# Efficacy of BGJ398, a Fibroblast Growth Factor Receptor 1–3 Inhibitor, in Patients with Previously Treated Advanced Urothelial Carcinoma with *FGFR3* Alterations

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**ABSTRACT**

BGJ398, a potent and selective pan-FGFR antagonist, was prospectively evaluated in patients with metastatic urothelial carcinoma bearing a diverse array of *FGFR3* alterations. Patients ($N = 67$) who were unable to receive platinum chemotherapy were enrolled. The majority (70.1%) had received two or more prior antineoplastic therapies. BGJ398 was administered orally at 125 mg/day on a 3 weeks on, 1 week off schedule until unacceptable toxicity or progression. The primary endpoint was the response rate. Among 67 patients treated, an overall response rate of 25.4% was observed and an additional 38.8% of patients had disease stabilization, translating to a disease control rate of 64.2%. The most common treatment-emergent toxicities were hyperphosphatemia, elevated creatinine, fatigue, constipation, and decreased appetite. Further examination of BGJ398 in this disease setting is warranted.

**SIGNIFICANCE:** BJG398 is active in patients with alterations in *FGFR3*, resulting in both reductions in tumor volume and stabilization of disease. Our data highlight putative mechanisms of resistance to the agent, which may be useful in following disease status. *Cancer Discov; 8(7); 812–21. ©2018 AACR.*

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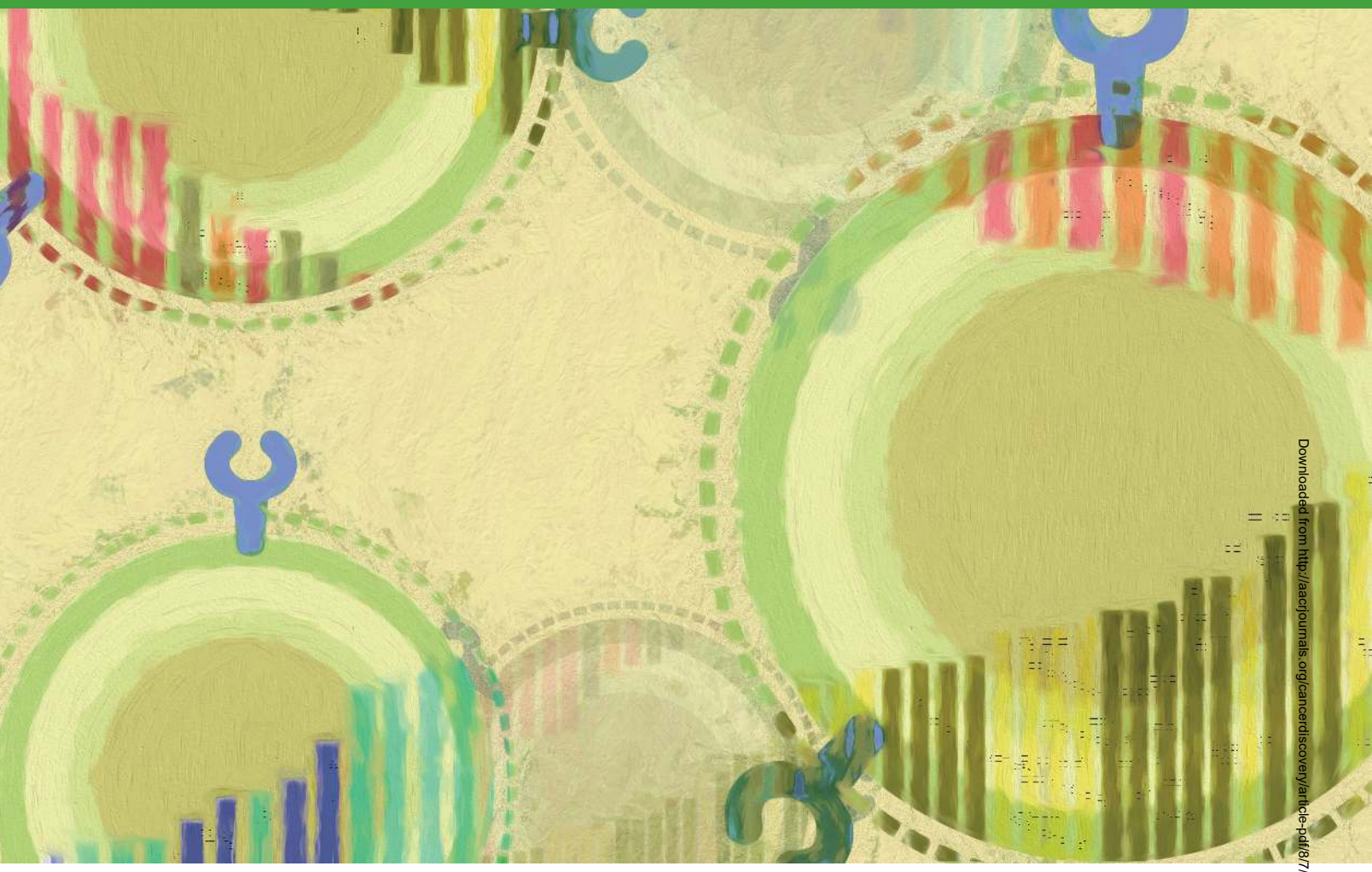



