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Targeted therapies for urothelial carcinoma: From FGFR inhibitors to next-generation antibody-drug conjugates (Review)

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Abstract. Treatment of urothelial carcinoma (UC), particularly in metastatic or cisplatin-ineligible patients, remains challenging because of limited durable responses to conventional chemotherapy and immune checkpoint inhibitors. Recent advances in targeted therapies, including FGFR inhibitors (for example, erdafitinib) and antibody-drug conjugates (ADCs) targeting Nectin-4 (enfortumab vedotin) and HER2 (disitamab vedotin), have reshaped treatment paradigms. FGFR3 alterations, which are present in 20-40% of patients with advanced UC, predict sensitivity to FGFR tyrosine kinase inhibitors, whereas ADCs demonstrate efficacy across biomarker-selected and unselected populations. However, clinical implementation is complicated by resistance mechanisms, such as kinase switching, phenotypic plasticity and tumor microenvironment interactions, as well as biomarker heterogeneity. The present review synthesizes current evidence on molecularly guided therapies, contrasts resistance mechanisms between FGFR inhibitors and ADCs, and evaluates strategies to overcome therapeutic limitations. By integrating translational insights and emerging preclinical data, it was aimed to provide a roadmap for optimizing biomarker-driven approaches, novel combinations and next-generation agents for the treatment of UC.

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1. Introduction

Urothelial carcinoma (UC) is a neoplastic growth that originates in the urinary tract lining and extends from the renal pelvis to the urethra. It encompasses a range of histological subtypes and anatomical locations, including upper tract UC (UTUC) and primary urethral cancer (1). UTUC accounts for 5-10% of UC cases, whereas primary urethral cancer is even rarer (2). In the United States, it is estimated that there were 87,840 new cases of bladder cancer and 17,840 deaths in 2024, making it the fifth most common cancer in men and the fourteenth in women. The incidence rates of bladder cancer in the US are ~82.3 per 100,000 in men and 21.3 per 100,000 in women (3). In Europe, bladder cancer ranks as the tenth most common cancer, with ~226,000 new cases and 69,000 deaths annually. The incidence rates vary across European countries, with higher rates observed in southern and eastern Europe (3). In Asia, the incidence of UC is lower than that in Western countries, but it still poses a significant health burden, especially in rapidly industrializing regions. For instance, in China, the incidence of bladder cancer is ~13.5 per 100,000, with higher rates in urban areas (3). However, bladder cancer remains a notable health issue in some regions, with incidence rates influenced by factors such as schistosomiasis infection. Globally, the aggressive nature and high recurrence rate of UC make it a challenging disease to manage globally.

Advanced UC, particularly in metastatic or cisplatin-ineligible patients, is associated with poor prognosis (4). The 5-year survival rate for patients with advanced UC is ~10%, highlighting an urgent need for more effective treatment strategies (5). Traditional treatment methods, such as platinum-based chemotherapy, have limitations related to achieving durable responses. For patients with advanced UC being treated with platinum-based chemotherapy, the median

OS is typically less than 15 months (6). While the use of immune checkpoint inhibitors (ICIs) has shown promise, their efficacy varies, and numerous patients eventually develop resistance (7). A meta-analysis of 11 trials including 1,630 previously treated patients with UC revealed that the pooled objective response rate (ORR) for single targeted agents was 10.7% (95% CI: 10.7-19.6%), the disease control rate was 33.2% (95% CI: 25-41.4%), and the 1-year OS was 31% (95% CI: 23.6-39.4%) (8). These findings underscore the critical need for novel approaches to improve patient outcomes in this patient population.

Over the past decade, the treatment landscape for UC has evolved significantly with the advent of targeted therapies. Erdafitinib, a fibroblast growth factor receptor (FGFR) inhibitor, and enfortumab vedotin (EV), an antibody-drug conjugates (ADCs) targeting Nectin-4, have demonstrated significant efficacy for the treatment of UC. Erdafitinib achieved a 40% ORR in a phase II trial for patients with FGFR2/3-altered UC (9). EV showed a robust ORR of 43% in a phase I trial, even in patients whose cancer had previously progressed on ICIs (10). These advancements mark a significant shift from traditional chemotherapy and underscore the importance of molecularly guided therapies in improving the prognosis of patients with UC. Ongoing research continues to explore the optimal sequencing of these therapies and the development of next-generation agents to further improve treatment outcomes.

Unlike prior reviews that have separately summarized FGFR inhibitors or ADCs, the present article integrates real-world evidence, biomarker analytics, and resistance biology into a single comparative framework. Recent literature gaps include insufficient head-to-head evaluation of FGFR inhibitors vs. ADCs sequences, limited dissection of convergent resistance pathways (for example, PI3K/AKT re-activation and TGF-β-mediated immune exclusion), and absence of a unified roadmap guiding biomarker-driven combination therapy. By synthesizing 2023-2025 trial data with spatial transcriptomic and urinary circulating-tumor-DNA studies, the present review offers a dynamic, systems-level perspective that links genomic alteration, tumor microenvironment (TME) phenotype, and clinical outcomes; such integration has not been previously accomplished in UC-focused commentaries. Consequently, the manuscript provides clinicians and translational researchers with an evidence-based hierarchy for selecting FGFR or ADCs-based regimens, forecasts emerging resistance mechanisms, and proposes biomarker-adaptive trial designs to accelerate precision medicine implementation.

2. Molecular biology of UC

In recent years, with advancements in genomics and molecular biology technologies, the molecular landscape of UC has been gradually unveiled. Various molecular alterations and signaling pathways interact synergistically, driving tumor development and progression (11). A deeper understanding of the molecular biology of UC provides a strong foundation for the development of targeted therapies. By identifying key molecular targets and pathways (Fig. 1), researchers can develop more effective therapeutic strategies to improve treatment outcomes and survival rates for patients with UC (12).

Key molecular pathways. UC development and progression involve complex molecular mechanisms. Among them, the Phosphatidylinositol 3-kinase (PI3K)/Protein Kinase B(AKT)/Mammalian Target of Rapamycin (mTOR) pathway plays a significant role (13). This pathway is frequently activated due to mutations in genes such as PIK3CA, PTEN deletion, or AKT1 mutation (14). PI3K catalyzes the production of PIP3, which activates AKT. Activated AKT, in turn, phosphorylates mTOR, promoting cell survival, proliferation and inhibiting apoptosis (14). Studies have shown that PIK3CA mutations are present in ~24-40% of UC cases (15). PTEN deletion occurs in ~17-30% of cases (16). Activation of this pathway contributes to UC progression and chemoresistance. For example, in a particular study, PTEN-deficient mice were more prone to developing UC and displayed more aggressive tumor characteristics, such as increased proliferation rates and higher metastatic potential (17).

