Clinical Cancer Research

A Phase II Trial of Dovitinib in BCG-Unresponsive Urothelial Carcinoma with *FGFR3* Mutations or Overexpression: Hoosier Cancer Research Network Trial HCRN 12-157

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Abstract

Purpose: To assess the clinical and pharmacodynamic activity of dovitinib in a treatment-resistant, molecularly enriched non–muscle-invasive urothelial carcinoma of the bladder (NMIUC) population.

Experimental Design: A multi-site pilot phase II trial was conducted. Key eligibility criteria included the following: Bacillus Calmette-Guerin (BCG)-unresponsive NMIUC (>2 prior intravesical regimens) with increased phosphorylated FGFR3 (pFGFR3) expression by centrally analyzed immunohistochemistry (IHC+) or *FGFR3* mutations (Mut+) assessed in a CLIA-licensed laboratory. Patients received oral dovitinib 500 mg daily (5 days on/2 days off). The primary endpoint was 6-month TURBT-confirmed complete response (CR) rate.

Results: Between 11/2013 and 10/2014, 13 patients enrolled (10 IHC+ Mut−, 3 IHC+ Mut+). Accrual ended prematurely due to cessation of dovitinib clinical development. Demographics included the following: median age 70 years; 85% male; carcinoma *in situ* (CIS; 3 patients), Ta/T1 (8 patients), and Ta/T1 + CIS (2 patients); median prior regimens 3. Toxicity was frequent with all patients experiencing at least one grade 3–4 event. Six-month CR rate was 8% (0% in IHC+ Mut−; 33% in IHC+ Mut+). The primary endpoint was not met. Pharmacodynamically active (94–5,812 nmol/L) dovitinib concentrations in urothelial tissue were observed in all evaluable patients. Reductions in pFGFR3 IHC staining were observed post-dovitinib treatment.

Conclusions: Dovitinib consistently achieved biologically active concentrations within the urothelium and demonstrated pharmacodynamic pFGFR3 inhibition. These results support systemic administration as a viable approach to clinical trials in patients with NMIUC. Long-term dovitinib administration was not feasible due to frequent toxicity. Absent clinical activity suggests that patient selection by pFGFR3 IHC alone does not enrich for response to FGFR3 kinase inhibitors in urothelial carcinoma. *Clin Cancer Res; 23(12); 3003–11. ©2016 AACR.*

Introduction

Urothelial carcinoma of the bladder is the fifth most common human cancer diagnosis. In 2016, more than 76,000 individuals are expected to be diagnosed with urothelial carcinoma and more than 16,000 patients to die from their disease (1). Most new urothelial carcinoma cases (∼50,000 patients) are non–muscle-invasive at diagnosis with disease limited to the mucosal epithelium (Ta/Tis) and immediate connective tissue layer beneath the

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Translational Relevance

This trial reports the toxicity, pharmacodynamics, and clinical efficacy profiles of the oral FGFR1-3 and VEGFR1-3 multitargeted tyrosine kinase inhibitor, dovitinib, in a pilot phase II investigation in patients with Bacillus Calmette-Guerin (BCG)-unresponsive non–muscle-invasive urothelial carcinoma of the bladder (NMIUC) with tumors harboring *FGFR3* alterations. In addition to demonstrating reductions in posttreatment pFGFR3, confirmed biologically active dovitinib concentrations were observed in the bladder urothelium. This trial is the first NMIUC study to require genomic testing as an eligibility requirement and to demonstrate successful achievement of therapeutic urothelial tissue concentrations of systemically administered targeted therapies. Thus, it greatly expands the potential therapeutic approaches to treat this high-risk population. Lack of clinical efficacy was hampered by frequent drug toxicity and a paucity of patients harboring *FGFR3* mutations. Additional *FGFR3* targeting approaches in molecularly enriched urothelial carcinoma populations are ongoing and clearly worthy of further study, including in patients with NMIUC.

mucosa (T1; ref. 2). The clinical course of non–muscle-invasive urothelial carcinoma of the bladder (NMIUC) is dominated by frequent recurrences requiring surveillance (with cystoscopy, bladder biopsy, urine cytology, etc.). The need for long-term invasive monitoring and treatment has significant cost and morbidity for patients with urothelial carcinoma. Compared with other malignancies, urothelial carcinoma ranks highest in lifetime per patient costs with an average cost from diagnosis to death of $96,500 per patient (3).

Standard therapy for high-risk patients with NMIUC includes transurethral resection of bladder tumor (TURBT) augmented by intravesical administration of Bacillus Calmette-Guerin (BCG), an attenuated bovine mycoplasma–derived agent. Two meta-analyses of randomized trials of TURBT plus BCG versus TURBT alone demonstrated a reduction in 12-month tumor recurrence rate from 56% to 29% ($P < 0.001$) and a reduction in progression to muscle-invasive stages from 13.8% to 9.8% ($P = 0.001$) in association with BCG therapy (4, 5). While BCG therapy is successful at preventing early tumor recurrences, most patients do not maintain sustained remissions. With 5-year follow-up, recurrent bladder tumors requiring repetitive TURBT and further cystoscopic surveillance are observed in 40% to 66% of patients (6, 7). For post-BCG tumor recurrences, BCG-unresponsive disease is defined by any of the following features: recurrent NMIUC after 2 prior adequate BCG regimens, recurrent T1 disease at the initial 3-month posttreatment TURBT, recurrent NMIUC within 6 months of last BCG administration, and NMIUC involving the prostatic urethra (8). Transient remissions are often observed with additional intravesical therapy approaches; however, only 10% to 15% of patients remain recurrence-free at 1 year (9, 10). Thus, cystectomy is considered a standard treatment in BCG-unresponsive patients (11). A need clearly exists to explore the clinical efficacy of novel agents in this high-risk NMIUC population.