## INTRODUCTION

For several decades, platinum-based chemotherapy has remained the cornerstone of treatment for patients with metastatic urothelial cancer. For cisplatin-eligible patients, median survival has been estimated in the range of 14 to 15 months with cytotoxic therapy (1). Second-line cytotoxic regimens have a limited impact on clinical outcome, with median survival projected at 6 to 9 months and few durable responses (2). More recently, inhibitors of programmed death-1 (PD-1) and its ligand (PD-L1) have supplanted cytotoxic therapies in this setting. Multiple phase Ib/II studies in metastatic urothelial cancer have demonstrated that these agents can elicit durable responses with limited toxicity, and a recent phase III study comparing the PD-1 inhibitor pembrolizumab with chemotherapy (docetaxel, paclitaxel, or vinflunine) showed a survival advantage for pembrolizumab (3–7). Furthermore, anti–PD-L1/PD-1 therapy with atezolizumab or pembrolizumab has recently garnered approval for the treatment of chemotherapy-naïve patients with advanced urothelial cancer who are ineligible for cisplatin (8, 9). Although these therapies represent a critical advance in the treatment of patients with urothelial cancer, only a minority of patients will respond. A recent report suggests that alterations in the gene encoding FGFR3 are enriched in The Cancer Genome Atlas luminal 1 subtype bladder cancers (10). Patients with this subtype have shown lower response rates to atezolizumab and nivolumab in phase II trials, indicating that molecular-driven therapeutic strategies may be applicable to individualize therapy in the future (5, 7).

Although urothelial carcinoma has high rates of somatic alterations, there are no approved targeted agents for this disease. *FGFR3* alterations commonly occur in urothelial carcinoma and act as an oncogenic driver. Although these alterations are more frequent in non–muscle-invasive bladder cancer, they are found in up to 21% of locally advanced or metastatic urothelial tumors (11). BGJ398 is an orally bioavailable, selective, ATP-competitive FGFR1–3 inhibitor with activity against tumor models harboring FGFR alterations (12, 13). In early-phase clinical evaluation, BGJ398 showed a tolerable safety profile and single-agent activity against *FGFR1*-amplified lung cancer, *FGFR3*-mutant bladder/urothelial cancer, and cholangiocarcinoma with *FGFR2* gene fusions (14). In a phase I trial of BGJ398, tumor regression was first noted in 4 of 5 patients with advanced urothelial carcinoma bearing *FGFR3* mutations (15). To examine this phenomenon further, an expansion cohort of patients with *FGFR3*-altered urothelial carcinoma was enrolled and treated with single-agent BGJ398.

## RESULTS

### Patient Characteristics and Disposition

At the data cutoff of January 30, 2017, 67 patients, none previously reported, had been enrolled in the expansion cohort and treated with BGJ398 (Table 1). The median age of the intent-to-treat population was 67 years (range, 39–85 years), and 46 patients (68.7%) were male. A total of 59 patients (88.1%) had received prior antineoplastic therapy that included a platinum-based regimen. Nineteen patients (28.4%) had received one prior antineoplastic therapy, and 47 patients (70.1%) had received two or more prior antineoplastic therapies; 1 patient was treatment naïve. As per study eligibility criteria, all patients had alterations in *FGFR3* as determined by local or central testing (Supplementary Table S1). Foundation Medicine (FM) next-generation sequencing data were available for 53 patients, and analysis using an FM sequencing panel of common genetic alterations found that the most common alterations outside of *FGFR3* were in *TERT* (68%), *CDKN2A* (58%), *CDKN2B* (51%), and *KDM6A* (45%). Other clinically relevant genomic alterations observed were in *PIK3CA* (23%) and *TSC1* (17%; Supplementary Fig. S1).

**Table 1. Baseline patient and disease characteristics**

| Variable, *n* (%) | Participants (*N* = 67) |
|---|---|
| Age group | |
| <65 years | 29 (43.3) |
| ≥65 years | 38 (56.7) |
| Sex | |
| Male | 46 (68.7) |
| Female | 21 (31.3) |
| WHO performance status | |
| 0 | 20 (29.9) |
| 1 | 36 (53.7) |
| 2 | 10 (14.9) |
| Missing | 1 (1.5) |
| Bellmunt criteria[a] | |
| Risk group 0 | 12 (17.9) |
| Risk group 1 | 27 (40.3) |
| Risk group 2 | 25 (37.3) |
| Risk group 3 | 3 (4.5) |
| Visceral disease | |
| Lung | 41 (61.2) |
| Liver | 25 (37.3) |
| Lymph node metastases | |
| Yes | 19 (28.4) |
| No | 46 (68.7) |
| Missing | 2 (3) |
| Bony metastases | |
| Yes | 25 (37.3) |
| No | 40 (59.7) |
| Missing | 2 (3) |
| Prior immunotherapy at last medication | 11 (16.4) |
| *FGFR3* status | |
| Not mutated | 0 |
| Mutated[b] | 67 (100) |
| Exon 7 R248C | 11 (16.4) |
| Exon 7 S249C | 38 (56.7) |
| Exon 10 Y375C | 3 (4.5) |
| Exon 15 K652E/Q | 0 |
| Other[b] | 15 (22.4) |

Abbreviation: WHO, World Health Organization.

[a]Patients who had none of the following risk factors were in risk group 1: 1, hemoglobin level <100 g/L; 2, Eastern Cooperative Oncology Group performance status ≥1; 3, presence of liver metastases. Patients who had one, two, or three risk factors were placed in risk groups 1, 2, or 3, respectively.

[b]Includes 5 patients with *FGFR3–TACC3* fusion, rearrangement.

