JAMA Oncology | Review

FGFR Alterations in Bladder Cancer—From Molecular Pathogenesis to Precision Oncology

Katrina Collins, MD; Liang Cheng, MD, MSc

IMPORTANCE Alterations in the fibroblast growth factor receptor (FGFR) pathway, particularly *FGFR3*, are among the most common genomic events in urothelial carcinoma (UC) and represent a cornerstone of precision oncology. Although *FGFR3* alterations predominate, selected *FGFR2* fusions also identify patients who may benefit from targeted therapy. This review summarizes the biology, molecular diagnostics, and evolving clinical applications of FGFR alterations in UC.

OBSERVATIONS *FGFR2/3* alterations are clinically actionable biomarkers across non–muscle-invasive, muscle-invasive, metastatic, and upper-tract UC. Comprehensive genomic profiling, tissue sequencing, plasma circulating tumor DNA, urine-based molecular assays, and molecular residual disease assessment are expanding their roles in diagnosis, treatment selection, surveillance, and disease monitoring. Recent clinical studies support combination strategies, next-generation FGFR inhibitors, and earlier use of FGFR-directed therapy, while emerging technologies, including artificial intelligence–assisted pathology and integrated multi-omic biomarkers, may further improve patient selection.

CONCLUSIONS AND RELEVANCE FGFR alterations have become integral to the molecular classification and precision management of UC. Continued advances in molecular diagnostics, liquid biopsy, biomarker-guided therapy, and next-generation FGFR inhibitors are expected to further personalize care. This review provides a practical framework for integrating FGFR biomarkers into contemporary management and highlights emerging developments likely to influence future clinical practice.

JAMA Oncol. doi:10.1001/jamaoncol.2026.4196
Published online October 29, 2026.

CME at jamacmelookup.com

Author Affiliations: Department of Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston (Collins); Department of Pathology and Laboratory Medicine, Brown University Warren Alpert Medical School, Providence, Rhode Island (Cheng); Division of Urology, Department of Surgery, Brown University Warren Alpert Medical School, Providence, Rhode Island (Cheng); Legorreta Cancer Center at Brown University, Brown University Health, Providence, Rhode Island (Cheng).

Corresponding Author: Liang Cheng, MD, MSSc, Department of Pathology and Laboratory Medicine, Brown University Warren Alpert Medical School, 593 Eddy St, APC12-105, Providence, RI 02903 (liang_cheng@yahoo.com).

Precision oncology has transformed the management of urothelial carcinoma (UC) by integrating biomarker-driven diagnosis and treatment. Fibroblast growth factor receptor (FGFR) alterations, an umbrella term encompassing activating point mutations, gene fusions, rearrangements, copy number alterations, and other structural abnormalities, are among the most clinically important molecular events in UC. *FGFR3* activating mutations predominate, whereas less frequent *FGFR2* alterations, most commonly gene fusions, also have therapeutic relevance.[1-5]

FGFR alterations are actionable biomarkers, and molecular testing for susceptible *FGFR2/3* alterations is established in advanced UC. Next-generation sequencing (NGS), liquid biopsy, and urine-based assays are extending molecular profiling across diagnosis, classification, treatment selection, surveillance, molecular residual disease (MRD) assessment, and clinical trial enrollment.[6-12] This review summarizes FGFR biology, clinicopathologic associations, molecular diagnostics, targeted therapies, resistance, and emerging applications, including liquid biopsy, urine-based biomarkers, artificial intelligence (AI), and MRD assessment, with emphasis on the dominant biologic and clinical role of *FGFR3*.

FGFR Biology and Pathophysiology

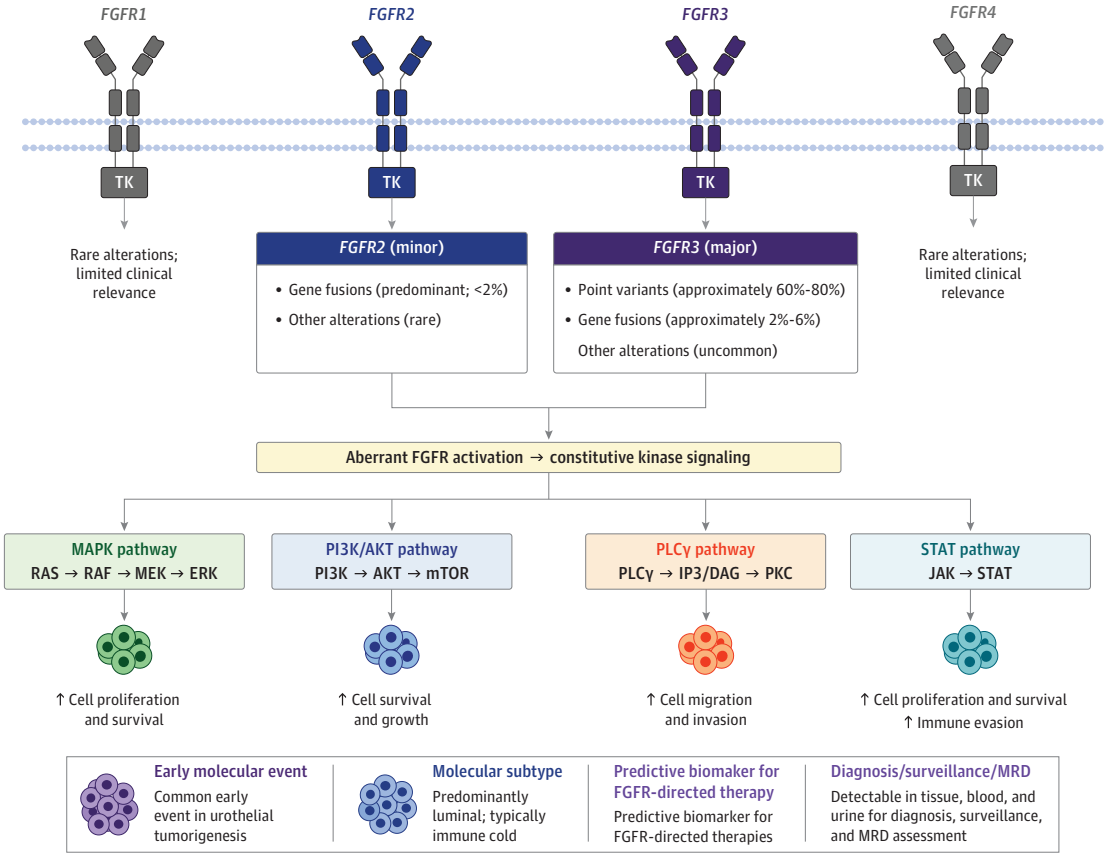
The FGFR family comprises 4 receptor tyrosine kinases (*FGFR1*, *FGFR2*, *FGFR3*, and *FGFR4*) that regulate development, tissue homeostasis, angiogenesis, and cellular proliferation. UC is characterized by the frequent *FGFR3* alterations and less common actionable *FGFR2* fusions, defining a therapeutically targetable molecular subset.[5,13,14]

Ligand binding normally induces receptor dimerization, autophosphorylation, and mitogen-activated protein kinase, phosphoinositide 3-kinase/protein kinase B, phospholipase C gamma, and signal transducer and activator of transcription signaling. FGFRs are expressed in epithelial mesenchymal and vascular tissues; *FGFR3* is the predominant transcript in normal urothelium, providing physiologic context for the on-target toxic effects of systemic FGFR inhibition. Aberrant signaling promotes proliferation, survival, stromal interactions, and immune regulation, and contributes to the immune-depleted phenotype of many *FGFR3*-altered tumors.[15]

Hotspot *FGFR3* alterations, including *S249C, R248C, Y373C*, and *G370C*, cause ligand-independent activation, whereas

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.
Downloaded from jamanetwork.com by Universidad Libre de Colombia, heiydar dolati on 10/30/2026

Figure. Illustration of the Fibroblast Growth Factor Receptor (FGFR) Pathway in Urothelial Carcinoma



Schematic overview of the FGFR family in urothelial carcinoma, highlighting the predominance of *FGFR3* alterations and less frequent *FGFR2* fusions. Aberrant FGFR activation results in constitutive kinase signaling through the mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), phospholipase C gamma (PLCγ), and signal transducer and activator of transcription (STAT) pathways, promoting tumor growth and progression. FGFR alterations also serve as clinically actionable biomarkers for targeted therapy and disease monitoring. DAG indicates diacylglycerol; ERK, extracellular signal-regulated kinase; IP3, inositol 1,4,5-trisphosphate; JAK, Janus kinase; MEK, mitogen-activated protein kinase kinase; MRD, molecular residual disease; mTOR, mechanistic target of rapamycin; PKC, protein kinase C; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma viral oncogene homolog; TK, tyrosine kinase.