Across multiple cancer types, the critical role of angiogenesis in tumor migration, proliferation, and metastasis is well established with VEGF and VEGFR serving as key mediators (12, 13). In urothelial carcinoma, associations between increased tumor VEGF expression and high-grade disease, advanced stage, and poor prognosis have been observed (14–16). Initial phase II trials in metastatic patients with urothelial carcinoma combining chemotherapy with the anti-VEGFR2 monoclonal antibody bevacizumab have demonstrated promising overall survival outcomes compared with historical controls with a definitive phase III trial of chemotherapy with or without bevacizumab completed and data maturing (17, 18).

In addition to VEGFR, FGFR3 has been implicated as a critical facilitator of urothelial carcinoma carcinogenesis, particularly in NMIUC (19, 20). *FGFR3* mutations or overexpression promote FGFR dimerization and constitutive activation of downstream signaling pathways in the absence of ligand in up to 80% of low-grade NMIUC tumors (21). These mutations result in a hyperplastic phenotype dominated by frequent tumor recurrences with infrequent progression to muscle-invasive stages. While *FGFR3* mutations are highly associated with low-grade NMIUC, overexpression of FGFR3 has been observed in up to 42% of high-grade muscle-invasive urothelial carcinoma tumors (22). Furthermore, either an *FGFR3* mutation or overexpression of the FGFR3 protein in the absence of mutation has been observed in 54% of muscle-invasive urothelial carcinoma tumors (22). Thus, while *FGFR3* mutations likely are an early event in the tumorigenesis of low-grade noninvasive urothelial carcinoma tumors, alterations of *FGFR3* may still play a role in the continued proliferation of high-grade urothelial carcinoma.

Dovitinib is an oral tyrosine kinase inhibitor of FGFR1-3, VEGFR1-3, PDGFRβ, c-Kit, RET, TrkA, CSF-1R, and FLT3 which has demonstrated a tolerable safety profile in single agent and combination regimens (23). Increasing evidence demonstrates that *FGFR1* is a crucial mediator of tumor angiogenesis (24). In preclinical tumor models, blockade of the FGF pathway has proven to be an effective method of overcoming resistance to VEGFR inhibitors (25). Given the previously described importance of VEGF in urothelial carcinoma progression and the frequent *FGFR3* aberrations in NMIUC, we conducted a multisite pilot trial in patients with BCG-unresponsive NMIUC harboring *FGFR3* gene alterations to evaluate the clinical and biologic outcomes of oral dovitinib therapy.

Materials and Methods

Study design

A single-arm, nonrandomized, multicenter phase II study (NCT01732107) was conducted between 3 sites: Indiana University Simon Cancer Center (Indianapolis, IN), Fox Chase Cancer Center (Philadelphia, PA), and Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (Baltimore, MD). Standard of care and correlative biospecimens were collected pre- and posttreatment from all patients. The study was approved by the institutional review boards of each site.

Patients

Key eligibility criteria included: histologically confirmed Ta, T1, or Tis stage NMIUC assessed by TURBT performed within 42 days of registration; somatic tumor mutations in *FGFR3* exons 7, 10, or 15 (S373C, G372C, Y375C, G382R, K652E, K652Q, K652T, K652M, A393E, S249C, and R248C) or tumor overexpression of phosphorylated (pFGFR3) by immunohistochemistry (IHC)

defined as 1+ or greater tumor pFGFR3 staining; recurrent NMIUC despite at least 2 prior intravesical treatment regimens (no limit), one of which must have been BCG; patients medically unfit for or refusing cystectomy; age >18 years; ECOG performance status 0–2; adequate hematologic and liver function; creatinine clearance >30 mL/min by modified Cockcroft–Gault equation; and documented, written informed consent. Major exclusion criteria included: evidence of muscle-invasive or metastatic disease on pre-study screening tests; concurrent upper tract urothelial carcinoma; prior VEGFR or FGFR-targeted therapy.

Treatment

Patients were treated with dovitinib 500 mg by oral administration once per day for 5 consecutive days followed by 2 days off each week. A cycle was defined as 4 weeks of therapy. No maximum number of treatment cycles was stipulated. Dose reductions to 400 and 300 mg were permitted in the event of treatment-related toxicity. Because of drug–drug interactions, full dose anti-coagulation with warfarin was not allowed, however, use of low-molecular weight heparin at full-dose was permitted. Usage of anti-emetic and colony-stimulating growth factor medications was at the discretion of the treating physician.

Disease evaluations

At baseline, the absence of metastatic disease was confirmed by abdomen and pelvis CT scan and chest X-ray or CT scan. Adequate cardiac function was confirmed by echocardiogram and electrocardiogram assessments. History and physical examination findings, vital signs, baseline symptoms, and laboratory assessments were performed within 14 days of registration. Exams, vital signs, toxicity evaluations (per CTCAE v4.0), and laboratory assessments were performed biweekly for the first 2 cycles of treatment and every 4 weeks thereafter.