### Efficacy

Among 67 treated patients, confirmed responses (including complete and partial responses) were observed in 17 patients (25.4%; Fig. 1). Forty-three patients (64.2%) demonstrated disease control (i.e., complete response, partial response, and stable disease). Progressive disease was documented as the best response in only 16 patients (23.9%). Best overall response was unknown in 8 patients (11.9%), either (1) due to clinical progression prior to first follow-up scans or (2) due to lack of appropriate imaging to evaluate response as specified in the protocol. Notably, 1 patient with bony metastatic disease and the primary tumor in the bladder exhibited a complete response to therapy; however, due to a change in imaging modalities between assessments, the RECIST response was reported as unknown. The patient in question had histologically confirmed metastatic disease in a humeral lesion, which had been confirmed by previous biopsy. The patient began therapy with BGJ398 and developed a suspected pathologic fracture at the same location. However, complete resection of the implicated area in the humerus showed no evidence of residual disease. Responses to prior immunotherapy are noted in Supplementary Table S1.

The median progression-free survival was estimated at 3.75 months (95% confidence interval, 3.09–5.39 months) with 51 events (46 progressions and five deaths; Fig. 2A). The median overall survival was estimated at 7.75 months (95% confidence interval, 5.65–11.60 months) with 41 events. The median duration of response for patients with confirmed complete response or partial response was estimated at 5.06 months (95% confidence interval, 3.91–7.36 months), and median duration of stable disease for patients with best overall response SD was estimated at 2 months (95% confidence interval, 1.84–3.45 months).

Figure 2B outlines the duration of therapy in individual patients and highlights the most commonly observed *FGFR3* alterations and overall survival. As depicted, the most frequent alterations were mutations in S249C, followed by R248C. Given the rather heterogeneous array of alterations observed in this cohort, it is challenging to draw any firm conclusions regarding the nature of *FGFR3* alterations and response to BGJ398. Response was also investigated in relation to baseline genetic alterations (Supplementary Fig. S1). No immediate correlations were apparent; however, a larger

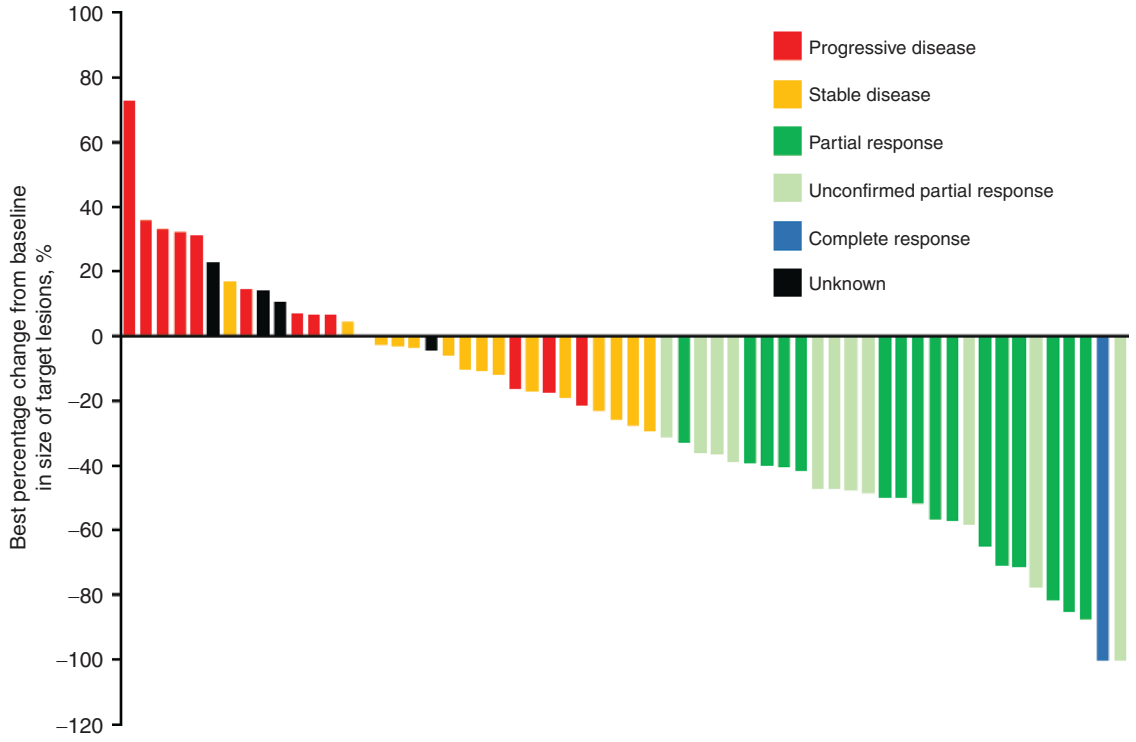


**Figure 1.** Waterfall plot delineating responses to BGJ398 in 60 evaluable patients ($n = 60$). Only patients with baseline and at least one post-baseline assessment of target lesion using the same assessment method are included; 7 patients are not included in this figure.

study population would be required to further explore any potential relationships.