The Receptor Tyrosine Kinase (RTK)/Rat Sarcoma (RAS)/V-Raf Murine Sarcoma Viral Oncogene Homolog (RAF)/Mitogen-Activated Protein Kinase Kinase (MEK)/Extracellular Signal-Regulated Kinase (ERK) pathway is another critical signaling pathway (18). Abnormal activation of this pathway can be caused by mutations in FGFR, RAS, or BRAF genes. FGFR gene alterations, including mutations, fusions and amplifications, can lead to ligand-independent receptor activation, subsequently activating downstream signaling pathways (19). RAS mutations are found in ~15-30% of UC cases, and BRAF mutations occur in ~5-10% of cases (20). Activation of this pathway promotes cell proliferation, differentiation and angiogenesis. For example, a study by Zhou *et al* (21) demonstrated that mutations in this pathway are associated with tumor progression and poor prognosis in patient with UC.

The Tumor Protein 53 (TP53) gene mutation pathway is also crucial in UC. TP53 is a tumor suppressor gene, and its encoded protein plays a pivotal role in cell cycle regulation, DNA repair and apoptosis (22). TP53 mutations are detected in ~40-50% of UC cases. Mutations in this gene lead to loss of its normal function, enabling cells with DNA damage to continue proliferating, thereby promoting tumor development and progression (22). Ecke *et al* (23) revealed that TP53 mutations are associated with higher tumor grade and stage in UC and are linked to poor patient prognosis.

FGFR alterations. FGFR gene alterations are prevalent in UC. FGFR family includes FGFR1-4. Among them, FGFR3 alterations are the most common in UC, occurring in ~10-30% of cases (24). FGFR3 gene mutations primarily involve point mutations in the tyrosine kinase domain, such as R248C, S249C and Y373C mutations, which lead to receptor constitutive activation (25). FGFR3 gene fusions, such as FGFR3-TACC3 fusions, can also result in abnormal receptor activation. FGFR gene amplifications can increase receptor expression levels, thereby enhancing downstream signaling pathway activation (26). These alterations contribute to tumor cell proliferation and progression. For example, Liu *et al* (26) showed that FGFR3 mutations are associated with tumor recurrence and progression in non-muscle-invasive bladder cancer. FGFR3 alterations are more common in non-muscle-invasive UC, with a detection rate of ~15-20%, while in muscle-invasive

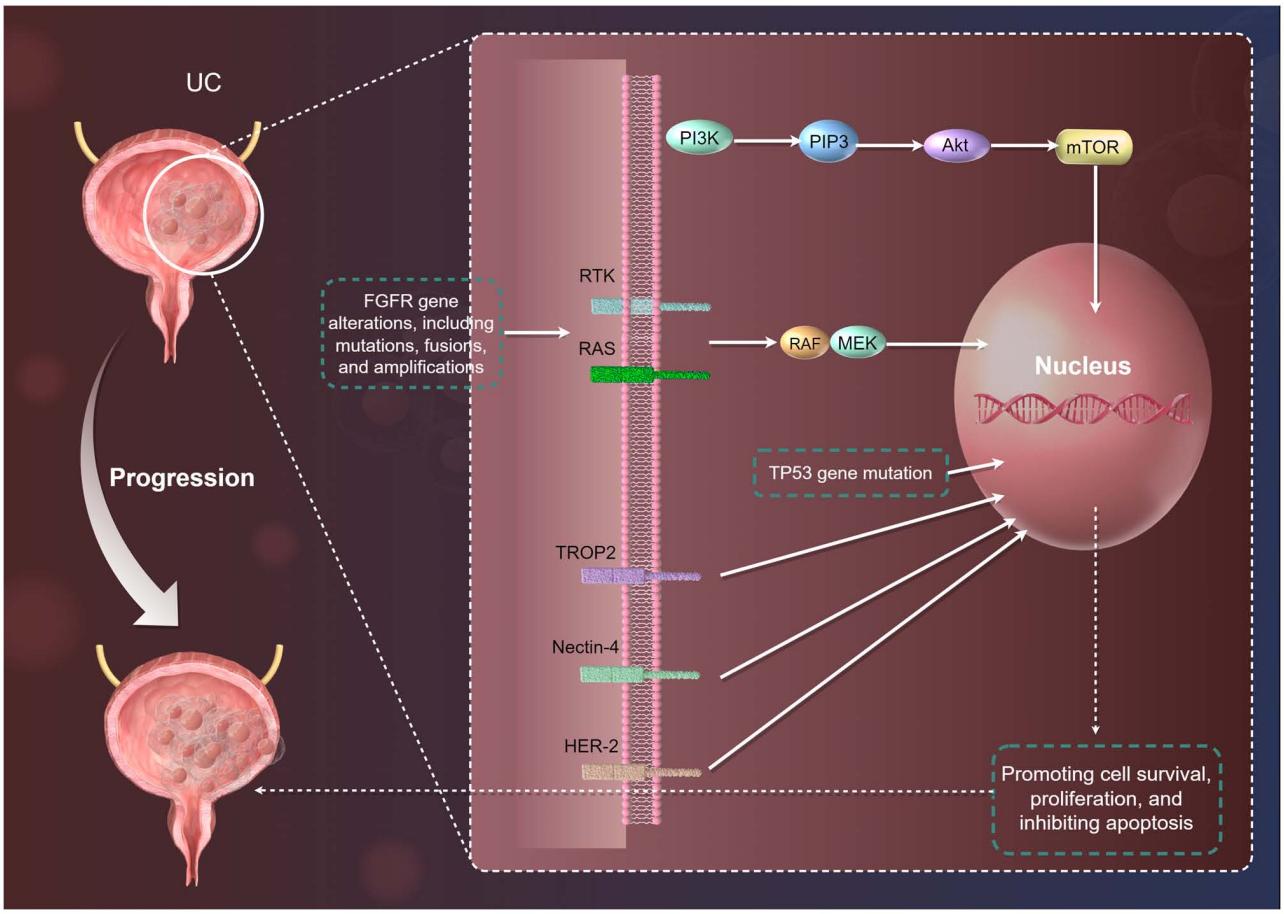

Figure 1. Molecular Landscape of UC. Key molecular targets and pathways discussed in the review are visually summarized. The molecular landscape of UC with the current targeted therapies is integrated, highlighting the pathways involved and the main targets. The image was designed using Figdraw.com. UC, urothelial carcinoma; FGFR, fibroblast growth factor receptor.