All patients were evaluated with urine cytology and cystoscopy every 3 months during the first year and per the treating physician's discretion thereafter. TURBT's were required at 3- and 6-month posttreatment with only for cause TURBT's thereafter. At each TURBT, biopsy tissue was obtained from all previous and new tumor sites, the bladder dome, anterior bladder wall, left lateral bladder wall, right lateral bladder wall, and the bladder trigone. Patients with any NMIUC at the 6-month evaluation or beyond were considered relapses as were patients with carcinoma *in situ* (CIS) at the 3-month evaluation. Patients with papillary-only disease at the 3-month cystoscopy/TURBT who declined further dovitinib therapy were classified as relapsed. Testing of urine for evidence of relapse by FISH was allowed but not required. The same was true for the use of blue light cystoscopy. An isolated FISH-positive urine finding was not classified as a relapse event. Complete response (CR) was defined as no evidence of any remaining urothelial carcinoma tumors of any T stage (including Tis) as assessed by cystoscopic examination and urine cytology. In addition to these criteria, the 6-month CR rate required no evidence of tumor within the 6-month posttreatment TURBT biopsies. The 1-year relapse-free survival rate was defined as the proportion of patients treated with dovitinib with no evidence of any urothelial carcinoma at 12 months of follow up. Patients with any evidence of muscle-invasive tumors (T2 or above) or metastatic disease in follow-up were considered as progressive disease.

At the time of all TURBTs or cystectomy, tumor samples were sent for standard-of-care diagnostic evaluation and complete pathologic staging information was recorded. Samples from the same blocks were cut and archived for correlative studies. Resolution of any treatment-related toxicities was confirmed 30 days after administration of a patient's last dovitinib dose. Patients were not followed for long-term overall survival outcomes.

FGFR3 mutation analysis

At baseline, 5 individual 5-μm-thick slides were cut from the patient's representative TURBT block with the highest grade tumor and greatest volume of tumor present. In slides with less than 40% tumor cells present, macrodissection was performed to ensure maximum tumor cell DNA content. Also, at baseline, a 30-mL urine sample was obtained from all patients and centrifuged at 3,500 rpm for 10 minutes. The resulting supernatant and cell pellet were transferred into separate cryovials and stored at −70°C until analyzed. Slides and urine cell pellets were shipped to the laboratory for Clinical Genomics and Advanced Technology (CGAT) at the Dartmouth Hitchcock Medical Center. Tumor and urine cell pellet DNA extraction was performed per manufacturer's specification [Qiagen Puregene (tissue) and Qiagen DNeasy (cell pellet)]. *FGFR3* mutational status was determined using a custom designed SNaPshot assay (ThermoFisher Scientific) for all common mutations in *FGFR3* coding exons including exons 7, 10, and 15. The presence or absence of specific *FGFR3* mutations (S373C, G372C, Y375C, G382R, K652E, K652Q, K652T, K652M, A393E, S249C, and R248C) was communicated to HCRN within 14 days of specimen receipt.

Phosphorylated FGFR3 IHC analysis

Simultaneously at baseline, 5 individual 5-μm-thick slides from the patient's tumor and a single hematoxylin and eosin (H&E) slide from the same block were shipped to the IUSCC Immunohistochemistry Core Laboratory for FGFR3 IHC analysis. Slides were heated to 60°C for 15 minutes. Slides were deparaffinized and rehydrated sequentially with xylene (5 minutes × 2), 100% ethyl alcohol solution (2 minutes × 2), and 95% ethyl alcohol solution (2 minutes × 2) on a Sakura linear stainer. Antigen retrieval utilized PT Link (PT10030, Dako) in conjunction with EnVision FLEX High pH target retrieval solution (K8000, Dako). Cycles began at 85°C and were heated to 100°C for 20 minutes followed by cooling back to 85°C and placement in wash buffer (K8002, Dako). Baseline phosphorylated FGFR3 staining for trial eligibility evaluation was performed on a Dako Autostainer platform utilizing the sc-33041 anti-FGFR3 (phospho Y724) antibody (Santa Cruz Biotechnology). The sc-33041 pFGFR3 antibody was optimized to a 1:100 dilution for 30 minutes prior to the conduct of this trial utilizing 15 breast cancer cases as positive controls. Following pFGFR3 staining, slides were dehydrated sequentially with 95% ethyl alcohol solution (2 minutes × 1), 100% ethyl alcohol solutions (3 minutes × 2), and xylene (5 minutes × 2) followed by coverslipping. The immunostained slides were evaluated by 2 different pathologists. Areas within the tumor were scored as follows: 0 = negative, 1+ = mild staining, 2+ = moderate staining, 3+ = strong staining. Both positive and negative controls were run in addition to the samples. Because a