## Safety

Of the 67 patients enrolled, 66 experienced treatment-emergent adverse events (AE) regardless of study drug relationship, with 46 patients (68.7%) developing grade 3/4 toxicities (Table 2). The most frequent AEs (all grades) were hyperphosphatemia (46.3%), elevated creatinine (41.8%), fatigue (37.3%), constipation (37.3%), anemia (35.8%), and decreased appetite (32.8%). The most frequent grade 3/4 AEs were hyperlipasemia (10.4%), fatigue (7.5%), anemia (7.5%), hypophosphatemia (7.5%), and palmar–plantar erythrodysesthesia (7.5%). Among AEs of interest, grade 3/4 hyperphosphatemia

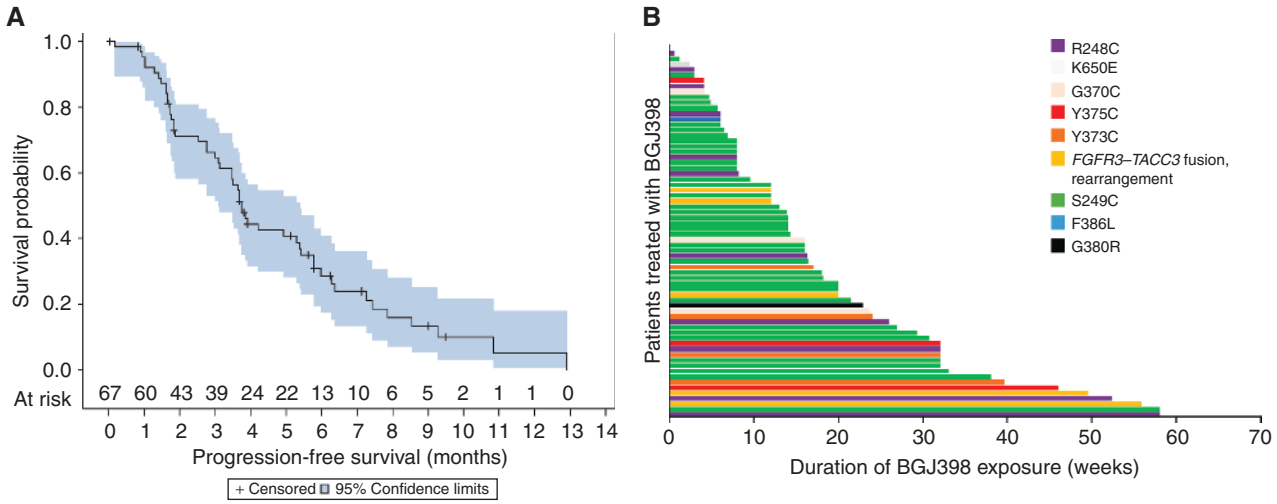


**Figure 2.** **A,** Kaplan–Meier estimate of progression-free survival (PFS). Median PFS was 3.75 months (95% confidence interval, 3.09–5.39 months). **B,** Duration of treatment with BGJ398 and associated *FGFR3* alterations.

**Table 2. AEs regardless of relationship to BGJ398 in patients with metastatic urothelial cancer**

| Treatment-emergent AEs reported in ≥10% of patients, *n* (%)[a] | BGJ398 125 mg/day 3 weeks on/1 week off *N* = 67 | |
|---|---|---|
| | All grades | Grade 3/4 |
| All AEs[b] | 66 (98.5) | 46 (68.7)[c] |
| Hyperphosphatemia | 31 (46.3) | 1 (1.5) |
| Elevated creatinine | 28 (41.8) | 0 |
| Fatigue | 25 (37.3) | 5 (7.5) |
| Constipation | 25 (37.3) | 0 |
| Anemia | 24 (35.8) | 5 (7.5) |
| Decreased appetite | 22 (32.8) | 3 (4.5) |
| Dry mouth | 21 (31.3) | 1 (1.5) |
| Alopecia | 21 (31.3) | 0 |
| Nausea | 19 (28.4) | 3 (4.5) |
| Stomatitis | 17 (25.4) | 2 (3) |
| Dysgeusia | 14 (20.9) | 0 |
| Nail disorder | 14 (20.9) | 0 |
| Vomiting | 13 (19.4) | 3 (4.5) |
| Diarrhea | 13 (19.4) | 2 (3) |
| Abdominal pain | 12 (17.9) | 1 (1.5) |
| Dyspnea | 12 (17.9) | 1 (1.5) |
| Arthralgia | 11 (16.4) | 2 (3) |
| Dry eye | 11 (16.4) | 0 |
| Hyperlipasemia | 10 (14.9) | 7 (10.4) |
| Hematuria | 10 (14.9) | 0 |
| Hyperkalemia | 9 (13.4) | 2 (3) |
| Urinary tract infection | 9 (13.4) | 2 (3) |
| Increased amylase | 9 (13.4) | 1 (1.5) |
| Hypercalcemia | 9 (13.4) | 1 (1.5) |
| Dizziness | 9 (13.4) | 0 |
| Palmar–plantar erythrodysesthesia syndrome | 8 (11.9) | 5 (7.5) |
| Hyponatremia | 8 (11.9) | 4 (6) |
| Dry skin | 8 (11.9) | 0 |
| Peripheral edema | 8 (11.9) | 0 |
| Hypophosphatemia | 7 (10.4) | 5 (7.5) |
| Myalgia | 7 (10.4) | 0 |
| Weight loss | 7 (10.4) | 0 |
| Blurred vision | 7 (10.4) | 0 |

[a]AEs with a frequency ≥10% in all grades occurring during treatment or within 28 days of the last dose. Patients with multiple occurrences of an AE were counted only once in each AE category.

[b]Patients with multiple AEs were counted only once in the "all AEs" row.