UC, the detection rate is ~5-10%. FGFR2 alterations are relatively rare in UC but are also involved in tumor progression.

Other molecular targets. In addition to the aforementioned molecular pathways and FGFR alterations, other molecular targets also play important roles in UC. TROP2 is a transmembrane glycoprotein that is highly expressed in UC and other solid tumors. Its overexpression is associated with tumor aggressiveness and poor prognosis (27). Sacituzumab govitecan, a TROP2-targeted ADCs, has demonstrated significant efficacy in the treatment of metastatic UC (28). Nectin-4 is another molecule highly expressed in UC. EV, an ADCs targeting Nectin-4, has shown remarkable therapeutic effects in locally advanced or metastatic UC (29). HER-2 is overexpressed in a subset of patients with UC. Trastuzumab deruxtecan, a HER-2-targeted ADCs, has shown promising efficacy in HER-2-overexpressing UC (30). The expression levels of these molecular targets are closely related to tumor biology and patient prognosis.

3. FGFR pathway-directed therapies: Foundations and clinical implementation

The increasing understanding of FGFR pathway dysregulation in UC has driven the development of targeted therapies. The molecular basis of FGFR abnormalities in UC are addressed in the present section, the clinical data of FGFR inhibitors such as erdafitinib and infigratinib are reviewed, and resistance mechanisms are discussed, aiming to guide optimal use of FGFR-targeted strategies in clinical practice (Fig. 2).

Molecular basis of FGFR dysregulation in UC. Dysregulation of the FGFR signaling pathway through amplifications, mutations and gene fusions has been implicated in UC (31). FGFR signaling plays crucial roles in tumor cell proliferation, angiogenesis, migration and survival (32) (Table I). FGFR pathway dysregulation is a hallmark of UC, primarily driven by genetic alterations in FGFR3 and, less frequently, FGFR2. These aberrations include activating mutations, gene fusions and amplifications, which constitutively activate downstream signaling cascades such as RAS/MAPK and PI3K/AKT, promoting tumor proliferation and survival (33,34).

Comprehensive genomic profiling of 295 advanced UC cases revealed FGFR3 alterations in 15% of tumors, predominantly point mutations (for example, S249C, R248C and Y375C) and fusions (for example, FGFR3-TACC3) (33). In muscle-invasive UC, FGFR3 mutations occur in 20% of cases, often co-occurring with TP53 mutations, suggesting a synergistic oncogenic role (34). Notably, large nested variant UC exhibits a higher prevalence of FGFR3 mutations (36%),

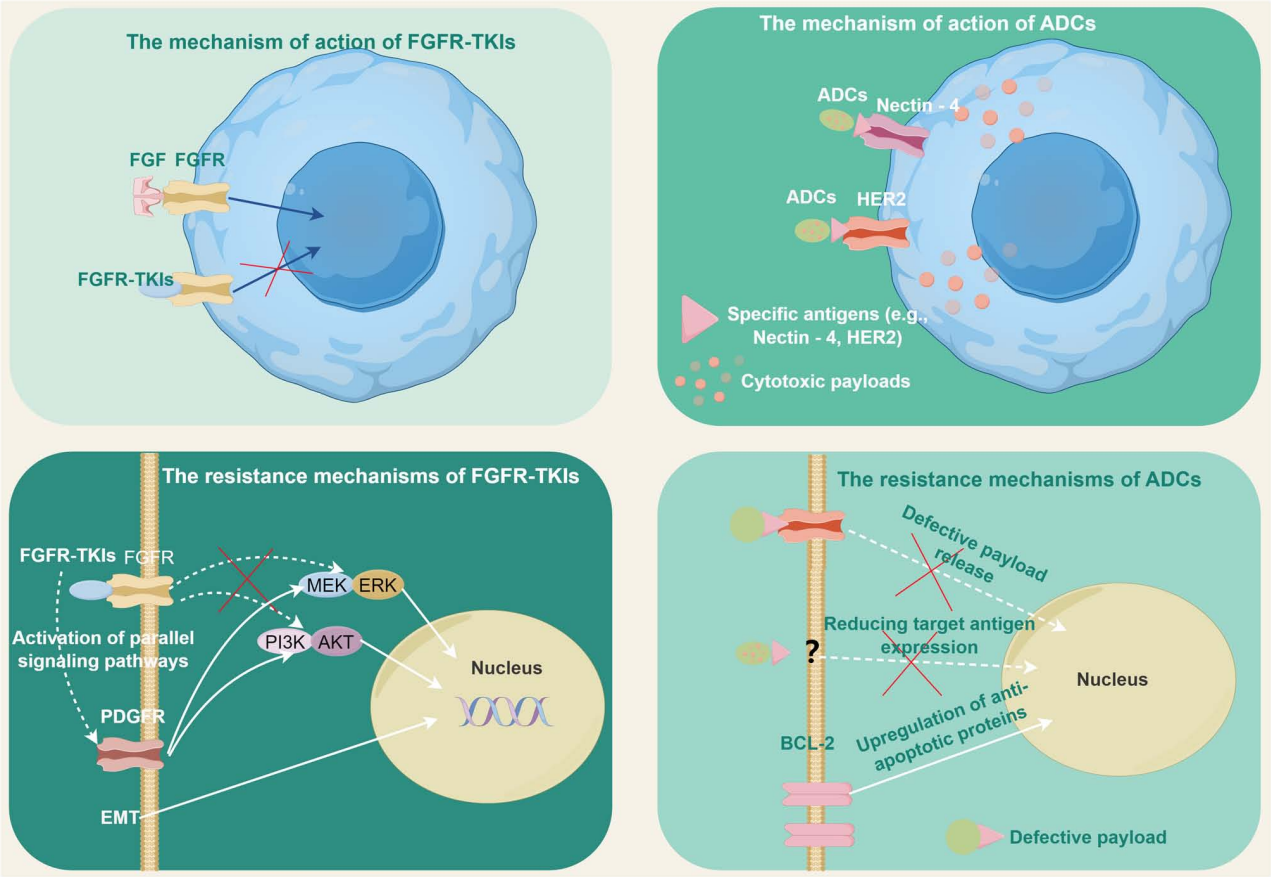

Figure 2. Mechanisms of action and resistance pathways of FGFR-TKIs and ADCs in urothelial carcinoma. The image was designed using Figdraw.com. FGFR, fibroblast growth factor receptor; TKIs, tyrosine kinase inhibitors; ADCs, antibody-drug conjugates; EMT, epithelial-mesenchymal transition.

underscoring subtype-specific molecular heterogeneity (35). At the mRNA level, FGFR3 overexpression correlates with DNA-level mutations in 65% of advanced UC cases, though discordances exist due to alternative splicing or epigenetic regulation (36).