clinically relevant cutoff for pFGFR3 IHC intensity had not previously been established, tumors with any staining intensity (1+ or greater) were considered pFGFR3-overexpressing. During the conduct of the trial, improved commercial pFGFR3 antibodies became available. The correlative pre- and posttreatment pFGFR3 analyses were, therefore, performed utilizing the ab155960 anti-FGFR3 (phospho Y724) antibody (Abcam). The ab155960 evaluation scheme was validated across 19 different individual cases of bladder cancer for antibody specificity. Triplicate runs of this validation scheme showed that low strainers (1+), moderate strainers (2+), and strong strainers (3+) were replicated across all runs. High, medium, and low staining positive controls were identified and used across all runs. All other antibody optimization procedures mirrored those of the sc-33041 antibody with the exception that the ab155960 antibody was optimized with to a 1:25 dilution for 40 minutes. The sc-33041 antibody continued to be utilized for eligibility determination throughout the entire conduct of the study. Aperio's ScanScope CS whole slide digital imaging system (Leica Biosystems) was used for baseline and posttreatment pFGFR3 pathology imaging. The system imaged all slides at 20×. The scan time ranged from 1 $^1/_2$ minutes to a maximum time of 2 $^1/_4$ minutes. The whole images were housed and stored in their Spectrum software system and images were shot from the whole slides. Quantification of pFGFR3 staining was performed on the HALO image analysis platform (Indica Labs). An algorithm was designed on the basis of pattern recognition that quantified tumor cells within pFGFR3-positive areas (tumor) and pFGFR3-negative areas (invasive margin). HALO's classifier package performed image analysis based on RGB (red, green, blue) spectra which was used to detect cells positively expressing pFGFR3 against negative expressing counterstained hematoxylin cells. The algorithm calculated the classified area (mm^2) and percentage of tumor expression (% positive cells/% of all nucleated cells) using the HALO classifier package. The total percentage of positive expression in each group was averaged and SD was calculated. Further analysis was performed on 3 hotspots on each tissue via HALO's area quantification package. An algorithm was designed to quantify positive pFGFR3-expressing tumor cells in weak, moderate, and high positivity values. An average of hotspots for the tissues collected at day 1 was calculated along with SD. These data were compared with an average of hotspots of the tissues collected between cycle 3 days 26 and 30 for their total positivity and according to weak, moderate, high, and total expression.

Dovitinib pharmacokinetic tissue analysis

At the 3-month posttreatment disease assessment, a bladder biopsy of tumor or normal appearing urothelium was obtained for pharmacokinetic analysis to confirm achievement of biologically active dovitinib tissue concentrations via oral drug administration. The pharmacokinetic biopsy sample was flash-frozen, stored in liquid nitrogen, and shipped to the IUSCC Clinical Pharmacology Analytical Core (CPAC) for analyses. Tissue samples were homogenized in PBS, internal standard (sorafenib) was added to each sample, the samples were extracted with ethyl acetate, and injected into an HPLC-MS/MS (API 4000; AB Sciex). Plasma was used for the matrix of the standard samples to estimate tissue concentrations. The lower limit of quantification was 8 ng/sample. For ease of comparison, tissue concentrations (ng/g) were converted to the nanomolar concentrations (assuming 1-g tissue is equivalent to 1-mL water).

Statistical considerations

The primary endpoint of the trial was 6-month CR rate. With a 6-month CR rate of clinical interest of $\geq$25%, a sample size of 20 patients provided an 80% power to exclude a lower bound of $\leq$10% utilizing a one-sided 90% confidence interval (CI) of Agresti–Couli type. With an estimated *FGFR3* mutation or overexpression present in 40% of BCG-unresponsive tumors, screening of 50 patients' tumors was estimated to enroll the required 20 patients on dovitinib therapy. An evaluation of early stopping was planned at the first 10 patients completing 3-month assessment for progression to T2 or greater stages, whose objective was to stop the study if the likelihood of progression rate was more than 20%. A rule was chosen that the study should be terminated if 5 or more progressions were observed of 10 patients, which is the minimal number that leads to a 90% Agresti–Coull CI with a lower bound above 20%. Rates of CR, progressive disease, and treatment-related toxicity were summarized by 95% CIs. Associations between pre- and posttreatment pFGFR3 IHC staining intensity were compared by paired *t* testing with significance set at $P < 0.05$.

Results

Patients

Between November 2013 and October 2014, 17 patients were screened and 13 patients were enrolled. Fifteen patients (88%) had sufficient tumor tissue for *FGFR3* mutation testing. Two patients with tumors demonstrating no *FGFR3* mutations were considered screen failures after the study amendment capping the enrollment of *FGFR3* mutation–negative patients was in place. Further accrual was stopped because of cessation of clinical development of dovitinib. Patient demographics are summarized in Table 1 and included: median age 70 years (range, 57–78 years), 85% male, and 85% Caucasian. Baseline TURBT tumor stages were: CIS, 3 patients; Ta or T1, 8 patients; and Ta or T1 with concurrent CIS, 2 patients. Patients had received a median of 3 prior intravesical regimens (range, 2–6) with all patients having received at least 2 prior BCG induction courses. The median time from last intravesical therapy was 6 months (range, 1–33). Tumor *FGFR3* mutations were detected in 3 patients (18% of screened patients) with a concordant urine *FGFR3* mutation detected in 1 of the 3 patients.

Dovitinib treatment

Patients received a median of 4 cycles of dovitinib treatment (range, 1–19). Ten patients (77%) required dovitinib dose reductions. Two patients (15%) discontinued dovitinib treatment prematurely and did not undergo planned 3-month posttreatment disease evaluations. Reasons for discontinuation included: physician discretion discontinuation of treatment due to a traumatic intracranial hemorrhage sustained in a ground-level fall unrelated to study treatment (1 patient) and patient choice to withdraw from study (1 patient). In addition, dovitinib therapy was discontinued per treating physician's discretion in a single patient after 19 cycles after the patient revealed a prior history of retinal detachment unknown to the treating team at study enrollment.