[c]21 patients (31.3%) did not experience a grade 3/4 AE.

was observed in only 1 patient (1.5%). Notably, hyperphosphatemia was proactively managed in the study with prophylactic administration and titration of sevelamer, and dose reduction or interruption if hyperphosphatemia did occur. Importantly, no grade 3 or higher ocular toxicities were observed. Hyperphosphatemia, ocular toxicity, and nail disorders, including onycholysis, are manageable and reversible on-target AEs associated with BGJ398 and have been described in detail previously (16).

The median duration of exposure was 14.3 weeks (range, 0.6–58.0 weeks), and 33 patients were on study for at least 16 weeks. Dose reductions occurred among 31 patients (46.3%). The average dose of drug rendered was 87% of the intended dose due to dose reductions and interruption. Of the 67 treated patients, 6 (9.0%) remained on therapy at the time of data cutoff, whereas 61 patients (91.0%) had discontinued treatment. The primary reasons for discontinuation were progressive disease (70.1%), AEs (14.9%), withdrawal of consent (3.0%), loss to follow-up (1.5%), and death (1.5%).

## Biomarkers

*FGFR3* alterations in cell-free DNA (cfDNA) at baseline were analyzed from 50 patient blood samples. Samples were not analyzed for the remaining patients due to plasma not being collected or analyses failing during either sequencing or quality control. Circulating tumor DNA (ctDNA) was identified based upon the detection of mutations reported in Catalogue of Somatic Mutations in Cancer (COSMIC). Of these 50 patients, 34 (68%) showed *FGFR3* alterations in cfDNA that matched the screening analysis, and 1 patient had *FGFR3* Y375C mutation at screening, but Y373C alteration in cfDNA. Eleven patients (22%) did not have any detectable ctDNA, and 4 patients (8%) had detectable ctDNA but no *FGFR3* alterations. FM tumor sequencing data were available for 2 of the 4 patients who had detectable ctDNA with absent *FGFR3* alterations and confirmed the same *FGFR3* mutations reported by screening in these 2 patients. A closer inspection of the tumor sequencing data for these 2 patients revealed that in one of the patients, *JAK2* V617F was the only FM tumor mutation detected in cfDNA. This mutation has not been reported in public datasets of bladder cancer and is frequently observed in essential thrombocythemia, suggesting that the ctDNA detected was not associated with an *FGFR3*-mutated bladder tumor. The patient did indeed have essential thrombocytopenia and could, therefore, be reclassified as not having detectable ctDNA originating from the bladder tumor. In the tumor sequencing data from the other patient, all mutations found in the tumor were detected in cfDNA except for *FGFR3* G370C. *FGFR3* G370C was not detected in cfDNA at any of the six time points of plasma sample collection, and manual review confirmed that there were no supporting reads for *FGFR3* G370C.

*FGFR3* resistance mutations, including *FGFR3* gatekeeper mutations (V443L, V443M, and L496V), as determined by preclinical studies (16), were detected in the cfDNA of 4 patients during treatment (Fig. 3A–D). Samples from 22 patients who progressed while on treatment were analyzed for novel resistance mutations. Of the 22 samples analyzed, 9 were taken at the time of progression and 13 were taken within 28 days of progression. No novel recurrent mutations