FGFR3 mutations induce ligand-independent dimerization and constitutive kinase activation. Huang *et al* (37) demonstrated that FGFR3 silencing in UC cell lines suppressed RAS/MAPK pathway activity, impairing invasion and proliferation. However, FGFR-driven tumors often develop resistance via parallel pathways. For instance, P4HA2-mediated HIF-1α stabilization was shown to bypass FGFR inhibition in FGFR3-mutant UC, highlighting metabolic adaptation as a resistance mechanism (38). Additionally, co-alterations in CDKN2A/B (frequently deleted in FGFR3-altered UC) may enhance dependency on CDK4/6, providing a rationale for combination therapies (39).

While FGFR3 mutations were initially associated with non-muscle-invasive UC and favorable prognosis, metastatic FGFR3-altered UC correlates with poorer responses to platinum chemotherapy (ORR: 28 vs. 45% in wild-type) (36). A meta-analysis of 1,574 patients with UC confirmed that FGFR3 mutations independently predict shorter OS in advanced stages (HR=1.42, 95% CI: 1.11-1.82) (40). Conversely, FGFR2 amplifications, observed in 5-8% of UC, are linked to aggressive phenotypes and resistance to ICIs due to TGF-β-mediated immunosuppression (41,42).

Recent studies highlight the immunosuppressive microenvironment in FGFR3-mutant UC, characterized by M2 macrophage infiltration and reduced $CD8^+$ T-cell activity. Preclinical models demonstrated that FGFR inhibition synergizes with anti-PD-1 therapy by reversing immunosuppression, offering a compelling strategy for clinical translation (42). However, the prognostic value of FGFR alterations remains context-dependent; for example, FGFR3 overexpression in non-metastatic UC lacks significant survival correlation (43). Therefore, FGFR dysregulation in UC is mechanistically diverse, influenced by alteration type, coexisting genomic events, and TME factors. Standardized detection methods and functional validation are critical to optimize patient stratification for FGFR-targeted therapies.

Application of FGFR-targeted strategies in the treatment of UC. FGFR-targeted therapies have emerged as a transformative approach in managing advanced UC, particularly for patients with FGFR3 alterations. This section critically evaluates the clinical efficacy, limitations and evolving strategies of FGFR inhibitors, supported by pivotal trials and real-world evidence (Table II).

Erdafitinib, a pan-FGFR inhibitor, is the first FDA-approved FGFR inhibitors for metastatic UC harboring susceptible FGFR2/3 alterations. The phase II BLC2001 trial (N=99) demonstrated an ORR of 40%, median progression-free survival (PFS) of 5.5 months, and median OS of 13.8 months

Table I. Related research on FGFR dysregulation in urothelial carcinoma.

First author/s, year	Aberration types	Study types	Mechanism of action	Relationship with prognosis	(Refs.)
Ross *et al*, 2016; Necchi *et al*, 2019	*FGFR3* mutations/ fusions	Genomic profiling	Activating mutations (for example, S249C, R248C) and fusions (for example, *FGFR3-TACC3*) constitutively activate RAS/MAPK and PI3K/AKT pathways.	Higher frequency in advanced UC; associated with resistance to platinum chemotherapy (ORR: 28% vs. 45% in wild-type).	(33,36)
Kim *et al*, 2018; Khalid *et al*, 2020	*FGFR3* mutations	Clinical cohort analysis	Co-occurrence with *TP53* mutations enhances oncogenicity; promotes ligand-independent kinase activation.	Correlates with aggressive MIUC phenotypes; shorter OS in metastatic UC (HR=1.42).	(34,40)
Gamallat *et al*, 2023	*FGFR3* mutations	Subtype-specific analysis	Enriched in large nested variant UC (36%); drives subtype-specific signaling dysregulation.	Subtype-specific heterogeneity linked to differential therapeutic responses.	(35)
Necchi *et al*, 2019	*FGFR3* mRNA overexpression	Comparative DNA/RNA analysis	Discordance between DNA mutations and mRNA levels due to alternative splicing or epigenetic regulation.	mRNA overexpression correlates with DNA alterations in 65% of cases; prognostic value context-dependent.	(36)
Song *et al*, 2023	*FGFR2* amplifications	Genomic and microenvironmental	Activates TGF-β-mediated immunosuppression; reduces CD8+ T-cell infiltration.	Associated with resistance to ICIs and aggressive phenotypes in advanced UC.	(41)
Okato *et al*, 2024	*FGFR3*-mutant TME	Preclinical/translational study	M2 macrophage polarization and immunosuppressive microenvironment; FGFR inhibition enhances anti-PD-1 efficacy.	Improved survival in murine models; synergy with immunotherapy in clinical trials.	(42)
Mahmoud *et al*, 2024	*FGFR3* overexpression	Immunohistochemical analysis	Protein overexpression detected in non-metastatic UC; lacks consistent survival correlation.	Limited prognostic significance in early-stage UC; potential biomarker for FGFR-targeted therapies.	(43)
Shohdy *et al*, 2019	Co-alterations (*CDKN2A/B*)	Mechanistic and combination study	*CDKN2A/B* deletions enhance dependency on CDK4/6; co-targeting FGFR and CDK4/6 delays resistance.	Rationale for combination therapies in *FGFR3*-altered UC.	(39)
Li *et al*, 2023	*FGFR3*-mediated resistance	Functional *in vitro* study	P4HA2 stabilizes HIF-1α, bypassing FGFR inhibition; metabolic adaptation drives resistance.	Identifies novel resistance mechanisms; informs strategies to overcome erdafitinib resistance.	(38)

UC, urothelial carcinoma; MIUC, muscle-invasive urothelial carcinoma; OS, overall survival; ORR, objective response rate; TME, tumor microenvironment; ICIs, immune checkpoint inhibitors.

Table II. Application of FGFR-targeted strategies in the treatment of urothelial carcinoma.