Table 1. Baseline patient and tumor characteristics

Patient	Gender	Age, y	Race	T-stage	Prior regimens	Time from last therapy, mo	Tumor *FGFR3* mutation	Urine *FGFR3* mutation	pFGFR3 IHC intensity
1	F	77	C	T1 + CIS	BCG × 2, Gem	58.3	G382R	None	3+
2	M	67	C	CIS	BCG × 2, MMC	8.3	None	None	3+
3	M	71	C	Ta	BCG × 2	6.3	None	None	3+
4	M	64	C	Ta	BCG × 2, MMC	23.7	None	None	3+
5	M	75	C	Ta	BCG × 4, MMC, Val	5.6	S249C	S249C	3+
6	M	70	AA	T1	BCG × 4, MMC	6.2	None	None	3+
7	M	69	U	CIS	BCG × 2, Val	3.7	None	None	3+
8	M	78	C	Ta	BCG × 2	5.7	None	None	3+
9	M	57	C	Ta	BCG × 2, MMC	1.4	None	None	3+
10	M	71	C	T1	BCG × 2	3.7	None	None	3+
11	F	67	C	CIS	BCG × 2, MMC, Val	15	None	None	3+
12	M	77	C	T1 + CIS	BCG × 3, Val	24.2	None	None	3+
13	M	57	C	Ta	BCG × 2	33.1	S249C	NE	2+

Abbreviations: AA, African-American; C, Caucasian, F, female; Gem, gemcitabine; M, male; MMC, mitomycin C; NE, not evaluable; U, unknown, Val, valrubicin.

Toxicity

Dovitinib therapy was associated with frequent toxicity. All 13 patients (100%) experienced at least 1 grade 3 or 4 event. Treatment-related grade 4 hypertriglyceridemia was observed in 1 patient (8%). Treatment-related grade 3 events included fatigue, elevated γ-glutamyl transferase (GGT), and elevated lipase in 2 patients (15%) each as well as headache, hypertriglyceridemia, stomatitis, and rash in 1 patient (8%) each. One patient (8%) suffered a subdural intracranial hemorrhage that did not require operative intervention in association with a ground-level fall on an ice-covered winter sidewalk that was not deemed treatment-related. All grade 3–4 events and other toxicities occurring in more than 20% of patients are summarized in Table 2. Complete all-grade toxicity is included in Supplementary Table S1.

Tumor response

Antitumor responses to dovitinib treatment were infrequent. Of the 13 patients enrolled, a pathologic CR was observed in 1 patient (8%). Nonresponse was observed in 11 patients (85%) and progression to muscle-invasive stage occurred in 1 patient (8%). The single patient with CR did harbor an *FGFR3* S249C mutation. Thus, the pathologic CR rate amongst *FGFR3* mut+ patients was 33% (1 of 3) as summarized in Table 3. The patient remains in a CR at 19+ months of follow-up. Eight patients (62%) underwent cystectomy per the discretion of their physician at any time point following completion of study therapy with a wide variety of pathologic stages ranging from pT0N0 to pN+ disease (Supplementary Table S2).

Dovitinib pharmacokinetic tissue analysis

Fresh tumor or adjacent normal urothelium biopsy tissue was available for dovitinib pharmacokinetic analysis from 9 of the 11 patients who underwent posttreatment disease evaluations. As shown in Fig. 1, dovitinib was detectable at pharmacologically active levels in all patients examined with tissue concentrations ranging from 94 to 5,813 nmol/L.

IHC analysis of dovitinib treatment on pFGFR3

All baseline slides for eligibility determination demonstrated positive pFGFR3 staining as assessed by the sc-33041 pFGFR3 antibody. Staining intensities according to the use of the sc-33041 and ab155960 pFGFR3 antibodies showed significant heterogeneity (Supplementary Table S3). Pre- and post-dovitinib treatment slides were available from 9 patients including 8 tumor pairs. Utilizing the quantitative Halo Classifier imaging platform, reductions in averaged pFGFR3 staining area from 41.2 to 31.3 mm^2 were observed following dovitinib treatment. As depicted in Fig. 2, this posttreatment reduction in mean pFGFR3 staining area showed a strong trend but did not reach statistical significance ($P = 0.08$). Marked reductions in pFGFR3 staining were observed in 4 of 9 patients, of which one reduction is demonstrated in Fig. 3.

Discussion

Until the recent FDA approval of the immunotherapy agent atezolizumab in metastatic urothelial carcinoma patients, nearly a quarter century had passed without any significant advances in systemic therapy for urothelial carcinoma (26). While the approval of atezolizumab is encouraging, it is important to note that only a small subset of patients derive benefit. Thus, additional novel approaches to treat urothelial carcinoma are clearly needed. In particular, innovative strategies for the two thirds of patients with urothelial carcinoma initially presenting with NMIUC are paramount. Given the established relevance of VEGFR in urothelial carcinoma cancer invasion and metastases and the striking frequency of *FGFR3* aberrations in low-grade NMIUC, we postulated that an FGFR3/VEGFR2-directed approach with dovitinib would prove both feasible and beneficial in patients with BCG-unresponsive NMIUC with tumors harboring *FGFR3* alterations.