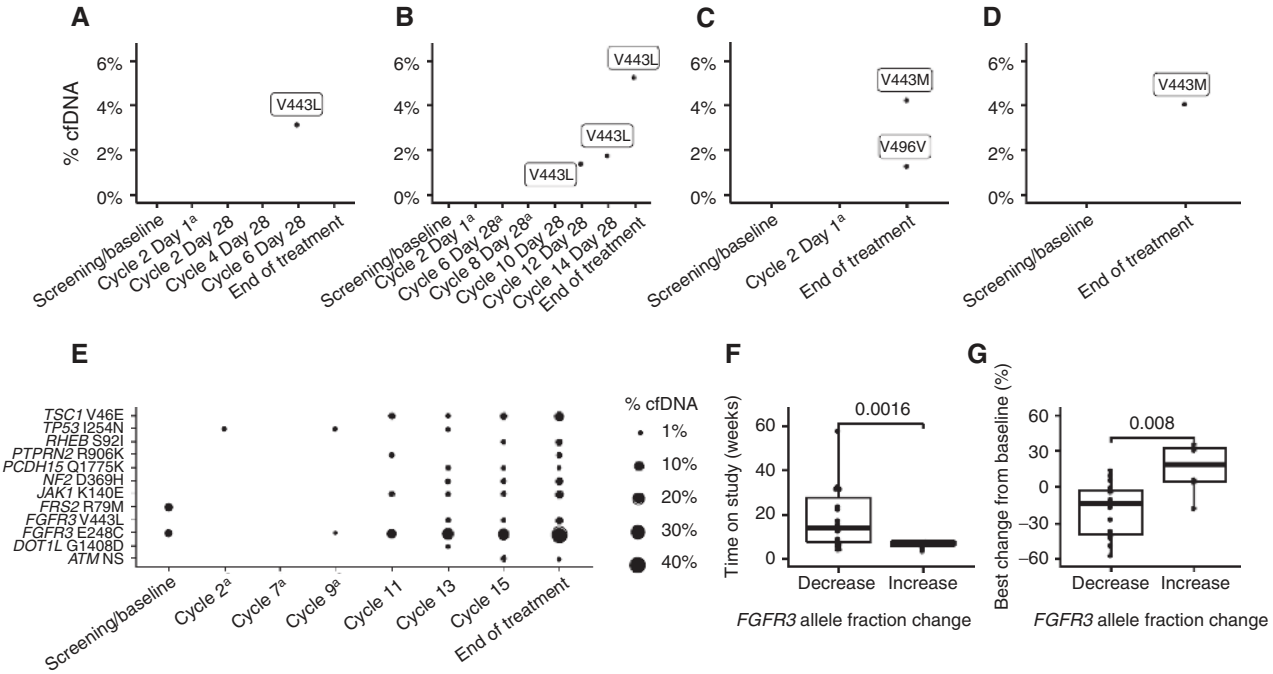


**Figure 3.** **A–D,** *FGFR3* gatekeeper mutations detected in 4 patients. **A,** *C2D1*; **B,** *C2D1*, *C6D28*, *C8D28*; **C,** *C2D1*; **D,** *C9*. **E,** *FGFR3* mutations in the cfDNA of 1 patient during the course of treatment with BGJ398. **F** and **G,** Change in allele fraction of *FGFR3* after the first cycle of treatment and correlation with (**F**) time on study and (**G**) best percentage change from baseline. *P* values were calculated using a two-sided *t* test. Increase is defined as Cycle 2 *FGFR3* allele fraction higher than the baseline value, whereas decrease is defined as Cycle 2 *FGFR3* allele fraction lower than the baseline value. [a]Time point with ctDNA level below the assay limit of detection (power < 0.8).

were detected that might be able to predict relapse. Notably, error correction techniques were not applied in our analysis which could have resulted in missed *FGFR3* resistance mutations.

A preliminary analysis of the correlation between *FGFR3* mutations in cfDNA and disease progression was performed. The length of time on study and best percentage change from baseline were also assessed in relation to whether the *FGFR3* allele fraction decreased or increased upon the second cycle of treatment with BGJ398. A decrease in *FGFR3* mutations with BGJ398 treatment appeared to correlate with a longer time on study and a greater percentage decrease in tumor size from baseline (Fig. 3F and G). Most patients in this *FGFR3*-altered cohort had a low-to-medium tumor mutational burden, and we observed a trend toward a better response in patients with fewer somatic mutations (Supplementary Fig. S2).

## DISCUSSION

The current series represents the largest prospective assessment of FGFR3-directed therapy in a molecularly selected population to date. The response rate of 25.4% with BGJ398 compares favorably with the response rates reported for other novel therapies in this setting, including PD-1/PD-L1–directed therapies (3–7). Furthermore, beyond the patients with a documented response to therapy, a subset of patients achieved disease stabilization. The toxicity profile of BGJ398 appears to be favorable, with manageable and reversible grade 3/4 toxicities that were predominantly biochemical in nature and unassociated with clinical symptomatology. Toxicities of particular concern in the context of previous FGFR inhibitors seemed to be either limited in incidence (e.g., ocular toxicity) or easily managed with proactive intervention (e.g., initiation and titration of sevelamer for hyperphosphatemia).

Although the treatment landscape of metastatic urothelial carcinoma is evolving, there is still a need for novel therapies in this domain. Following platinum-based chemotherapy, cytotoxic therapy has been associated with limited responses. Although there is much excitement surrounding immunotherapy, a phase III trial demonstrating superiority of checkpoint blockade inhibitor therapy over chemotherapy reported a response rate of just 21% (3). Current preliminary data suggest that tumors that harbor *FGFR3* alterations are more likely to be resistant to immune checkpoint blockade, indicating a role for molecularly targeted therapies. Recent guidelines from the National Comprehensive Cancer Network (NCCN) support molecular testing in a Clinical Laboratory Improvement Amendments (CLIA)–certified laboratory for all patients with advanced urothelial carcinoma, thereby facilitating this approach (17). For the roughly 20% of patients with *FGFR3*-mutated disease, a clinical conundrum is whether treatment with BGJ398 or checkpoint inhibition should be preferred. Although prospective studies are needed to clarify this, the emerging evidence suggests that patients whose cancer bears *FGFR3* alterations (and other actionable targets) may have non–T cell–inflamed tumors (18).

In contrast, patients with high levels of PD-L1 expression (ostensibly better responders to PD-1/PD-L1–directed therapy) are more likely to have T cell–inflamed tumors. Consistently, we observed a low tumor mutational burden in most samples (Supplementary Fig. S3).

Another dilemma that arises, particularly with respect to the implementation of broad molecular profiling panels, is identifying alterations that are drivers versus passengers. In our cohort, *FGFR3*-altered tumors frequently demonstrated concomitant alterations in *CDKN2A/B* (potentially sensitizing to CDK4/6 inhibition) and *TSC1* (potentially sensitizing to mTOR inhibition), although a correlation between patterns of genetic alterations and response was not immediately apparent from the data (Supplementary Fig. S1); however, it is not possible to draw any firm conclusions with the limited sample size of this particular study.

Acquired resistance to tyrosine kinase inhibitors, including FGFR inhibitors, remains a problem for patients receiving these targeted therapies, and several mechanisms of resistance to FGFR3-directed therapy have been postulated (19–21). Although several patients remained on BGJ398 therapy at the time of data cutoff, the benefit of BGJ398 was not durable in most patients. Preclinical studies have identified *FGFR3* resistance mutations (22), and these were detected in 4 patients in the current study. Further examination of acquired resistance was carried out by investigating *FGFR3* mutations in blood samples from patients who had relapsed following treatment with BGJ398. No novel markers of resistance to treatment could be identified outside of those that had previously been determined preclinically. Analysis of *FGFR3* mutations in the cfDNA of a patient in this study predicted disease progression ahead of CT scans, suggesting a role for the collection and analysis of cfDNA over the course of FGFR3 inhibitor treatment. Consistent with these findings was the observation that a decrease in allelic fractions of *FGFR3* driver mutations in the second cycle of treatment correlated with improved response. The finding of resistance mutations in the *FGFR* gene family in response to BGJ398 therapy is not unique; in the setting of intrahepatic cholangiocarcinoma, point mutations in the *FGFR2* kinase domain have been identified in cfDNA (22).