FGFR3::TACC3 and other fusions produce constitutive kinase signaling (**Figure**).[13,14,16] Clinicopathologic features are summarized in **Table 1**.

Clinicopathologic Landscape of FGFR-Altered Urothelial Carcinoma

FGFR3 alterations are early events in urothelial tumorigenesis and are enriched in low-grade papillary non–muscle-invasive bladder cancer (NMIBC) but remain clinically relevant in muscle-invasive, metastatic, and upper tract urothelial carcinoma (UTUC). *FGFR* alterations occur in approximately 22% to 40% of UTUCs, depending on disease stage, population, and testing method.[17,18] Their frequency and therapeutic actionability support molecular profiling, particularly in advanced UC and UTUC (Table 1).[1,19,20]

FGFR3-mutated tumors typically show low-grade papillary architecture, whereas *FGFR3* fusions are more often associated with high-grade, muscle-invasive, or metastatic disease. However, hotspot mutations also occur in morphologically diverse tumors. In a recent clinicopathologic study, 76% of *FGFR3*-altered UCs demonstrated variant histology, most commonly micropapillary and squamous differentiation, confirming that *FGFR3* alterations are not restricted to conventional low-grade papillary tumors.[13,14,16,21] Histology alone cannot determine FGFR status but may prompt molecular testing.

Transcriptomically, *FGFR3*-altered tumors are usually luminal, with expression of *GATA3*, PPARγ, and uroplakins, and reduced expression of basal markers such as *KRT5*, *KRT14*, and CD44. Compared with basal tumors, they generally have lower genomic instability and proliferative activity and an immune-depleted microenvironment.[6,7,15,16,22]

Common co-alterations involve chromatin-remodeling genes, including *KDM6A, ARID1A, KMT2D, CREBBP*, and *EP300*, and the *TERT* promoter. *TP53* and *RB1* alterations are less frequent in early-stage tumors but increase with progression.[7,14,20] These features distinguish FGFR-altered UC within contemporary molecular classifications.[2,3,21]

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.
Downloaded from jamanetwork.com by Universidad Libre de Colombia, heiydar dolati on 10/30/2026

Table 1. Clinically Relevant Fibroblast Growth Factor Receptor (FGFR) Alterations in Urothelial Carcinoma (UC)

Alteration	Approximate frequency	Mechanism of activation	Clinicopathologic phenotype	Preferred detection method	Clinical utility	Therapeutic actionability
Activating *FGFR3* point mutations (*S249C*, *R248C*, *Y373C*, *G370C*, *K652E/Q/M*)	60%-80% Of low-grade NMIBC, 15%-20% of MIBC, and enriched in UTUC	Ligand-independent receptor dimerization and constitutive kinase activation	Low-grade papillary UC, luminal subtype, immune-cold phenotype, and variant histologies (eg, micropapillary, squamous)	DNA NGS or PCR-based companion diagnostic	Early molecular event and diagnostic, predictive, and surveillance biomarker	FDA-approved predictive biomarker for FGFR-targeted therapy
FGFR3::TACC3 fusion	2% to 6% of UC	Fusion-mediated constitutive kinase activation	MIBC and metastatic UC (predominantly luminal subtype)	RNA sequencing (preferred) or comprehensive NGS	Predictive biomarker for FGFR-targeted therapy	FDA-approved predictive biomarker
Other *FGFR3* fusions (*FGFR3::BAIAP2L1*, *FGFR3::BICC1*, *FGFR3::FGFR3OP*, *FGFR3::GOLGA5*, *FGFR3::ACTG1*, and *FGFR3::DACH1*)	Rare (<1% individually)	Constitutive activation through fusion partner	Advanced UC	RNA sequencing	Potentially actionable alterations; comprehensive fusion testing recommended	Potentially actionable
FGFR2 fusions	Rare (<2%)	Fusion-mediated constitutive kinase activation	Advanced UC (uncommon but clinically relevant)	RNA sequencing	Predictive biomarker for FGFR-directed therapy	Clinically actionable
FGFR3 amplification/ copy number gain	2%-5%	Increased gene dosage and receptor expression	Variable histologic and molecular settings	DNA NGS	Clinical significance remains uncertain	Investigational
Alternative *FGFR3* splicing/isoform switching	Rare	Altered ligand specificity and signaling	Under investigation	RNA sequencing	Biological significance incompletely defined	Investigational
FGFR3 overexpression	Variable	Increased protein expression without genomic alteration	Multiple UC subtypes	Immunohistochemistry (research use)	Protein expression alone is not predictive of response	Not clinically validated

Abbreviations: FDA, US Food and Drug Administration; MIBC, muscle-invasive bladder cancer; NGS, next-generation sequencing; NMIBC, non–muscle-invasive bladder cancer; PCR, polymerase chain reaction; UTUC, upper tract urothelial carcinoma.

Molecular Testing and Biomarkers

Molecular testing is essential for identifying actionable *FGFR2/3* alterations in advanced UC. Because different alteration types require different analytical approaches, combined DNA/RNA NGS is generally preferred for initial molecular characterization. DNA-based NGS detects *FGFR3* point mutations, insertions/deletions, and copy number alterations, whereas RNA sequencing is more sensitive for *FGFR3::TACC3* and other gene fusions.[4,5,8]

Once a patient-specific alteration has been identified, targeted polymerase chain reaction provides rapid, sensitive monitoring of plasma circulating tumor DNA (ctDNA) or urinary tumor DNA for surveillance and MRD assessment, although it interrogates only predefined genomic targets. Comprehensive sequencing therefore remains the preferred approach for initial profiling and discovery of novel alterations.[5,8,23-25]

Although tissue remains the reference standard, plasma ctDNA provides a minimally invasive approach for detecting actionable alterations, monitoring treatment response, identifying acquired resistance, and supporting perioperative risk assessment and MRD evaluation, with high concordance to tissue testing.[2,8,24,26,27] Urine-based assays complement tissue testing by supporting molecular diagnosis, recurrence detection, surveillance, and patient selection for intravesical FGFR-directed therapy. Urinary tumor DNA demonstrates high concordance with tissue genomic profiling and is being investigated for MRD assessment and prediction of response to neoadjuvant immunotherapy.[28,29] In the TAR-210 development program, urinary testing identified actionable FGFR alterations in patients without adequate tissue.[5,10] Increasing analytical sensitivity and prospective validation continue to expand the clinical utility of urinary biomarkers (**Table 2**).[5,9-12,30,31]

Clinical Applications Across the Disease Continuum

FGFR2/3 alterations are clinically actionable biomarkers that inform diagnosis, treatment selection, and disease monitoring across the UC disease continuum.[4,5,8,9] In NMIBC, *FGFR3* alterations occur early in tumorigenesis and are highly enriched in low-grade papillary tumors. In contrast, urothelial carcinoma in situ harbors *FGFR3* alterations far less frequently and is more commonly associated with *TP53* alterations and the basal molecular subtype. Consequently, *FGFR3*-directed urinary biomarkers are expected to have greater utility in papillary NMIBC than in urothelial carcinoma in situ, although cystoscopy and histopathologic evaluation remain the standards for diagnosis and surveillance.[10,13,19,32]