Our study failed to demonstrate significant clinical activity with dovitinib therapy in the enrolled study population. Limitations in the enrollment criteria for the study population likely played a major factor in the absent antitumor activity observed. At the time the study was designed, the relative importance of *FGFR3* mutations versus gene fusions versus overexpression was unknown. Furthermore, clinically relevant cutoffs for pFGFR3 IHC staining had not been established and available commercial pFGFR3 antibodies were limited. Therefore, even though robust methodology was developed prior to study initiation to optimize pFGFR3 antibody procedures, our trial allowed patients with any degree of pFGFR3 IHC staining at baseline to enroll. This allowed for an early influx of IHC+ Mut− patients. As demonstrated by the frequent heterogeneity that was observed in baseline IHC intensities according to the pFGFR3 antibody utilized, this likely resulted in a less

Table 2. All grade 3–4 adverse events and other adverse events occurring in more than 20% of patients

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Constitutional				
Fatigue	5 (39%)	4 (31%)	2 (15%)	0 (0%)
Pain	6 (46%)	6 (46%)	0 (0%)	0 (0%
Fall	0 (0%)	0 (0%	1 (8%)	0 (0%)
Other constitutional	3 (23%)	2 (15%)	0 (0%)	0 (0%)
Vascular				
Hypertension	0 (0%)	2 (15%)	2 (15%)	0 (0%)
Headache	5 (39%)	1 (8%)	1 (8%)	0 (0%)
Intracranial hemorrhage	0 (0%)	0 (0%	1 (8%)	0 (0%)
Gastrointestinal				
GERD	2 (15%)	3 (23%)	1 (8%)	0 (0%)
Constipation	2 (15%)	2 (15%)	0 (0%)	0 (0%)
Diarrhea	8 (62%)	2 (15%)	0 (0%)	0 (0%)
Anorexia	4 (31%)	1 (8%)	0 (0%)	0 (0%)
Weight loss	4 (31%)	0 (0%)	0 (0%)	0 (0%)
Dysgeusia	5 (39%)	2 (15%)	0 (0%)	0 (0%)
Nausea/Emesis	6 (46%)	0 (0%)	0 (0%)	0 (0%)
Emesis	4 (31%)	0 (0%)	0 (0%)	0 (0%)
Other gastrointestinal	2 (15%)	3 (23%)	0 (0%)	0 (0%)
Skin				
Stomatitis	0 (0%)	0 (0%)	1 (8%)	0 (0%)
Rash	4 (31%)	1 (8%)	1 (8%)	0 (0%)
Hand–foot syndrome	2 (15%)	1 (8%)	0 (0%)	0 (0%)
Dry mouth	4 (31%)	0 (0%)	0 (0%)	0 (0%)
Other skin	6 (46%)	2 (15%)	0 (0%)	0 (0%)
Genitourinary				
Bladder spasms	0 (0%)	3 (23%)	0 (0%)	0 (0%)
Other urinary	7 (54%)	1 (8%)	0 (0%)	0 (0%)
Infection				
Fever	4 (31%)	0 (0%)	0 (0%)	0 (0%)
Infection	0 (0%)	8 (62%)	0 (0%)	0 (0%)
Pulmonary				
Hoarseness	3 (23%)	0 (0%)	0 (0%)	0 (0%)
Other pulmonary	4 (31%)	1 (8%)	0 (0%)	0 (0%)
Musculoskeletal				
Arthralgia/Myalgia	4 (31%)	2 (15%)	0 (0%)	0 (0%)
Metabolic				
Hypertriglyceridemia	1 (8%)	2 (15%)	1 (8%)	1 (8%)
Elevated alkaline phosphatase	2 (15%)	1 (8%)	0 (0%)	0 (0%)
Elevated GGT	0 (0%)	1 (8%)	2 (15%)	0 (0%)
Hypoalbuminemia	2 (15%)	1 (8%)	0 (0%)	0 (0%)
Elevated lipase	0 (0%)	0 (0%)	2 (15%)	0 (0%)
Other metabolic	6 (46%)	0 (0%)	0 (0%)	0 (0%)
Hematologic				
Anemia	4 (31%)	0 (0%)	0 (0%)	0 (0%)

biologically enriched population than intended. An amendment to cap the number of IHC+ Mut− patient enrollment at 10 patients was instituted; however, the trial was closed after enrolling only 3 Mut+ patients. In recent trial reports of other FGFR3 inhibitors (JNJ-42756493, BGJ398, AZD4547) in metastatic patients with urothelial carcinoma, it now appears clear that activating *FGFR3* mutations or fusions are required for tumor responses (27–29). In trials of these agents mandating either *FGFR3* mutation or fusions, reduction of tumor size was observed in 50% to 60% of metastatic patients with urothelial carcinoma (27, 29). Interestingly, in a prior report of dovitinib in metastatic patients with urothelial carcinoma, no responses were observed among 12 patients with *FGFR3* mutations (30). It is not clear whether differences in *FGFR3* mutation testing methodology or individual drug FGFR3-binding site properties explain discordant clinical activity. An observed CR 1 of the 3 Mut+ patients treated with dovitinib in our trial is consistent with the more recent FGFR3 inhibitor results. With only 3 Mut+ patients enrolled, it is impossible for our study to provide any meaningful CIs around the true CR rate. However, it is encouraging that the single CR patient has demonstrated a sustained remission out to 19+ months. Furthermore, a strong trend in decreased posttreatment pFGFR3 staining was observed regardless of *FGFR3* mutation status.