Notably, distinct alterations in *FGFR3* may sensitize to BGJ938 differently. For example, the K650E mutation, in the kinase domain, is a known FGFR3 kinase–activating mutation that leads to destabilization of the inactive conformation of the kinase domain and stabilization of the active conformation of the activation loop of the kinase domain of the receptor. Even though this residue is not in direct contact with BGJ398, its mutation destabilizes the inactive conformation to which BGJ398 preferentially binds, and this explains the lower activity of BGJ398 against K650E-mutant FGFR3. We have data that indeed show that BGJ398 is 5- to 10-fold less active against this kinase mutant than against a form of the receptor that is kinase wild-type (12). Analysis of the F386L alteration suggests that it is likely a germline polymorphism as opposed to a somatic mutation, also providing a plausible explanation for primary progressive disease noted in the single patient bearing this mutation. Other mutations occurring outside the kinase domain are not expected to affect the ability of BGJ398 to bind and inhibit the kinase of FGFR3. An analysis of clinical outcome limited to patients with documented activating mutations in *FGFR3* (S249C, R248C, Y375C, and Y373C) yields a confirmed response rate of 28.6% (16 of 56 patients); including unconfirmed responses, the response rate rises further to 42.9% (24 of 56 patients).

In summary, BGJ398 appears to have moderate anticancer activity in patients with metastatic urothelial carcinoma. The response rate of 25.4% and disease control rate of 64.2% exceed outcomes with most agents in this setting, and toxicities associated with BGJ398 appear to be manageable. Enriching for patients who carry known activating mutations in *FGFR3* appears to increase response rates considerably. The high specificity of BGJ398 for *FGFR3* likely accounts for the substantial improvement in activity seen relative to previous FGFR family inhibitors such as dovitinib, which has shown limited benefit in both *FGFR3*-mutant and wild-type metastatic urothelial carcinoma (23). Updated guidelines from the NCCN that support molecular testing (17) will facilitate the entry of patients into further prospective trials, which will hopefully validate the findings noted here. Despite advances in immunotherapy for metastatic urothelial carcinoma, there remains a tremendous unmet need in this space. For selected patients, FGFR3-targeted therapies may represent a viable alternative strategy. Alternatively, combinatorial strategies with immunotherapy could be considered, but require further preclinical and clinical validation.

## METHODS

### *Patient Selection*

An expansion cohort to the initial open-label, multicenter phase I trial including patients with advanced or metastatic urothelial carcinoma was enrolled. Patients eligible for this cohort had either progressed on or were intolerant of platinum-based chemotherapy, or were deemed to have contraindications to these agents. Specimens for molecular profiling were mandated; patients had to demonstrate alterations in *FGFR3* as defined in the subsequent section. Patients were required to have measurable disease by RECIST 1.0. A World Health Organization performance status of 0 to 2 was also mandated, and patients were required to have adequate bone marrow and hepatic and renal function. Normal calcium and phosphate levels were required at baseline. Exclusion criteria included prior therapy with FGFR or MEK inhibitors and the presence of active, untreated brain metastases.

The study protocol and consent were approved by an institutional review board and, where required, an institutional scientific review committee. All patients enrolled provided written informed consent, and the study was conducted in accordance with the amended Declaration of Helsinki and Good Clinical Practice and International Conference on Harmonisation Guidelines.

### *Biomarker Assessment*

Patients were either prescreened for alterations in *FGFR3* or underwent genomic assessment identifying these alterations in the course of routine clinical care. In either case, a tumor block or unstained slides with a representative tumor specimen were sent to a CLIA-certified laboratory, where comprehensive genomic profiling was performed using previously published methods (24). *FGFR3*

mutations permitted in the study included mutations in exon 7 (R248C, S249C), exon 10 (G372C, A393E, Y375C), or exon 15 (K652M/T, K652E/Q). *FGFR3* gene fusions were permitted, including but not limited to *FGFR3–TACC3* fusion. Blood was collected at baseline, on the first day of the second cycle of treatment, and on every even cycle thereafter.

Total cfDNA was extracted from frozen plasma specimens using the QIAamp Circulating Nucleic Acid Kit. The Illumina TruSeq Nano DNA Library Prep Kit was used to construct libraries. Libraries were then enriched for a 600-gene PanCancer gene panel using Agilent SureSelect XT Custom baits, and sequenced on an Illumina HiSeq 2500 sequencer to a median of 103 million reads, yielding a median coverage of 775X. Sequence data were aligned to the hg19 reference genome, and variants were called using MuTect (25), Pindel (26), and Socrates (27). The tumor mutational burden in plasma was calculated using PureCN (28) for all samples with detectable *FGFR3* driver mutations. In brief, all variant calls were first assigned a prior probability of being somatic versus germline based on their presence in the Database of Single Nucleotide Polymorphisms (29) and the COSMIC database (30). Allelic fractions were then adjusted for purity, ploidy, local copy number, and mapping biases. Private variants in coding regions with an assigned probability of more than 0.5 of being somatic were counted. Mutation rates per megabase were obtained by calculating the total number of coding bases with sufficient coverage and mapping quality using the GATK CallableLoci tool (31). Artifacts were removed using 50 internal normal control samples. Single-nucleotide variants were further filtered based on coverage and position-specific sequencing errors observed in the pool of normals using beta-binomial distributions. Power to detect somatic mutations was calculated as in Carter and colleagues (32). Given a fixed sequencing error rate of 0.001 and the sample's median sequencing coverage, this procedure calculates the probability of observing a variant with the same allelic fraction as the *FGFR3* driver mutation.