In muscle-invasive and metastatic UC, comprehensive molecular profiling identifies patients eligible for FGFR-directed therapy, facilitates enrollment in biomarker-driven clinical trials, and may identify co-occurring genomic alterations associated with prognosis and therapeutic resistance.[4,5,8,33] Liquid biopsy further expands the clinical utility of FGFR biomarkers. Plasma

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.
Downloaded from jamanetwork.com by Universidad Libre de Colombia, heiydar dolati on 10/30/2026

Table 2. Molecular Testing Platforms for Detection of *FGFR2/3* Alterations in Urothelial Carcinoma (UC)

Testing platform	Specimen	Primary alterations detected	Analytical performance	Typical turnaround time	Advantages	Limitations	Clinical application
PCR-based companion diagnostics	FFPE tissue	Hotspot *FGFR2/3* mutations and selected fusions	High analytical sensitivity for recurrent hotspot mutations	1-3 d	Rapid, standardized, relatively low cost, and clinically validated companion diagnostic approach	Limited to predefined variants and may miss rare mutations, novel fusions, and broader genomic context	Companion diagnostic testing for FGFR-targeted therapy
DNA-based NGS	FFPE tissue	Mutations, insertions/deletions, and copy number alterations	High analytical sensitivity for mutations but limited for fusion detection	Approximately 7-14 d	Comprehensive genomic profiling and detects co-alterations and trial-eligible alterations	Requires adequate tissue and fusion detection may be limited	Preferred tissue-based profiling in advanced UC
RNA sequencing/ anchored multiplex PCR	FFPE tissue	*FGFR2/3* fusions and expressed splice variants	Highest sensitivity for expressed *FGFR2/3* fusions	Approximately 7-14 d	Best method for fusion detection and can identify novel partners	RNA quality dependent and less available than DNA NGS	Fusion detection when actionable rearrangement is suspected or DNA NGS is negative/ incomplete
Combined DNA/RNA NGS	FFPE tissue	Mutations, insertions/ deletions, copy number alterations, and fusions	Highest overall molecular yield and assay dependent	Approximately 10-21 d	Most comprehensive single-platform approach	Higher cost, longer turnaround, and tissue requirements	Preferred comprehensive molecular profiling
Plasma ctDNA	Peripheral blood	Mutations, selected fusions, and resistance alterations	High tissue concordance (approximately 90%) and reduced sensitivity in low-volume/ localized disease[a]	Approximately 5-10 d	Noninvasive, complements tissue profiling, and enables serial monitoring and resistance detection	False negative results with low tumor shedding and tissue confirmation may still be required	Treatment monitoring, resistance detection, and MRD assessment
Urinary cfDNA/utDNA	Urine	Tumor-derived mutations, including *FGFR3*	Variable and often higher sensitivity for intravesical disease than plasma, but assay and setting dependent	Approximately 3-10 d	Noninvasive and biologically attractive for bladder-localized disease, surveillance, and patient selection when tissue is inadequate	Limited standardization with prospective validation still evolving	NMIBC surveillance, recurrence detection, bladder-preservation monitoring, and investigational MRD
Urinary RNA/exosomal RNA	Urine	Gene expression signatures, expressed fusions, and noncoding RNA	Variable and platform dependent	Approximately 3-10 d	May capture transcriptionally active disease and exosomes protect RNA from degradation	Preanalytic variability and limited clinical availability	Investigational diagnostic, surveillance, and MRD applications
AI-assisted histopathology	H&E whole-slide images	Predicted *FGFR3* mutation status	Sensitivity, 0.96-1.00; NPV, 0.99-1.00; specificity, 0.32-0.47[22]; and proof-of-concept performance lower in earlier studies[21]	Potentially rapid once deployed	May reduce molecular testing burden and uses routine H&E slides	Prescreen only and not a replacement for molecular confirmation	Emerging prescreening tool for molecular testing

Abbreviations: AI, artificial intelligence; cfDNA, cell-free DNA; ctDNA, circulating tumor DNA; FFPE, formalin-fixed paraffin-embedded; FGFR, fibroblast growth factor receptor; H&E, hematoxylin and eosin; MRD, molecular residual disease; NGS, next-generation sequencing; NMIBC, non–muscle-invasive bladder cancer; NPV, negative predictive value; PCR, polymerase chain reaction; utDNA, urinary tumor DNA.

[a] Sensitivity and specificity vary according to assay design, specimen quality, disease stage, and study population; reported values represent approximate ranges from the contemporary literature. Plasma ctDNA performance is supported by a prospective multicenter study demonstrating approximately 90% concordance with tissue-based FGFR testing and identification of additional actionable alterations.[20]

ctDNA enables longitudinal assessment of tumor genomics, treatment response, acquired resistance, and MRD, while urine-based assays support molecular diagnosis and surveillance in patients with an intact bladder. Because urine-based assays depend on continued tumor DNA shedding into the urinary tract, their clinical utility is limited following radical cystectomy, when plasma

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Downloaded from jamanetwork.com by Universidad Libre de Colombia, heiydar dolati on 10/30/2026

Table 3. Landmark Clinical Trials of Fibroblast Growth Factor Receptor (FGFR)–Targeted Therapies in Urothelial Carcinoma (UC)

Agent (mechanism)	Trial	Phase	Clinical setting	Biomarker/eligibility[a]	Key findings	Clinical impact
Approved FGFR-targeted therapy						
Erdafitinib (pan-*FGFR1-4* inhibitor)[35-41]	BLC2001 (NCT02365597)[42]	2	Locally advanced/metastatic UC after platinum chemotherapy	*FGFR2/3* mutations or fusions	ORR, approximately 40%; durable responses established proof-of-concept for FGFR inhibition	Supported accelerated FDA approval
	THOR (NCT03390504)[43]	3	Previously treated advanced/ metastatic UC	*FGFR3/2* alterations	Improved OS, PFS, and ORR vs chemotherapy (median OS, 12.1 mo vs 7.8-8.7 mo; ORR, 46.9% vs 12.6%)	Established current standard targeted therapy
Combination therapy						
Erdafitinib + cetrelimab[44-46]	NORSE (NCT03473743)[47]	2	First-line cisplatin-ineligible metastatic UC	*FGFR2/3* alterations	ORR, 44.2% (erdafitinib) vs 54.5% (erdafitinib + cetrelimab) with durable responses	Supports FGFR inhibitor immunotherapy combinations
Futibatinib + pembrolizumab (irreversible pan-*FGFR1-4* inhibitor)[48,49]	TAS-120-203 (NCT04601857)[50]	2	First-line platinum-ineligible metastatic UC	*FGFR2/3* alterations	Preliminary safety data only in a small UC cohort (n=6; median treatment, approximately 48 d); efficacy outcomes not yet reported	Supports continued development of FGFR inhibitor immunotherapy combinations
NMIBC/bladder-preserving therapy						
Erdafitinib (oral)[51,52]	Window-of-opportunity erdafitinib trial (NCT04917809)[53]	2	Recurrent *FGFR3*-altered NMIBC	*FGFR3* alterations	High CR rate with short-course oral therapy (approximately 75% [6 of 8 evaluable] in FGFR-altered intermediate-risk NMIBC)	Demonstrates biologic activity in bladder-preserving therapy
Erdafitinib (TAR-210 intravesical drug delivery system)[4,54,55]	MoonRISe-1 (NCT06319820)[56]	3	Intermediate-risk FGFR-altered NMIBC	FGFR alterations	Ongoing randomized trial vs single-agent intravesical chemotherapy with efficacy results pending (phase 1 TAR-210 reported approximately 87% CR at 3 mo)	Expands FGFR-directed therapy into localized disease
Investigational next-generation therapies						
Infigratinib (*FGFR1-3* inhibitor)[57-59]	Phase 1 expansion cohort (NCT01004224)[60]	1b	Advanced/ metastatic UC	FGFR3 alterations	ORR, 25.4%; disease control, 64.2%; and first clinical proof-of-concept for selective FGFR inhibition	Development discontinued
Rogaratinib (pan-FGFR inhibitor)[61-63]	FORT-1 (NCT03410693)[64]	2/3	Advanced UC	*FGFR1/3* mRNA overexpression	Failed to improve OS despite responses in selected patients	Demonstrated limitations of mRNA expression as a predictive biomarker
Dabogratinib (selective *FGFR3* inhibitor)[65,66]	SURF301 (NCT05544552)[67]	1/2	Advanced/ metastatic UC	*FGFR3* alterations	Early clinical activity with pharmacodynamic ctDNA responses	Ongoing clinical development
Vepugratinib (LY3866288/ LOXO-435; selective *FGFR3* inhibitor)[68,69]	FORAGER-1 (NCT05614739)[70]	1	Advanced solid tumors, including metastatic UC	*FGFR3* mutations or fusions	ORR, approximately 42%-45%; encouraging activity after prior FGFR inhibition; and favorable early safety profile	Promising next-generation *FGFR3*-selective inhibitor