First author/s, year	Intervention strategies	Targets	Study types	Setting	Sample size (N)	Therapeutic effect	(Refs.)
Loriot *et al*, 2019	Erdafitinib monotherapy	Pan-FGFR (FGFR1-4)	Phase II BLC2001 trial	Post-platinum, FGFR2/3-altered UC	N=99	ORR: 40%; median PFS: 5.5 months; median OS: 13.8 months in platinum-refractory UC.	(44)
Loriot *et al*, 2023	Erdafitinib vs. chemotherapy	Pan-FGFR (FGFR1-4)	Phase III THOR trial	FGFR3-altered, post-ICI metastatic UC	N=266	Improved median OS (12.1 vs. 7.8 months; HR=0.64); ORR: 45.6% vs. 22.4%.	(47)
Siefker-Radtke *et al*, 2024	Erdafitinib vs. pembrolizumab	Pan-FGFR (FGFR1-4)	Phase III THOR Cohort 2	FGFR-altered, PD-L1-high metastatic UC	N=352	No OS benefit (10.9 vs. 11.1 months; HR=1.18) in PD-L1-high tumors.	(48)
Lyou *et al*, 2022	Infigratinib monotherapy	FGFR1-3	Phase II trial	Post-platinum, FGFR3-altered metastatic UC	N=67	ORR: 25.4%; median OS: 10.3 months in platinum-refractory UC.	(50)
Pal *et al*, 2022	Infigratinib adjuvant therapy	FGFR1-3	Phase III PROOF-302 trial	FGFR3-mutant muscle-invasive UC	N=630	Preliminary data: 35% reduction in recurrence rates in *FGFR3*-mutant MIUC.	(51)
Sternberg *et al*, 2023	Rogaratinib monotherapy	FGFR1-4	Phase II/III FORT-1 trial	FGFR1/3 mRNA-high metastatic UC	N=126	ORR: 20.7% vs. 19.3% (chemotherapy); median OS: 8.3 vs. 9.8 months (HR=1.02).	(52)
Necchi *et al*, 2024	Pemigatinib monotherapy	FGFR1-3	Phase II FIGHT-201 trial	FGFR-altered, post-platinum metastatic UC	N=40	ORR: 12%; no survival benefit in UC.	(53)
Siefker-Radtke and Loriot, 2022	Erdafitinib + pembrolizumab	Pan-FGFR + PD-1	Phase II trial	FGFR-altered, ICI-naïve metastatic UC	N=58	ORR: 47%; median OS: 12.2 months; increased grade ≥3 AEs (e.g., rash, diarrhea).	(55)
Necchi *et al*, 2024	Derazantinib + atezolizumab	FGFR/ CSF1R + PD-L1	Phase I/II trial	FGFR-altered, post-ICI metastatic UC	N=45	ORR: 33%; CSF1R inhibition counteracts macrophage-mediated resistance.	(56)

ORR, objective response rate; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; MIUC, muscle-invasive urothelial carcinoma; AEs, adverse events.

in platinum-refractory patients (44). However, the single-arm design and absence of a control group limit the interpretability of these outcomes, particularly in the context of post-immunotherapy efficacy. Furthermore, the enrichment for FGFR3-altered tumors, without stratification by mutation subtype, may overestimate the true treatment effect, as

FGFR3-TACC3 fusions have been associated with more favorable responses than point mutations (45). Hyperphosphatemia, a class-effect toxicity due to FGFR1 inhibition, occurred in 77% of patients but correlated with antitumor efficacy (P=0.02) (46). Long-term follow-up confirmed sustained responses, with a 24-month OS rate of 27% (9). The phase III THOR trial validated erdafitinib's superiority over chemotherapy in FGFR3-altered metastatic UC (Cohort 1: N=266), showing improved median OS (12.1 vs. 7.8 months; HR=0.64) and ORR (45.6% vs. 22.4%) (47). However, in Cohort 2 comparing erdafitinib to pembrolizumab in programmed death-Ligand 1(PD-L1)-high tumors, no OS benefit was observed (10.9 vs. 11.1 months; HR=1.18), underscoring the need for biomarker-driven selection (48). Real-world studies corroborated these findings, with Guercio *et al* (49) reporting an ORR of 38% and median OS of 11.2 months in 112 patients.

Infigratinib, an FGFR1-3 inhibitor, showed modest activity in a phase II trial (N=67) with an ORR of 25.4% and median OS of 10.3 months in platinum-refractory UC (50). Hyperphosphatemia again emerged as a common adverse event (AE), observed in 73% of patients (46). The phase III PROOF-302 trial is evaluating adjuvant infigratinib in *FGFR3*-mutant muscle-invasive UC, with preliminary data suggesting a 35% reduction in recurrence rates (51). Besides, Rogaratinib, an FGFR1-4 inhibitor, failed to outperform chemotherapy in the phase II/III FORT-1 trial (N=126) despite selecting patients with high FGFR1/3 mRNA expression. ORR was comparable (20.7 vs. 19.3%), and median OS was shorter (8.3 vs. 9.8 months; HR=1.02), highlighting challenges in biomarker validation (52). Furthermore, Pemigatinib, approved in cholangiocarcinoma, showed limited efficacy in UC (ORR: 12%) in the FIGHT-201 trial (N=40), with no survival benefit (53). Its combination with pembrolizumab was explored in cisplatin-ineligible patients but discontinued due to strategic reasons (54).

Combining FGFR inhibitors with ICIs aims to overcome immunosuppressive microenvironments. Erdafitinib plus pembrolizumab achieved an ORR of 47% and median OS of 12.2 months in a phase II trial (N=58), though grade ≥3 AEs (for example, rash and diarrhea) increased significantly (47). Preclinical models suggest FGFR inhibition reverses M2 macrophage polarization and enhance $CD8^+$ T-cell infiltration, supporting this strategy (55). Derazantinib, a dual FGFR/CSF1R inhibitor, combined with atezolizumab (anti-PD-L1), showed promise in a phase I/II trial (N=45) with an ORR of 33%. CSF1R targeting may counteract tumor-associated macrophage-mediated resistance, offering a novel therapeutic angle (56).

Resistance to FGFR-tyrosine kinase inhibitors (TKIs). Resistance to FGFR-TKIs remains a critical challenge in UC, driven by diverse molecular mechanisms. Preclinical and clinical studies have identified several pathways contributing to acquired or intrinsic resistance, including compensatory signaling activation, genomic evolution, and TME adaptations. Datta *et al* (57) demonstrated that Akt activation mediates resistance to BGJ398 (infigratinib) in FGFR3-mutant UC models, highlighting compensatory PI3K/AKT/mTOR pathway activation as a key escape mechanism. This finding aligns with Pettitt *et al* (58), who observed *in vitro* resistance to FGFR inhibitors via multiple pathways, including MAPK reactivation and epithelial-mesenchymal transition (EMT), underscoring the heterogeneity of resistance mechanisms. Conversely, Kim *et al* (59) reported that FGFR1-overexpressing UC cells develop resistance to BGJ398 through sustained MAPK/ERK signaling, which could be reversed by MEK inhibitors, suggesting combinatorial strategies to delay resistance.