### *Treatment*

Eligible patients with metastatic urothelial carcinoma and prespecified *FGFR3* alterations received oral BGJ398 125 mg/day for 21 days followed by 7 days without treatment, constituting a 28-day cycle. Baseline imaging included CT of the chest, abdomen, and pelvis, and magnetic resonance imaging or CT of the brain as clinically indicated. Patients underwent serial tumor assessments using CT and bone scanning (if bone metastases were present) every 8 weeks. Treatment was continued until disease progression or unacceptable toxicity. Following discontinuation of therapy, disease progression was assessed every 4 months for 1 year and survival for up to 2 years. In the setting of significant treatment-related toxicity attributable to BGJ398, two stepwise dose reductions were permitted—first to 100 mg/day, then to 75 mg/day; further dose reductions were allowed if clinical benefit had been demonstrated. With all dose reductions, the schedule of drug delivery (21 days on followed by 7 days off) was maintained.

### *Statistical Analysis*

The primary objective within the expanded cohort of patients with metastatic urothelial carcinoma was to estimate the response rate associated with BGJ398. Secondary objectives included assessment of safety and tolerability and pharmacokinetic analyses (reported separately). With response rates associated with cytotoxic therapy following platinum-based chemotherapy in metastatic urothelial cancer of approximately 10%, it was suggested that an objective response rate of more than 25% would be considered preliminary evidence of substantial efficacy with BGJ398 in this disease setting. With a planned sample size of 60 patients, there was 93.4% chance of declaring evidence of substantial efficacy if the true underlying objective response rate is 35%.

## Disclosure of Potential Conflicts of Interest

S.K. Pal has received honoraria from the speakers bureau of Genentech and is a consultant/advisory board member for Pfizer, Ipsen, Exelixis, Eisai, BMS, Astellas, and Novartis. J.E. Rosenberg reports receiving commercial research grants from Novartis, Roche/Genentech, Astellas, Seattle Genetics, and Bayer; has received honoraria from the speakers bureaus of Chugai and AstraZeneca; has ownership interest (including patents) in Illumina; and is a consultant/advisory board member for Bioclin, AstraZeneca, and Bayer. J.H. Hoffman-Censits reports receiving commercial research support from Genentech and is a consultant/advisory board member for Foundation Medicine. D.I. Quinn is a consultant/advisory board member for Novartis, Janssen, Bayer Healthcare, Genentech, BMS, Merck, AstraZeneca, Pfizer, and Astellas. M.D. Galsky is a consultant/advisory board member for Merck, Genentech, AstraZeneca, and BMS. J. Wolf has received honoraria from the speakers bureau of Novartis and is a consultant/advisory board member for the same. C. Dittrich has received honoraria from the speakers bureau of Novartis. V. Sriuranpong has received honoraria from the speakers bureaus of AstraZeneca, Novartis, Roche, Pfizer, Sanofi, Merck Sorono, Eisai, Beringer, Taiho, Janssen, and MSD; served as an advisory board member for MSD, Novartis, Pfizer, Roche, and Eisai; and has received clinical research support through institution from AstraZeneca, Novartis, Roche, Pfizer, Sanofi, Boehringer, Eisai, Taiho, Lilly, BMS, and MSD. V. Grünwald reports receiving commercial research grants from Novartis, BMS, AstraZeneca, MSD, and Pfizer; has received honoraria from the speakers bureaus of BMS, Novartis, MSD, Roche, Pfizer, Ipsen, AstraZeneca, EISAI, EUSAPharma, and MedKomAkademi; and is a consultant/advisory board member for BMS, Novartis, MSD, Pfizer, Roche, and EUSAPharma. D. Petrylak reports receiving commercial research grants from Genentech, Merck, Lilly, Novartis, Bayer, Astellas, and Pfizer; has received honoraria from the speakers bureaus of Genentech, Bayer, Merck, Astellas, Lilly, Pfizer, and Bristol; has ownership interest (including patents) in Tyme and Bellicum; and has received remuneration from Sanofi and Celgene. S. Gupta reports receiving commercial research grants from Parexel International, Five Prime Therapeutics, LSK, Methylgene, Inc., University of Minnesota, Hoosier Oncology Group, Viralytics, Rexahn, Incyte, Novartis, Bristol-Myers Squibb, Merck, and Clovis, and has ownership interest (including patents) in Salarius Pharmaceutical. A. Mortazavi is a consultant/advisory board member for Genentech-Roche and has received remuneration from Motive Medical Intelligence. K. Parker has received remuneration from Novartis. D.F. Bajorin has received honoraria from the speakers bureau of Merck and is a consultant/advisory board member for Merck, Pfizer, Bristol-Myers Squibb, Urogen, Genentech, and Eli Lilly. No potential conflicts of interest were disclosed by the other authors.

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