In addition to patient selection limitations, the high rate of treatment-related toxicity led to frequent dose reductions including 2 of the 3 *FGFR3* Mut+ patients discontinuing dovitinib early. These dose modifications led to reduced dovitinib dose intensity in most patients and may have compromised antitumor effects. For future trials, particularly in the NMIUC population, our study provides a good example of the need to have a drug that is not only effective but also tolerable at therapeutic doses to impart true benefit. Specifically, as in the case of dovitinib, the acceptance of relatively high rates of chronic toxicity in heavily pretreated metastatic solid tumor phase I trials may be greater than in NMIUC, given that NMIUC can be cured with cystectomy (31). In future design of NMIUC trials, particular attention to high rates of acute or chronic grade 1–2 toxicities is warranted particularly if a drug will require chronic or lifelong administration to prevent tumor recurrence. In addition, perioperative complication rates from patients who proceed to posttreatment cystectomies are of critical importance in NMIUC trials, particularly when agents with known effects on bleeding and wound-healing such as FGFR or VEGFR inhibitors

Table 3. Tumor response to dovitinib treatment

Patient	Baseline T-stage	Tumor *FGFR3* mutations	Duration of treatment, mo	Posttreatment T-stage	Response category
1	T1 + CIS	G382R	0.8	NE	NR
2	CIS	None	2.7	CIS	NR
3	Ta	None	4.4	Ta	NR
4	Ta	None	2.8	Ta	NR
5	Ta	S249C	0.7	NE	NR
6	T1	None	2.7	T1	NR
7	CIS	None	5.3	CIS	NR
8	Ta	None	3.3	T1	NR
9	Ta	None	3	Ta	NR
10	T1	None	2.7	T2	PD
11	CIS	None	4.4	CIS	NR
12	T1 + CIS	None	3.2	T1	NR
13	Ta	S249C	17.5	T0	CR

Abbreviations: NE, not evaluable; NR, nonresponder; PD, progressive disease.

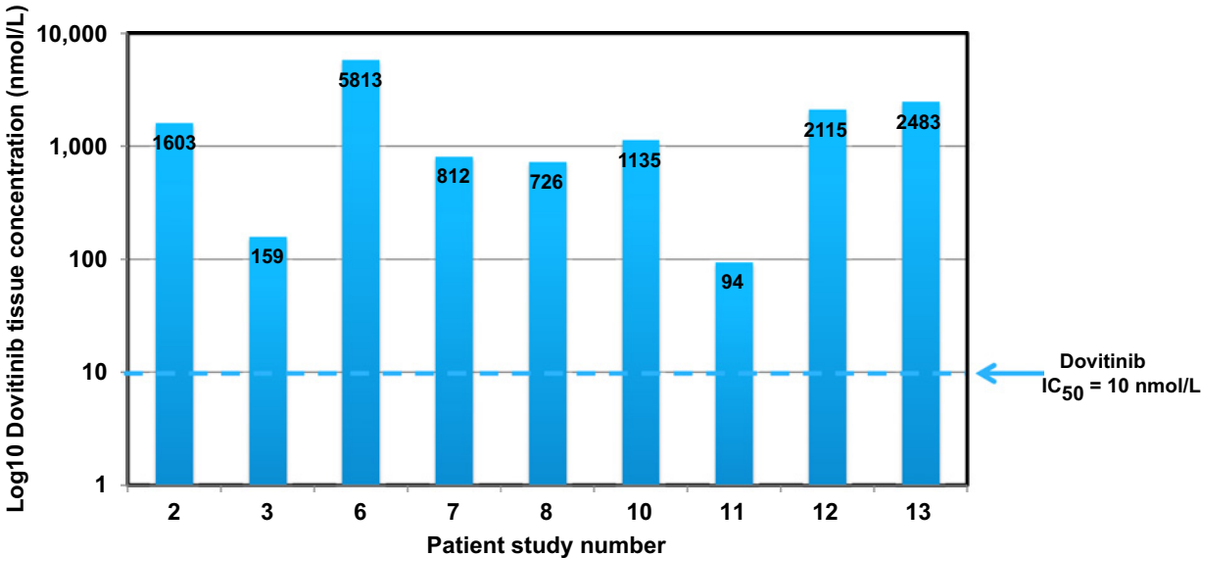

Figure 1.
Posttreatment dovitinib tissue concentration.

are studied. While no life-threatening perioperative complications were observed in our trial, our sample size is insufficient to discount the possibility of such risks.

Despite the absent clinical activity, our study establishes several innovative principles in the design of NMIUC trials that should facilitate improved future clinical trial designs in this population. First, our study demonstrated the feasibility of tumor genomic testing as an eligibility requirement in the NMIUC population in a multisite setting. In fact, of the 17 patients screened, 15 (88%) had sufficient tumor available for *FGFR3* mutation testing. While investigation of oral kinase inhibitors in patients with NMIUC has been pursued by other investigators, to our knowledge, our trial is the first to be undertaken in a molecularly enriched NMIUC population (32). With the establishment of intrinsic basal and luminal tumor subtypes from analysis of The Cancer Genome Atlas (TCGA) urothelial carcinoma samples, we expect an increased need for future urothelial carcinoma clinical trials to target specific genomically defined patient subsets (33). Our study demonstrates that, despite the small tumor samples obtained from standard-of-care TURBT specimens, enrichment of NMIUC patient subsets based on molecular testing is possible and should be pursued if scientific hypotheses warrant it.