Clinical studies further reveal the impact of FGFR alterations on therapeutic outcomes. Rezazadeh Kalebasty *et al* (60) observed that patients with UC with FGFR mutations exhibited reduced clinical benefit from anti-PD-(L)1 therapies post-FGFR inhibition, suggesting cross-resistance linked to immunosuppressive TME reprogramming. By contrast, Bellmunt *et al* (61) found that everolimus/pazopanib combination therapy improved outcomes in genomically selected patients with UC, including those with FGFR pathway alterations, though efficacy was limited by mTOR pathway feedback activation. Divergent resistance patterns are also influenced by tumor histology. Brunelli *et al* (62) identified reduced TROP-2 and NECTIN-4 expression in sarcomatoid UC variants, correlating with poor ADCs responses and potential cross-resistance to FGFR-targeted therapies. Additionally, Audisio *et al* (63) emphasized the role of clonal evolution under FGFR inhibition, where subpopulations with secondary FGFR2/3 mutations or parallel oncogenic drivers (for example, EGFR) emerge, necessitating longitudinal genomic profiling.

These studies collectively highlight the multifactorial nature of FGFR-TKI resistance. While compensatory signaling (for example, PI3K/AKT and MAPK) and genomic evolution are predominant mechanisms, TME interactions and histological subtypes further modulate therapeutic vulnerability. Future research should prioritize combinatorial approaches (for example, FGFR inhibitors + MEKi/mTORi) and biomarker-driven adaptive therapies to circumvent resistance.

4. ADCs

ADCs have emerged as a transformative therapeutic class in UC, leveraging tumor-specific antigens to deliver cytotoxic payloads with precision. ADCs have redefined UC treatment, with Nectin-4 and HER2 as validated targets (Fig. 2). Relevant studies have optimized the selection of biomarkers, clarified the pathways of action, and integrated ADCs into multimodal regimens (Table III). Real-world evidence and innovative imaging modalities (for example, Nectin-4 PET) will further personalize ADCs therapy.

Nectin-4-targeted ADCs. Nectin-4, a cell adhesion molecule overexpressed in 60-90% of UCs, has become a pivotal therapeutic target. EV, an ADCs comprising a Nectin-4-directed antibody conjugated to monomethyl auristatin E, received FDA approval based on the EV-301 trial (64). The recent phase III EV-302 trial (NCT04223856) established enfortumab vedotin plus pembrolizumab as a new first-line standard for metastatic UC, demonstrating superior OS and PFS compared with platinum-based chemotherapy (median OS: 31.5 vs. 16.1 months; HR=0.47; median PFS: 12.5 vs. 6.3 months; HR=0.45) (65). Recent studies corroborate its efficacy in

Table III. Application of antibody-drug conjugates strategies in the treatment of UC.

First author/s, year	Intervention strategies	Targets	Study types	Setting	Sample size (N)	Therapeutic effect	(Refs.)
Li *et al*, 2024	EV monotherapy	Nectin-4	Phase II trial (China)	Post-platinum metastatic UC (Asian cohort)	N=60	ORR 50%, median PFS 5.8 months in previously treated metastatic UC	(66)
Rizzo *et al*, 2025	EV post-ICI failure	Nectin-4	Retrospective study (ARON-2)	Post-ICI metastatic UC	N=237	Median OS 12.1 months vs. chemotherapy 8.3 months (HR=0.62)	(67)
Uchimoto *et al*, 2025	BMI impact on EV efficacy	Nectin-4	Cohort study (Japan)	Post-ICI metastatic UC (ULTRA-Japan)	N=166	BMI ≥25: ORR 42.9% vs. 23.1%, OS 14.2 vs. 9.1 months	(68)
Mishra *et al*, 2024	Nectin-4 PET-guided dosing	Nectin-4	Translational imaging study	Metastatic UC with heterogeneous Nectin-4 expression	N=12	Tracer uptake correlates with EV response (r=0.72, P=0.008)	(69)
Jindal *et al*, 2023	TP53/MDM2 biomarker analysis	Nectin-4	Biomarker analysis	Post-ICI metastatic UC	N=45	TP53 wild-type: PFS 6.4 vs. 3.1 months (P=0.03)	(70)
Hovelroud *et al*, 2024	EV-associated diabetic ketoacidosis	Nectin-4	Case report	Post-ICI metastatic UC	N=1	Severe insulin resistance in a nondiabetic patient	(71)
Desimpel *et al*, 2024	EV-associated lung toxicity	Nectin-4	Retrospective analysis	Post-ICI metastatic UC	N=1,892	Interstitial lung disease incidence 0.5%	(72)
Pipitone *et al*, 2025	EV extravasation management	Nectin-4	Case report & literature review	Metastatic UC receiving EV	N=1 (case)	Protocol for tissue necrosis prevention	(73)
Zhu *et al*, 2025	EV + pembrolizumab cost-effectiveness	Nectin-4	Cost-effectiveness model	First-line metastatic UC	Model-based	Incremental cost-effectiveness ratio>$150,000/QALY; requires price reduction	(74)
Sheng *et al*, 2024	Disitamab vedotin monotherapy	HER2	Phase II trial	HER2-positive metastatic UC	N=107	HER2-positive metastatic UC: ORR 51.2%, median OS 14.2 months	(77)
Chen *et al*, 2023	Disitamab vedotin monotherapy	HER2	Phase II trial	HER2-positive locally advanced or metastatic UC	N=76	HER2-positive metastatic UC: ORR 51.2%, median OS 14.2 months	(78)
Yan *et al*, 2025	Disitamab vedotin in HER2-low populations	HER2	Phase II trial	HER2-negative metastatic UC	N=82	HER2-negative metastatic UC: ORR 28.6%, median OS 11.8 months	(79)
Wang *et al*, 2025	Disitamab vedotin in HER2-null populations	HER2	Real-world study	HER2-low/null metastatic UC	N=154	ORR 18.2%, median PFS 4.1 months	(80)
Yao *et al*, 2025	Disitamab vedotin + tislelizumab combination	HER2 + PD-1	Phase II trial	HER2-expressing, ICI-naïve metastatic UC	N=36	ORR 58.3%, median PFS 8.5 months	(82)
Ge *et al*, 2025	RC48 + PD-1 inhibitors	HER2 + PD-1	Real-world study	HER2-expressing metastatic UC	N=112	ORR 54.5%, median OS 16.1 months	(83)

Table III. Continued.