Abbreviations: BCG, Bacillus Calmette-Guérin; CR, complete response; ctDNA, circulating tumor DNA; FDA, US Food and Drug Administration; mRNA, messenger RNA; NA, not applicable; NMIBC, non–muscle-invasive bladder cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

[a] FGFR alterations include activating mutations and gene fusions unless otherwise specified.

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Downloaded from jamanetwork.com by Universidad Libre de Colombia, heiydar dolati on 10/30/2026

Table 4. Emerging Fibroblast Growth Factor Receptor (FGFR)–Directed Therapeutic Platforms in Urothelial Carcinoma (UC)

Therapeutic platform	Representative agent(s)	Delivery method	Disease setting[a]	Advantages	Development status
Oral FGFR TKIs	Erdafitinib, infigratinib, rogaratinib, and futibatinib	Oral systemic	Advanced/ metastatic UC	Established efficacy and biomarker-selected therapy	Approved/clinical trials
Selective *FGFR3* inhibitors	Dabogratinib and LY3866288	Oral systemic	Advanced UC	Greater target selectivity and potential reduction in off-target toxic effects	Early clinical development
Intravesical sustained-release FGFR inhibition	TAR-210	Intravesical controlled-release device	*FGFR3*-altered NMIBC	High local drug concentration with reduced systemic exposure	Phase 2
FGFR3 antibody-drug conjugates	LZU-WZLYCS01	Intravenous	Advanced UC	Selective cytotoxic payload delivery	Preclinical
FGFR3 × CD3 bispecific T-cell engagers	Investigational	Intravenous	Advanced UC	Redirects cytotoxic T cells toward *FGFR3*-expressing tumor cells	Early clinical development
FGFR inhibitor + epigenetic modulators	Investigational combinations	Systemic combination therapy	FGFR-altered advanced UC	May overcome therapeutic resistance by targeting epigenetic dysregulation and chromatin remodeling pathways	Preclinical
Nanoparticle-based delivery	Lipid/polymeric nanoparticles	Intravesical or systemic	Experimental	Improved drug stability and tumor targeting	Preclinical
Liposomal formulations	Investigational	Intravesical	Experimental	Enhanced urothelial penetration	Preclinical
Gene/RNA-based FGFR targeting	siRNA and antisense oligonucleotides	Intravesical/ systemic	Experimental	Direct suppression of FGFR signaling	Preclinical

Abbreviations: NMIBC, non–muscle-invasive bladder cancer; siRNA, small interfering RNA; TKI, tyrosine kinase inhibitor.

[a] FGFR alterations include activating mutations and gene fusions unless otherwise specified.

ctDNA may provide a more informative biomarker. Although prospective validation is ongoing, these approaches may enable earlier recurrence detection and more personalized longitudinal disease monitoring.[10-12,27,29,31,33,34]

Molecular Residual Disease and Liquid Biopsy

Assessment of MRD using ctDNA is an emerging application of precision oncology in UC. Detection of ctDNA following radical cystectomy or systemic therapy is associated with an increased risk of recurrence and may ultimately guide postoperative risk stratification, surveillance, and adjuvant treatment selection. Although FGFR-specific MRD strategies remain investigational, ongoing ctDNA-guided clinical trials are expected to define their role in personalized management.[6,25]

Integration of plasma ctDNA, urine-derived biomarkers, and multi-omic approaches may further improve early recurrence detection and refine individualized surveillance strategies. Although prospective validation remains necessary, MRD assessment has the potential to become an integral component of personalized FGFR-directed management across the UC disease continuum.[6,10,25,29,32,34]

Treatments

FGFR-Targeted Therapy

FGFR-targeted therapy has transformed the management of advanced UC, with susceptible *FGFR2/3* alterations serving as clinically actionable biomarkers. Erdafitinib remains the only approved FGFR inhibitor and the first biomarker-selected therapy to demonstrate an overall survival benefit in advanced UC (**Table 3**).[4,5,35-70].

The phase 2 BLC2001 trial demonstrated durable clinical activity of erdafitinib in patients with locally advanced or metastatic UC harboring susceptible *FGFR2/3* alterations after platinum-based chemotherapy, supporting accelerated regulatory approval. The phase 3 THOR trial subsequently demonstrated statistically significant improvements in overall survival, progression-free survival, and objective response rate compared with investigator's choice chemotherapy, establishing erdafitinib as the standard targeted therapy for patients with susceptible *FGFR2/3* alterations who have been previously treated.[4,35]

Because FGFR regulates phosphate homeostasis and epithelial tissue maintenance, FGFR inhibitors produce characteristic on-target toxic effects. Hyperphosphatemia is the most common adverse effect. Additional toxic effects include stomatitis, diarrhea, dry mouth, skin and nail changes, and ocular toxic effects, particularly central serous retinopathy/retinal pigment epithelial detachment, which require biochemical and ophthalmologic monitoring and may necessitate dose interruption or modification.[4,35] Ocular toxic effects are thought to result, in part, from *FGFR2* inhibition within the retinal pigment epithelium, providing the rationale for the development of *FGFR3*-selective inhibitors that may reduce ocular toxic effects while maintaining antitumor activity.[71]

Treatment of NMIBC

FGFR-directed therapy is moving into earlier disease settings, particularly recurrent *FGFR3*-altered NMIBC. In a phase 2 window-of-opportunity study, patients receiving short-course oral erdafitinib achieved an objective response rate of 75% and a complete response rate of 55%, providing proof-of-concept for biomarker-selected therapy in NMIBC.[51]

Intravesical delivery may further improve the therapeutic index by maximizing local drug exposure while minimizing systemic toxic effects. The investigational TAR-210 sustained-release erdafitinib delivery system has demonstrated encouraging activity in recurrent *FGFR3*-altered NMIBC, including intermediate- and high-risk disease.[5,10] Additional intravesical approaches are under investigation and may further expand

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Downloaded from jamanetwork.com by Universidad Libre de Colombia, heiydar dolati on 10/30/2026

bladder-preserving treatment options and clarify integration with conventional intravesical therapy and surgery.[5,19]

Combination Therapy

Combination strategies are being explored to overcome acquired resistance and improve response durability. Aberrant FGFR signaling promotes an immune-depleted (immune-cold) tumor microenvironment, providing a biologic rationale for combining FGFR inhibition with immune checkpoint blockade.[5,15]

In the phase 2 NORSE study, first-line erdafitinib plus the programmed cell death protein 1 inhibitor cetrelimab demonstrated higher confirmed objective response rates than erdafitinib alone (54.5% vs 44.2%) in cisplatin-ineligible patients with metastatic UC harboring susceptible *FGFR2/3* alterations, with durable responses and a manageable safety profile.[44] Similarly, the irreversible *FGFR1-4* inhibitor futibatinib combined with pembrolizumab achieved a confirmed objective response rate of approximately 47% and a median duration of response of 12.3 months in the phase 2 TAS-120-203 trial among patients with *FGFR3* alterations or *FGFR1-4* fusions/rearrangements. Toxic effects were consistent with the established safety profile of FGFR inhibition, supporting continued evaluation of this combination.[48]