In addition, our results establish the frequency of *FGFR3* mutations in the BCG-unresponsive NMIUC population at 18% (3 of 17 patients), a previously unknown benchmark. Our *a priori* design assumption that the *FGFR3* mutation rate in patients with BCG-unresponsive NMIUC would fall somewhere between the reported rates in low-grade NMIUC (65%) and muscle-invasive urothelial carcinoma (15%)

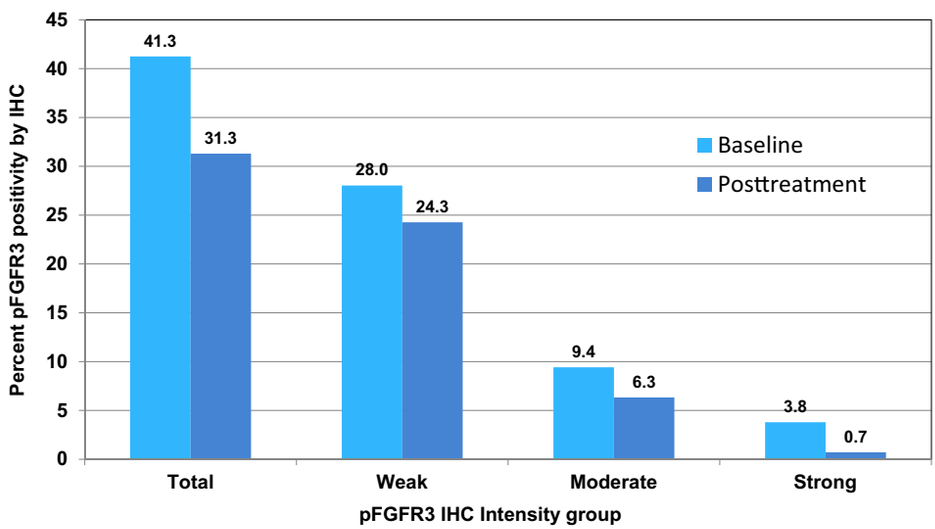

Figure 2.
Pre- and post-dovitinib pFGFR3 IHC results.

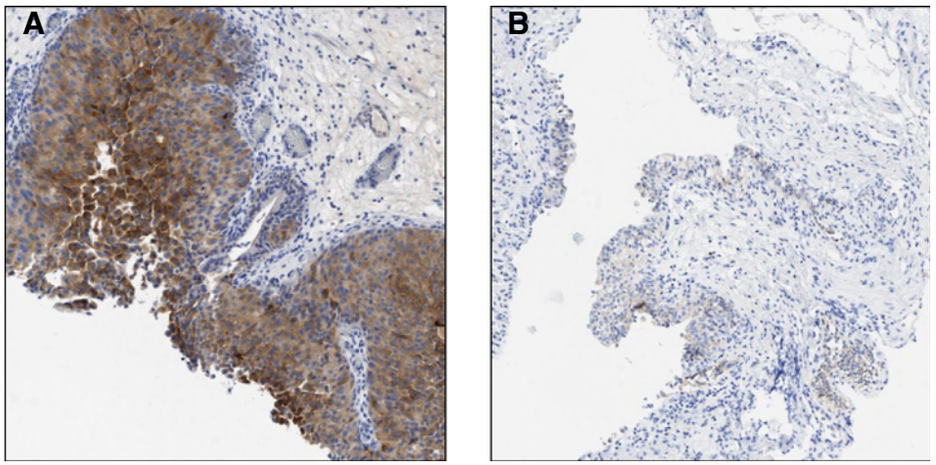

Figure 3.
Dovitinib pFGFR3 IHC pathology samples. **A,** Patient 3 – Baseline. **B,** Patient 3 – Posttreatment cycle 3 day 26.

patients proved incorrect. Our results suggest that BCG-unresponsive NMIUC more closely resembles muscle-invasive and metastatic urothelial carcinoma than a low-grade NMIUC predecessor tumor. The lower rate of FGFR3 mutations observed in the BCG-unresponsive NMIUC population has implications on future sample size considerations of FGFR3-targeting trials in this population.

Importantly, our trial showed that oral administration of dovitinib unanimously achieved pharmacologically active urothelial tissue concentrations. This finding suggests that lack of clinical activity was related to drug toxicity and study population design issues rather than drug delivery failure. These results support further investigation of systemically administered agents in the NMIUC population. A caveat, however, is the fact that the urothelial tissue bioavailability is not usually investigated or provided in preclinical testing data provided in investigator brochures of most novel cancer drugs. A high intact urinary excretion of drug can be reassuring of adequate urothelial tumor drug concentration exposure. However, if urothelial tissue concentrations are critical in the decision process to assess the effectiveness of systemic versus intravesical routes of drug administration, development of clinical pharmacology assays to measure urothelial tissue drug concentrations are strongly recommended.

Finally, our study demonstrates the importance of multispecialty investigator engagement in the conduct of early-stage urothelial carcinoma trials. At each participating center, a urologist, medical oncologist, and pathologist were identified to serve as local champions for the trial. While multidisciplinary teams in varying forms are often utilized in the administration of neoadjuvant cisplatin-based chemotherapy for muscle-invasive urothelial carcinoma, our study highlights the importance of also developing highly functional cross-discipline research collaborations in NMIUC patients. The need for urothelial carcinoma multispecialty research infrastructure is increasing in parallel with the rapid expansion of clinical trials being conducted in the muscle-invasive adjuvant, neoadjuvant, and BCG-unresponsive NMIUC populations.

In summary, our study firmly establishes that pFGFR3 IHC alone should not be used as a solitary qualifying criteria for enrollment in future urothelial carcinoma trials of FGFR3 kinase inhibitors. In addition, the unfavorable toxicity profile of dovitinib precludes further development in the NMIUC population. However, antitumor activity consistent with other reports in *FGFR3* Mut+ patients was observed further implying *FGFR3* as a viable therapeutic target in urothelial carcinoma across all stages including NMIUC. The demonstration that genomic testing as an eligibility requirement in NMIUC patients is feasible and the detection of pharmacologically active dovitinib urothelial tissue concentrations by oral drug administration are novel findings with implications for future NMIUC trial designs.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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