First author/s, year	Intervention strategies	Targets	Study types	Setting	Sample size (N)	Therapeutic effect	(Refs.)
Yang *et al*, 2025	HER2 prognostic value (shorter OS)	HER2	Retrospective cohort	Muscle-invasive UC	N=412	HER2+ associated with HR=1.58 (P=0.02) in multivariable analysis	(84)
Chen *et al*, 2025	HER2 in bladder-preservation therapy	HER2	Clinical cohort	HER2$^+$ muscle-invasive UC treated with bladder-sparing therapy	N=127	No OS difference in HER2+ MIBC patients	(85)
Chou *et al*, 2022	TROP-2 in luminal subtypes	TROP-2	Molecular subtyping analysis	Luminal papillary UC cohort	N=120	Enriched in luminal papillary UC	(86)
Bahlinger *et al*, 2024	FGFR3/Nectin-4 co-alterations	FGFR3	Translational study	Advanced UC with Nectin-4-high expression	N=200	FGFR3 mutations in 25% of Nectin-4-high tumors	(87)

ORR, objective response rate; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; AEs, adverse events; UC, urothelial carcinoma; MIUC, muscle-invasive urothelial carcinoma; TME, tumor microenvironment; ICIs, immune checkpoint inhibitors; BMI, body mass index; utDNA, urine tumor DNA; PD-L1, programmed death-ligand 1; FGFR, fibroblast growth factor receptor.

diverse clinical settings (66-68). The phase II trial in Chinese patients with previously treated metastatic UC demonstrated an ORR of 50% and median PFS of 5.8 months, validating EV's activity in Asian populations (66). Notably, the aforementioned study lacked central imaging review and biomarker stratification beyond Nectin-4 expression, raising concerns about response assessment heterogeneity. Additionally, the absence of post-progression treatment details introduces potential immortal time bias, particularly in a single arm setting without comparator arm. Real-world data from the ARON-2 retrospective study (n=237) further revealed that EV achieved a median OS of 12.1 months post-ICI failure, outperforming chemotherapy (8.3 months; HR=0.62, P<0.001) (67). Notably, efficacy of EV was influenced by body mass index (BMI): patients with BMI ≥25 had superior tumor response rates (ORR 42.9% vs. 23.1%, P=0.04) and longer OS (14.2 vs. 9.1 months, P=0.02), suggesting metabolic factors may modulate ADCs activity (68).

Biomarker-driven strategies are under exploration. Mishra *et al* (69) developed a Nectin-4 PET tracer to non-invasively quantify target expression, revealing heterogeneous intratumoral distribution. Higher tracer uptake correlated with EV response (r=0.72, P=0.008), supporting personalized dosing. Additionally, TP53/MDM2 alterations were associated with reduced EV benefit in a biomarker analysis (n=45): TP53 wild-type tumors had longer PFS (6.4 vs. 3.1 months, P=0.03) (70).

EV's toxicity profile remains consistent across studies, with peripheral neuropathy (40-50%), rash (30%) and hyperglycemia (5-10%) as key AEs (66,67). A pharmacovigilance study (n=1,892) identified rare but severe AEs, including diabetic ketoacidosis (0.3%) and interstitial lung disease (0.5%) (71,72). Extravasation management protocols have been proposed following case reports of tissue necrosis (73). In addition, cost-effectiveness analyses weigh EV's benefits against its economic burden. Zhu *et al* (74) modeled EV + pembrolizumab as first-line therapy for metastatic UC, showing incremental cost-effectiveness ratios exceeding $150,000/QALY, necessitating price reductions for broader adoption.

HER2-directed ADCs. HER2 expression in UC is heterogeneous, with 5-15% classified as HER2-positive (IHC 3+ or 2+/FISH+) and 30-40% as HER2-low (IHC 1+ or 2+ with negative *in situ* hybridization), consistent with the ASCO-CAP guidelines (75), which are commonly extrapolated to UC in the absence of disease-specific criteria. Disitamab vedotin (DV; RC48), an anti-HER2 ADCs, has shown promise across HER2 expression levels (76). In the combined analysis of the phase II trials (n=107), DV monotherapy achieved an ORR of 51.2% and median OS of 14.2 months in HER2-positive metastatic UC, with grade ≥3 AEs (for example, neutropenia: 20%) deemed manageable (77). Real-world studies reinforce these findings: Chen *et al* (78) reported an ORR of 48.6% and median PFS of 6.9 months in 76 HER2-positive patients treated with DV ± ICIs.

Intriguingly, DV exhibits activity even in HER2-low/null cohorts. Yan *et al* (79) conducted a phase II trial (n=82) in HER2-negative metastatic UC, demonstrating an ORR of 28.6% and median OS of 11.8 months, suggesting off-target effects or HER2 detection limitations. Similarly, Wang *et al* (80) observed ORRs of 24.1% (HER2-low) and 18.2% (HER2-null) in a real-world study (n=154), though responses were less durable (median PFS: 4.1 vs. 5.3 months).

These findings challenge traditional HER2 thresholds and advocate for refined scoring systems.

The combination of DV with ICIs has demonstrated synergistic efficacy, representing a significant advancement. In the phase Ib/II RC48-C014 trial (NCT04264936), DV plus the PD-1 inhibitor toripalimab achieved a confirmed ORR of 71.8% and a median PFS of 9.2 months in patients with HER2-expressing (IHC 1+/2+/3+) locally advanced or metastatic UC (81). Notably, efficacy was consistent across HER2-low (IHC 1+ or 2^+/FISH-) and HER2-positive (IHC 3^+ or 2^+/$FISH^+$) subgroups, challenging traditional HER2 positivity thresholds and suggesting broader applicability.

DV-ICI combinations synergize efficacy. Yao *et al* (82) reported an ORR of 58.3% and median PFS of 8.5 months in 36 ICI-naïve patients with metastatic UC receiving DV + tislelizumab, with immune-related AEs in 22%. Ge *et al* (83) corroborated these results in a larger cohort (n=112; ORR: 54.5%, median OS: 16.1 months), highlighting enhanced antitumor immunity. While HER2 overexpression correlates with aggressive features (for example, higher grade, nodal metastases), its prognostic value remains contested. Yang *et al* (84) analyzed 412 UC specimens, finding HER2 positivity (12.6%) associated with shorter OS (HR=1.58, P=0.02) in multivariable analysis. Conversely, Chen *et al* (85) reported no OS difference in HER2-positive muscle-invasive UC treated with bladder-preservation therapy, underscoring context-dependent roles.