Another promising combination strategy combines erdafitinib with the nectin-4–directed antibody-drug conjugate enfortumab vedotin. In the phase 1b ETCTN 10483 trial, the combination demonstrated a manageable safety profile, established the recommended phase 2 dose, and showed encouraging preliminary antitumor activity in patients with metastatic UC harboring susceptible *FGFR2/3* alterations, supporting further evaluation of dual FGFR and nectin-4 targeting.[72]

Combinations with antibody-drug conjugates, chemotherapy, and other targeted agents are under investigation to overcome resistance and improve long-term disease control. Biomarker-guided sequencing and rational combinations may further optimize treatment for FGFR-altered UC.[4,5,38]

Novel FGFR Therapeutic Platforms

Beyond erdafitinib, additional FGFR inhibitors and novel delivery platforms are being investigated to overcome resistance and expand treatment options for FGFR-altered UC. Infigratinib demonstrated clinical activity in patients with previously treated advanced UC harboring *FGFR3* alterations, with an objective response rate of 25.4% and a disease control rate of 64.2%, although its clinical development in UC has not advanced further.[57] Rogaratinib was evaluated in the phase 2/3 FORT-1 trial using *FGFR1/3* messenger RNA (mRNA) overexpression rather than genomic alterations for patient selection.[61] *FGFR1/3* mRNA expression was assessed using RNA in situ hybridization (RNAscope), with high expression defined as a score of 3 or higher or 4 or higher. Although transcript-based selection identified a broader population than activating genomic alterations, rogaratinib did not improve survival compared with chemotherapy. These findings highlight the complementary roles of genomic and transcriptomic biomarkers and the need for continued refinement of predictive biomarker strategies. Beyond direct inhibition of tumor-cell FGFR signaling, FGFR inhibition may also modulate the tumor microenvironment by influencing stromal signaling, angiogenesis, and immune-cell infiltration, potentially contributing to responses in tumors with *FGFR1/3* mRNA overexpression.[15,61]

Notably, *FGFR1/3* mRNA overexpression is more common than FGFR genomic alterations, occurring in approximately 40% to 50% of UCs compared with 15% to 20% harboring activating mutations or fusions. Rogaratinib and futibatinib trials therefore enrolled patients using transcript-based assays with prespecified expression cutoffs rather than genomic sequencing alone. Although this strategy expanded eligibility, clinical experience suggests that mRNA overexpression alone is less predictive of therapeutic benefit than activating genomic alterations, underscoring the need for continued refinement of predictive biomarkers.[61,73]

Next-generation *FGFR3*-selective inhibitors are being developed to overcome resistance and improve therapeutic selectivity. In the phase 1/2 SURF301 study, dabogratinib demonstrated pharmacodynamic activity, including reductions in ctDNA, in patients with metastatic *FGFR3*-altered UC.[65] Similarly, vepugratinib (LY3866288) demonstrated preliminary clinical activity in the phase 1 FORAGER-1 study, supporting continued development of this therapeutic class.[68]

Novel delivery platforms are also being explored to enhance local drug delivery while limiting systemic toxic effects. The sustained-release intravesical TAR-210 system has demonstrated early clinical activity in *FGFR3*-altered NMIBC.[5,10] Additional approaches, including *FGFR3*-targeted antibody-drug conjugates (ADCs), nanoparticle-based delivery systems, liposomal formulations, and RNA-directed therapeutics, remain in preclinical or early clinical development (**Table 4**).

Among these emerging platforms, *FGFR3*-targeted ADCs selectively deliver cytotoxic payloads to *FGFR3*-expressing tumor cells, potentially enhancing efficacy while limiting systemic toxic effects. The investigational ADC LZU-WZLYCS01 demonstrated potent antitumor activity in cell lines, patient-derived organoids, and xenograft models while maintaining favorable tumor selectivity.[74] Although early in development, *FGFR3*-targeted ADCs represent a promising strategy for patients with *FGFR3*-expressing UC, including those with resistance to current FGFR inhibitors. FGFR3 and CD3 bispecific T-cell engagers and combinations of FGFR inhibitors with epigenetic modulators are also under early clinical and preclinical investigation.

Mechanisms of Resistance to FGFR Inhibition

Acquired resistance remains the principal limitation of FGFR-targeted therapy in advanced UC. Mechanisms include secondary FGFR kinase domain alterations, activation of bypass signaling pathways, intratumoral heterogeneity, and clonal evolution, providing the rationale for next-generation inhibitors and combination strategies.[5,6]

Secondary FGFR Kinase Domain Mutations

On-target resistance most commonly results from secondary mutations within the FGFR kinase domain mutations that reduce inhibitor binding while preserving receptor signaling. Gatekeeper and molecular brake mutations are frequent mechanisms of acquired resistance following first-generation FGFR inhibitors.[5,57,75,76] Clinical and ctDNA analyses have identified recurrent resistance-associated FGFR kinase domain mutations, confirming clonal

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.
Downloaded from jamanetwork.com by Universidad Libre de Colombia, heiydar dolati on 10/30/2026

evolution under therapeutic pressure.[5,57,76] Similar to *EGFR*- and *ALK*-directed therapy in non–small cell lung cancer, next-generation FGFR inhibitors are being developed to overcome specific resistance mutations. Highly selective *FGFR3* inhibitors, including dabogratinib (TYRA-300) and vepugratinib (LY3866288), have shown promising preclinical activity and encouraging early clinical efficacy while reducing off-target toxic effects.[68,71]

Activation of Bypass Signaling Pathways

Resistance also arises through activation of alternative oncogenic pathways, including phosphoinositide 3-kinase/protein kinase B, mitogen-activated protein kinase/*ERK*, *EGFR*/*ERBB2*, and *MET*, providing the rationale for combination therapies targeting complementary signaling pathways.[5,15]

Role of ctDNA

Serial ctDNA analysis can identify emerging resistance-associated FGFR kinase domain mutations and clonal evolution before radiographic disease progression, providing earlier therapeutic intervention and adaptive treatment strategies and biomarker-directed treatment sequencing as next-generation FGFR inhibitors are developed.[24,57]

Strategies to Overcome Resistance

Understanding resistance mechanisms is driving development of selective and irreversible FGFR inhibitors, rational combination therapies, and biomarker-guided treatment sequencing. Integration of molecular profiling with longitudinal ctDNA monitoring may further personalize management of FGFR-altered UC.[4,5,65]

Future Directions

The role of FGFR alterations in UC continues to expand beyond targeted therapy through advances in molecular diagnostics, AI, and biomarker-driven management, supporting earlier diagnosis, individualized treatment, and longitudinal disease monitoring.[9] AI-assisted pathology is an emerging complement to molecular profiling. Deep-learning algorithms can predict *FGFR3* alteration status from routine hematoxylin and eosin–stained slides, potentially prioritizing patients for confirmatory genomic testing while reducing reliance on tissue-intensive molecular assays.[30,31]

Therapeutic development is moving beyond first-generation FGFR inhibition. Next-generation inhibitors, biomarker-guided treatment strategies, and rational combinations are being investigated to overcome acquired resistance and improve the durability of response. In NMIBC, future studies may evaluate systemic or intravesical FGFR inhibitors in combination with Bacillus Calmette-Guérin, intravesical chemotherapy, or immune checkpoint blockade to enhance local disease control and potentially expand bladder-preserving treatment options. In advanced disease, systemic FGFR inhibitor combinations with immune checkpoint inhibitors, chemotherapy, and other targeted agents remain under investigation. As these strategies mature, integration of comprehensive genomic profiling with dynamic biomarker assessment and computational pathology is likely to become a central component of personalized UC management.[4,6,38]

