeaGen and has received grants to his institution from AAA, AstraZeneca, Bayer, BMS, Genentech/Roche, Genome & Company, Incyte, Merck, Nektar, Peloton Therapeutics, Pfizer, SeaGen, Tricon Pharmaceuticals, and Xencor for work carried out as outside of the current study. PRD received grants to institution from Pfizer; received consulting fees for participation on advisory boards from BMS, Ipsen, Merck, and Pfizer; received honoraria for lectures from Bayer; received travel support from Janssen; serves as a substitute board member for the Clinical Trials College, Federal Public Service, Kingdom of Belgium; and holds stock or stock options in Alkermes and Biocartis Group NV. MIM received research grants paid to his institution from Alliance for Clinical Trials in Oncology, Alliance Foundation Trials, ALX Oncology, Arvinas, BMS, Clovis Oncology, G1 Therapeutics, Hoosier Cancer Research Network, Incyte, Loxo, Merck, Mirati Therapeutics, Roche/Genentech, and Seagen; served as a consultant for Loxo/Lilly; owns stock in Gilead Sciences, Merck, and Pfizer; and reports a relationship with Elsevier, Research to Practice, and Medscape. TF received honoraria and payments for travel and accommodations from Astellas; had a consulting or advisory role for AADi Therapeutics, Basilea Pharmaceutica, and Seagen/Astellas; and received research funding paid to the institution from BMS, Roche/Genentech, Seagen, and Trishula. MM served as a consultant and/or advisor to Alfasigma, Amgen, AstraZeneca, BMS, Eli Lilly, GlaxoSmithKline, Incyte, Merck Serono, Merck Sharpe & Dohme, Pierre Fabre, Roche, Sanofi, and Sciclone and owns shares in Epigen Therapeutics and Theravance. AG, XL, and MLV are employees and shareholders of Incyte. YL received honoraria from AstraZeneca, Astellas, BMS, Gilead, Janssen, Merck KGaA, MSD, and Pfizer and received payments for travel and accommodations from Astellas, BMS, Janssen, Merck KGaA, MSD, Pfizer, and Roche.

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