Protein expression alone is unlikely to serve as a reliable biomarker for FGFR inhibitor selection. Variable immunohistochemical expression may reflect assay limitations, intratumoral heterogeneity, preanalytic factors, and the absence of validated thresholds, whereas high protein expression does not necessarily indicate oncogenic FGFR dependence. FGFR alterations and overexpression are not mutually exclusive: activating mutations or fusions may increase expression, while overexpression may also occur without a detectable DNA alteration. Similar to *ERBB2*-positive bladder cancer, integrated DNA-, RNA-, and protein-based assessment may ultimately provide more accurate patient selection than any single assay. Prospective validation is needed to define clinically meaningful thresholds and determine which biomarker combinations best predict response.[61,73]

The relationship between FGFR alterations and *ERBB2* expression remains incompletely defined, and these biomarkers should not be considered mutually exclusive. This overlap may be particularly relevant in micropapillary UC, where *ERBB2* overexpression and activating *FGFR3* alterations may coexist. Further study is needed to define the therapeutic implications of dual biomarker expression and potential combination strategies with *ERBB2*-directed therapies.[21,77,78]

Collectively, these advances support an expanding role for *FGFR* alterations beyond treatment selection. Integration of molecular pathology, liquid biopsy, AI-assisted pathology, and targeted therapeutics may establish FGFR-directed precision oncology as a longitudinal framework for UC management.[2,3,79]

Conclusions

FGFR alterations have transformed the management of UC and represent one of the clearest examples of precision oncology in genitourinary cancer. Beyond guiding targeted therapy, FGFR biomarkers now contribute to molecular classification, risk stratification, disease monitoring, and emerging applications in liquid biopsy and MRD assessment.[4,5,9] Continued integration of molecular diagnostics, biomarker development, targeted therapies, next-generation FGFR inhibitors, rational combination strategies, intravesical drug delivery, and AI-assisted pathology is expected to further personalize and simplify the management of FGFR-altered UC.[79]

ARTICLE INFORMATION

Accepted for Publication: August 14, 2026.

Published Online: October 29, 2026. doi:10.1001/jamaoncol.2026.4196

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Al-Obaidy KI, Cheng L. Fibroblast growth factor receptor (*FGFR*) gene: pathogenesis and treatment implications in urothelial carcinoma of the bladder. *J Clin Pathol*. 2021;74(8):491-495. doi:10.1136/jclinpath-2020-207115

2. Lopez-Beltran A, Cookson MS, Guercio BJ, Cheng L. Advances in diagnosis and treatment of bladder cancer. *BMJ*. 2024;384:e076743. doi:10.1136/bmj-2023-076743

3. Ye T, Qadir J, Peng G, Liu L, Cheng L. Evolving landscape of precision medicine in bladder cancer: from challenges to clinical impact. *iLABMED*. 2025;3(4):427-447. doi:10.1002/ila2.70045

4. Loriot Y, Matsubara N, Park SH, et al; THOR Cohort 1 Investigators. Erdafitinib or chemotherapy in advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2023;389(21):1961-1971. doi:10.1056/NEJMoa2308849

5. Li R, Linscott J, Catto JWF, et al. FGFR inhibition in urothelial carcinoma. *Eur Urol*. 2025;87(2):110-122. doi:10.1016/j.eururo.2024.09.012

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Downloaded from jamanetwork.com by Universidad Libre de Colombia, heiydar dolati on 10/30/2026

6. McKay RR, Pal S, Xie W, et al. Advanced Urologic Cancer Consensus Conference (AUC3) 2025: expert consensus on the management of renal cell and urinary tract cancers. *CA Cancer J Clin*. 2026;76(1):e70052. doi:10.3322/caac.70052

7. Alhalabi O, Hahn AW, Msaouel P, et al. Molecular profiling of metastatic bladder cancer early-phase clinical trial participants predicts patient outcomes. *Mol Cancer Res*. 2021;19(3):395-402. doi:10.1158/1541-7786.MCR-20-0751

8. Tateo V, Cigliola A, Mercinelli C, et al. Optimizing the use of next-generation sequencing assays in patients with urothelial carcinoma: recommendations by the 2023 San Raffaele Retreat Panel. *Clin Genitourin Cancer*. 2024;22(4):102091. doi:10.1016/j.clgc.2024.102091

9. Coca Membribes S, Szabados B, Powles T. Towards biomarker-driven therapies for urothelial carcinoma. *Nat Rev Clin Oncol*. 2026;23(2):92-106. doi:10.1038/s41571-025-01095-x

10. Daneshmand S, Zaucha R, Catto JWF, et al. Erdafitinib in patients with high- and intermediate-risk non–muscle-invasive bladder cancer: final analysis of the THOR-2 study. *Eur Urol*. 2026;89(2):165-173. doi:10.1016/j.eururo.2025.09.4152

11. Lee J, Chen F, Lopez-Beltran A, et al. Urinary tumor DNA-based liquid biopsy in bladder cancer management: a systematic review. *Eur Urol Focus*. 2025;11(6):978-990. doi:10.1016/j.euf.2025.06.009

12. Chen F, Simsir A, Cheng L. Molecular testing in urinary cytology specimens: current status and future directions. *Urol Oncol*. 2025;43(10):565-578. doi:10.1016/j.urolonc.2025.02.009

13. Costa R, Carneiro BA, Taxter T, et al. *FGFR3-TACC3* fusion in solid tumors: mini review. *Oncotarget*. 2016;7(34):55924-55938. doi:10.18632/oncotarget.10482

14. Xiao JF, Caliri AW, Duex JE, Theodorescu D. Targetable pathways in advanced bladder cancer: FGFR signaling. *Cancers (Basel)*. 2021;13(19):4891. doi:10.3390/cancers13194891

15. Ruan R, Li L, Li X, et al. Unleashing the potential of combining FGFR inhibitor and immune checkpoint blockade for FGF/FGFR signaling in tumor microenvironment. *Mol Cancer*. 2023;22(1):60. doi:10.1186/s12943-023-01761-7

16. Pederzoli F, Bandini M, Marandino L, et al. Targetable gene fusions and aberrations in genitourinary oncology. *Nat Rev Urol*. 2020;17(11):613-625. doi:10.1038/s41585-020-00379-4

17. Nguyen NJ, Olkhov-Mitsel E, Craddock KJ, Flood TA, Downes MR. Reflex somatic testing for the detection of FGFR alterations in urinary tract carcinomas: a dual-institutional experience. *Am J Clin Pathol*. 2025;164(6):861-869. doi:10.1093/ajcp/aqaf108

18. Audenet F, Isharwal S, Cha EK, et al. Clonal relatedness and mutational differences between upper tract and bladder urothelial carcinoma. *Clin Cancer Res*. 2019;25(3):967-976. doi:10.1158/1078-0432.CCR-18-2039

19. Ascione CM, Napolitano F, Esposito D, et al. Role of *FGFR3* in bladder cancer: treatment landscape and future challenges. *Cancer Treat Rev*. 2023;115:102530. doi:10.1016/j.ctrv.2023.102530

20. Haas M, Mayr R, Sikic D, et al; BRIDGE Consortium e.V. Clinical and genomic landscape of *FGFR3* alterations across different stages of urothelial cancer. *Eur Urol Open Sci*. 2025;77:1-9. doi:10.1016/j.euros.2025.04.005

21. Collins K, Cheng L. *FGFR3*-altered urothelial carcinoma: clinicopathologic observations with emphasis on variant histology. *Lab Invest*. 2026;106(8):106133. doi:10.1016/j.labinv.2026.106133

22. Blanca A, Lopez-Beltran A, Gomez-Gomez E, et al. Prognostic significance of programmed cell death-1, programmed cell death-ligand 1, programmed cell death-ligand 2, and fibroblast growth factor receptor 3 mRNA expression in bladder cancer. *Pathobiology*. 2025;92(4):202-215. doi:10.1159/000544733

23. Ecke T, Weißbach R, Weber A, et al. Detection of *FGFR3* mutations and fusions in bladder cancer samples: comparison of the MODAPLEX FGFR panel with the therascreen FGFR Kit. Paper presented at the 40th Annual European Association of Urology Congress; March 23, 2025; Madrid, Spain.

24. Müller DC, Murtha AJ, Bacon JVW, et al. Prospective multicenter study of ctDNA versus tumor tissue guiding FGFR-targeted therapy in metastatic urothelial cancer. *Nat Commun*. 2026;17(1):3263. doi:10.1038/s41467-026-69927-7

25. Membribes SC, Nally E, Jackson-Spence F, et al. Established and emerging biomarkers approaches in urothelial carcinoma. *Expert Rev Anticancer Ther*. 2025;25(11):1235-1241. doi:10.1080/14737140.2025.2543454

26. Maughan BL, Dyrskjøt L, Grivas P, et al. The role of liquid biopsy in the management of patients with genitourinary malignancies. *Eur Urol*. 2025;88(5):449-461. doi:10.1016/j.eururo.2025.07.016

27. Zang J, Zhang R, Jin D, et al. Integrated longitudinal circulating tumor DNA profiling predicts immunotherapy response of metastatic urothelial carcinoma in the POLARIS-03 trial. *J Pathol*. 2023;261(2):198-209. doi:10.1002/path.6166

28. Zhang R, Zang J, Xie F, et al. Urinary molecular pathology for patients with newly diagnosed urothelial bladder cancer. *J Urol*. 2021;206(4):873-884. doi:10.1097/JU.0000000000001878

29. Zhang R, Zang J, Jin D, et al. Urinary tumor DNA MRD analysis to identify responders to neoadjuvant immunotherapy in muscle-invasive bladder cancer. *Clin Cancer Res*. 2023;29(20):4040-4046. doi:10.1158/1078-0432.CCR-23-0513

30. Loeffler CML, Ortiz Bruechle N, Jung M, et al. Artificial intelligence–based detection of *FGFR3* mutational status directly from routine histology in bladder cancer: a possible preselection for molecular testing? *Eur Urol Focus*. 2022;8(2):472-479. doi:10.1016/j.euf.2021.04.007

31. Bannier PA, Saillard C, Mann P, et al. AI allows pre-screening of *FGFR3* mutational status using routine histology slides of muscle-invasive bladder cancer. *Nat Commun*. 2024;15(1):10914. doi:10.1038/s41467-024-55331-6

32. Katims AB, White C, Alam SM, et al. Urinary biomarkers objectively measure minimal residual disease in non–muscle-invasive bladder cancer. *Clin Cancer Res*. 2026;32(9):1755-1765. doi:10.1158/1078-0432.CCR-25-3395

33. Rodón J, Damian S, Furqan M, et al. Pemigatinib in previously treated solid tumors with activating *FGFR1-FGFR3* alterations: phase 2 FIGHT-207 basket trial. *Nat Med*. 2024;30(6):1645-1654. doi:10.1038/s41591-024-02934-7

34. Huelster HL, Gould B, Schiftan EA, et al. Novel use of circulating tumor DNA to identify muscle-invasive and non–organ-confined upper tract urothelial carcinoma. *Eur Urol*. 2024;85(3):283-292. doi:10.1016/j.eururo.2023.09.017

35. Loriot Y, Necchi A, Park SH, et al; BLC2001 Study Group. Erdafitinib in locally advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2019;381(4):338-348. doi:10.1056/NEJMoa1817323

36. Katoh M, Loriot Y, Brandi G, Tavolari S, Wainberg ZA, Katoh M. FGFR-targeted therapeutics: clinical activity, mechanisms of resistance and new directions. *Nat Rev Clin Oncol*. 2024;21(4):312-329. doi:10.1038/s41571-024-00869-z

37. Roviello G, Santoni M, Sonpavde GP, Catalano M. The evolving treatment landscape of metastatic urothelial cancer. *Nat Rev Urol*. 2024;21(10):580-592. doi:10.1038/s41585-024-00872-0

38. Siefker-Radtke AO, Matsubara N, Park SH, et al; THOR cohort 2 investigators. Erdafitinib versus pembrolizumab in pretreated patients with advanced or metastatic urothelial cancer with select FGFR alterations: cohort 2 of the randomized phase III THOR trial. *Ann Oncol*. 2024;35(1):107-117. doi:10.1016/j.annonc.2023.10.003

39. Loriot Y, Matsubara N, Park SH, et al; THOR Cohort 1 Investigators. Erdafitinib or chemotherapy in advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2023;389(21):1961-1971. doi:10.1056/NEJMoa2308849

40. Loriot Y, Matsubara N, Park SH, et al. Full enrollment results from cohort 1 of the phase III randomized THOR trial of erdafitinib versus chemotherapy in FGFR-altered advanced urothelial carcinoma. *ESMO Open*. 2026;11(10):108583. doi:10.1016/j.esmoop.2026.108583

41. Maguire WF, Chang E, Mulkey F, et al. FDA approval summary: erdafitinib for *FGFR3*-altered locally advanced or metastatic urothelial carcinoma. *Clin Cancer Res*. 2026. doi:10.1158/1078-0432.CCR-26-1154

42. An efficacy and safety study of erdafitinib (JNJ-42756493) in participants with urothelial cancer. ClinicalTrials.gov identifier: NCT02365597. Updated September 25, 2026. Accessed October 8, 2026. https://clinicaltrials.gov/study/NCT02365597

43. A study of erdafitinib compared with vinflunine or docetaxel or pembrolizumab in participants with advanced urothelial cancer and selected fibroblast growth factor receptor (FGFR) gene aberrations (THOR). ClinicalTrials.gov identifier: NCT03390504. Updated September 25, 2026. Accessed October 8, 2026. https://clinicaltrials.gov/study/NCT03390504

44. Loriot Y, Powles T, Moreno V, et al. Erdafitinib or erdafitinib plus cetrelimab for patients with metastatic urothelial carcinoma and FGFR alterations: final results from the phase II NORSE study. *J Clin Oncol*. 2026;44(8):676-684. doi:10.1200/JCO-25-00826

45. Roviello G, Santoni M, Sonpavde GP, Catalano M. The evolving treatment landscape of metastatic urothelial cancer. *Nat Rev Urol*. 2024;21(10):580-592. doi:10.1038/s41585-024-00872-0

46. Nadal R, Valderrama BP, Bellmunt J. Progress in systemic therapy for advanced-stage urothelial carcinoma. *Nat Rev Clin Oncol*. 2024;21(1):8-27. doi:10.1038/s41571-023-00826-2

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Downloaded from jamanetwork.com by Universidad Libre de Colombia, heiydar dolati on 10/30/2026

47. A study of erdafitinib in participants with metastatic or locally advanced urothelial cancer. ClinicalTrials.gov identifier: NCT03473743. Updated August 28, 2026. Accessed October 8, 2026. https://clinicaltrials.gov/study/NCT03473743

48. Koshkin VS, Barthelemy P, Gravis G, et al. Phase II study of futibatinib plus pembrolizumab in patients (pts) with advanced or metastatic urothelial carcinoma (mUC): final analysis of efficacy and safety. Abstract presented at the European Society for Medical Oncology Congress; September 15, 2024; Barcelona, Spain.

49. Syed YY. Futibatinib: first approval. *Drugs*. 2022;82(18):1737-1743. doi:10.1007/s40265-022-01806-z

50. Futibatinib and pembrolizumab combination in the treatment of advanced or metastatic urothelial carcinoma. ClinicalTrials.gov identifier: NCT04601857. Updated December 31, 2025. Accessed October 8, 2026. https://clinicaltrials.gov/study/NCT04601857

51. Alkazemi MH, Ostrovnaya I, Zhang A, et al. Chemoablation with oral erdafitinib in recurrent *FGFR3*-altered non–muscle-invasive bladder cancer: a phase II window-of-opportunity trial. Paper presented at the 2026 American Society of Clinical Oncology Annual Meeting; May 31, 2026; Chicago, IL.

52. Guercio BJ, Sarfaty M, Teo MY, et al. Clinical and genomic landscape of *FGFR3*-altered urothelial carcinoma and treatment outcomes with erdafitinib: a real-world experience. *Clin Cancer Res*. 2023;29(22):4586-4595. doi:10.1158/1078-0432.CCR-23-1283

53. A study of oral erdafitinib in people with recurrent non-invasive bladder cancer. ClinicalTrials.gov identifier: NCT04917809. Updated September 2, 2025. Accessed October 8, 2026. https://clinicaltrials.gov/study/NCT04917809

54. Wen L, Miyagi H, Spiess PE, et al. Low-grade non–muscle-invasive bladder cancer: molecular landscape, treatment strategies and emerging therapies. *Nat Rev Urol*. 2025;22(12):846-861. doi:10.1038/s41585-025-01072-0

55. Pichler R, van Creij NCH, Subiela JD, et al; Asociación Europea de Urología-Jóvenes Urólogos Académicos (EAU-YAU): Grupo de Trabajo de Carcinoma Urotelial. Biological and therapeutic implications of FGFR alterations in urothelial cancer: a systematic review from non–muscle-invasive to metastatic disease. *Actas Urol Esp (Engl Ed)*. 2025;49(5):501719. doi:10.1016/j.acuro.2025.501719

56. A study to evaluate TAR-210 versus single agent intravesical cancer treatment in participants with bladder cancer (MoonRISe-1). ClinicalTrials.gov identifier: NCT06319820. Updated September 25, 2026. Accessed October 8, 2026. https://clinicaltrials.gov/study/NCT06319820

57. Pal SK, Rosenberg JE, Hoffman-Censits JH, et al. Efficacy of BGJ398, a fibroblast growth factor receptor 1-3 inhibitor, in patients with previously treated advanced urothelial carcinoma with *FGFR3* alterations. *Cancer Discov*. 2018;8(7):812-821. doi:10.1158/2159-8290.CD-18-0229

58. Kang C. Infigratinib: first approval. *Drugs*. 2021;81(11):1355-1360. doi:10.1007/s40265-021-01567-1

59. Lyou Y, Rosenberg JE, Hoffman-Censits J, et al. Infigratinib in early-line and salvage therapy for *FGFR3*-altered metastatic urothelial carcinoma. *Clin Genitourin Cancer*. 2022;20(1):35-42. doi:10.1016/j.clgc.2021.10.004

60. A dose escalation study in adult patients with advanced solid malignancies. ClinicalTrials.gov identifier: NCT01004224. Updated October 4, 2019. Accessed October 9, 2026. https://clinicaltrials.gov/study/NCT01004224

61. Sternberg CN, Petrylak DP, Bellmunt J, et al. FORT-1: phase II/III study of rogaratinib versus chemotherapy in patients with locally advanced or metastatic urothelial carcinoma selected based on *FGFR1/3* mRNA expression. *J Clin Oncol*. 2023;41(3):629-639. doi:10.1200/JCO.21.02303

62. Roviello G, Santoni M, Sonpavde GP, Catalano M. The evolving treatment landscape of metastatic urothelial cancer. *Nat Rev Urol*. 2024;21(10):580-592. doi:10.1038/s41585-024-00872-0

63. Nadal R, Valderrama BP, Bellmunt J. Progress in systemic therapy for advanced-stage urothelial carcinoma. *Nat Rev Clin Oncol*. 2024;21(1):8-27. doi:10.1038/s41571-023-00826-2

64. Study of rogaratinib (BAY1163877) vs chemotherapy in patients with FGFR (fibroblast growth factor receptor)–positive locally advanced or metastatic urothelial carcinoma (FORT-1). ClinicalTrials.gov identifier: NCT03410693. Updated September 28, 2022. Accessed October 9, 2026. https://clinicaltrials.gov/study/NCT03410693

65. Murtha AJ, Boni V, Loriot Y, et al. ctDNA monitoring of *FGFR3*-altered metastatic urothelial cancer treated with dabogratinib (formerly TYRA-300) in the SURF301 trial. *J Clin Oncol*. 2026;44(7)(suppl). doi:10.1200/JCO.2026.44.7_suppl.809

66. Starrett JH, Allen EL, Neal M, et al. Dabogratinib (TYRA-300), an *FGFR3* isoform-selective inhibitor: preclinical and initial clinical evidence of antitumor activity. *Mol Cancer Ther*. 2026;25(3):408-415. doi:10.1158/1535-7163.MCT-25-0652

67. Safety and preliminary anti-tumor activity of TYRA-300 in advanced urothelial carcinoma and other solid tumors with *FGFR3* gene alterations (SURF301). ClinicalTrials.gov identifier: NCT05544552. Updated January 12, 2026. Accessed October 9, 2026. https://clinicaltrials.gov/study/NCT05544552

68. Drakaki A. Phase 1 study of LY3866288, a potent, highly isoform-selective *FGFR3* inhibitor in *FGFR3*-altered advanced solid tumors (FORAGER-1): dose optimization. Abstract presented at the European Society for Medical Oncology Congress; October 17, 2025; Barcelona, Spain.

69. Coca Membribes S, Szabados B, Powles T. Towards biomarker-driven therapies for urothelial carcinoma. *Nat Rev Clin Oncol*. 2026;23(2):92-106. doi:10.1038/s41571-025-01095-x

70. A study of vepugratinib (LY3866288; LOXO-435) in participants with cancer with a change in a gene called *FGFR3* (FORAGER-1). ClinicalTrials.gov identifier: NCT05614739. Updated August 20, 2026. Accessed October 9, 2026. https://clinicaltrials.gov/study/NCT05614739

71. Starrett JH, Allen EL, Neal M, et al. Dabogratinib (TYRA-300), an *FGFR3* isoform-selective inhibitor: preclinical and initial clinical evidence of antitumor activity. *Mol Cancer Ther*. 2026;25(3):408-415. doi:10.1158/1535-7163.MCT-25-0652

72. Jain RK, Yang YA, Graham L, et al. ETCTN 10483: phase Ib trial of erdafitinib (E) combined with enfortumab vedotin (EV) following prior therapies for metastatic urothelial carcinoma (mUC) with *FGFR2/3* genetic alterations (GAs). *J Clin Oncol*. 2026;44(7)(suppl). doi:10.1200/JCO.2026.44.7_suppl.770

73. Ellinghaus P, Neureiter D, Nogai H, Stintzing S, Ocker M. Patient selection approaches in FGFR inhibitor trials—many paths to the same end? *Cells*. 2022;11(19):3180. doi:10.3390/cells11193180

74. Cui S, Luo X, Fan G, et al. A novel *FGFR3*-targeting antibody-drug conjugate induces tumor cell apoptosis through the cGAS-STING pathway in bladder cancer. *Adv Sci (Weinh)*. 2026;13(4):e09933. doi:10.1002/advs.202509933

75. Goyal L, Saha SK, Liu LY, et al. Polyclonal secondary *FGFR2* mutations drive acquired resistance to FGFR inhibition in patients with *FGFR2* fusion-positive cholangiocarcinoma. *Cancer Discov*. 2017;7(3):252-263. doi:10.1158/2159-8290.CD-16-1000

76. Wu Q, Ellis H, Siravegna G, et al. Landscape of clinical resistance mechanisms to FGFR inhibitors in *FGFR2*-altered cholangiocarcinoma. *Clin Cancer Res*. 2024;30(1):198-208. doi:10.1158/1078-0432.CCR-23-1317

77. Kiss B, Wyatt AW, Douglas J, et al. Her2 alterations in muscle-invasive bladder cancer: patient selection beyond protein expression for targeted therapy. *Sci Rep*. 2017;7(1):42713. doi:10.1038/srep42713

78. Robertson AG, Kim J, Al-Ahmadie H, et al; TCGA Research Network. Comprehensive molecular characterization of muscle-invasive bladder cancer. *Cell*. 2017;171(3):540-556. doi:10.1016/j.cell.2017.09.007

79. Sonpavde GP, Subbiah V. Unlocking precision oncology with FGFR inhibition in urothelial carcinoma. *Ann Oncol*. 2024;35(2):150-153. doi:10.1016/j.annonc.2023.11.006

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Downloaded from jamanetwork.com by Universidad Libre de Colombia, heiydar dolati on 10/30/2026