Emerging targets. TROP-2, expressed in 70% of UCs, is under investigation with sacituzumab govitecan. Preclinical data reveal TROP-2 overexpression in sarcomatoid UC (80%) vs. conventional UC (40%), suggesting histology-specific targeting (62). Chou *et al* (86) identified TROP-2 enrichment in luminal papillary subtypes, potentially guiding patient selection. FGFR3-directed ADCs (for example, erdafitinib combinations) and tissue factor-targeting agents (for example, tisotumab vedotin) are in early trials. Bahlinger *et al* (87) observed FGFR3 mutations in 25% of Nectin-4-high tumors, advocating dual-target approaches.

5. Translational insights: Biomarker-driven patient selection

The advent of targeted therapies in UC has underscored the critical role of biomarker-driven patient selection to maximize therapeutic efficacy and minimize toxicity (88). This section evaluates the translational insights from key clinical trials, focusing on FGFR inhibitors and ADCs, and discusses the challenges and opportunities in biomarker validation, heterogeneity, and clinical implementation.

FGFR alterations: From discovery to clinical validation. FGFR alterations, particularly FGFR3 mutations and fusions, have emerged as pivotal oncogenic drivers in UC. These genetic aberrations, identified in 20-40% of metastatic UC and 35-40% of high-risk non-muscle-invasive bladder cancer (NMIBC) tumors, lead to constitutive activation of downstream signaling pathways such as RAS-MAPK and PI3K-AKT, promoting tumor proliferation, survival and angiogenesis (41). Preclinical studies highlighted FGFR3's role in bladder carcinogenesis, spurring the development of selective FGFR inhibitors. Erdafitinib, a first-in-class pan-FGFR-TKI, demonstrated early promise in the phase 2 BLC2001 trial, achieving an ORR of 40% in FGFR-altered metastatic UC, which laid the groundwork for subsequent phase 3 validation (47). The discovery of FGFR3's oncogenic role and its high prevalence in UC established a strong rationale for biomarker-driven therapeutic strategies, positioning FGFR status as a critical predictive biomarker for patient stratification.

The THOR trial (NCT03390504) marked a milestone in the clinical validation of FGFR-targeted therapy. In this phase 3 study, erdafitinib significantly outperformed chemotherapy in patients with FGFR3-altered metastatic UC, demonstrating a median OS of 12.1 months vs. 7.8 months (HR=0.64) and a doubling of PFS (5.6 vs. 2.7 months) (47). Nevertheless, the trial's open-label design may introduce assessment bias, particularly in subjective endpoints such as PFS. Moreover, the exclusion of patients with prior immunotherapy limits the generalizability of these findings to contemporary real-world cohorts, where ICI exposure is now standard of care. These transformative outcomes, coupled with durable responses and manageable toxicity, led to erdafitinib's regulatory approvals in China, USA and other regions, cementing FGFR3 alteration as a validated biomarker for patient selection. However, challenges persist, including tumor heterogeneity, the emergence of resistance mutations (for example, FGFR3 gatekeeper mutations), and the need for standardized biomarker testing protocols (89). Ongoing research focuses on optimizing FGFR inhibitor sequencing, exploring combination therapies with ICIs, and validating liquid biopsy-based FGFR detection to address spatial and temporal heterogeneity in advanced UC (42). These efforts aim to refine precision medicine approaches and extend the benefits of FGFR-targeted therapy to broader patient subsets.

HER2 as an emerging target: Expanding the ADCs landscape. Human epidermal growth factor receptor 2 (HER2) overexpression or amplification is observed in 10-20% of UC and has emerged as a promising target for ADCs (90). Disitamab vedotin (DV), an HER2-targeted ADCs, combined with the PD-1 inhibitor toripalimab, demonstrated unprecedented efficacy in the RC48-C016 trial (NCT04879329), achieving significant OS (11.5 vs. 9.5 months) and PFS (4.2 vs. 2.9 months) benefits over chemotherapy in HER2-expressing metastatic UC, including cisplatin-ineligible patients (81). Notably, efficacy was consistent across HER2-low and HER2-high subgroups, challenging the traditional HER2 positivity thresholds and suggesting broader applicability.

By contrast, EV, a NECTIN-4-directed ADCs, has shown remarkable activity in unselected UC populations (ORR: 67.7%; CR: 29% in EV-302) (91). While EV does not require biomarker preselection, retrospective analyses suggest that NECTIN-4 expression levels correlate with response durability, raising questions about the need for quantitative biomarker thresholds (92). This contrasts with HER2-targeted ADCs, where even low expression may suffice for clinical benefit, as observed in DV trials. Such differences underscore the need for target-specific biomarker frameworks.

Navigating tumor heterogeneity and resistance in biomarker-driven therapies. UC exhibits significant

intratumoral heterogeneity, with FGFR and HER2 status varying between primary and metastatic lesions (93). For example, FGFR3 mutations are more common in primary NMIBC, while metastatic sites often acquire additional genomic alterations (for example, TP53 and RB1) (94). Longitudinal studies reveal that FGFR alterations may be lost after BCG therapy or chemotherapy, necessitating repeat biopsies for dynamic biomarker assessment (95). Liquid biopsy approaches [for example, circulating tumor DNA (ctDNA)] are under investigation but require validation for real-time monitoring (96).

Co-mutations (for example, TP53 with FGFR3) may modulate response to targeted therapies. In the THOR trial, patients with FGFR3-TACC3 fusions had superior outcomes compared with those with FGFR3 mutations, suggesting fusion-specific sensitivity (45). Similarly, HER2 amplification often coexists with PI3K/AKT pathway activation, which may confer resistance to DV unless combined with PI3K inhibitors (97). These findings highlight the importance of comprehensive genomic profiling to identify co-targetable pathways.

Biomarker-driven selection has revolutionized UC treatment, yet challenges in standardization, heterogeneity, and resistance persist. FGFR and HER2 inhibitors exemplify the success of precision medicine, while ADCs such as EV demonstrate the potential of target-agnostic approaches. Future research must prioritize biomarker validation, combinatorial strategies and real-world evidence to bridge the gap between trial populations and clinical practice. Recent evidence indicates that urine tumor DNA (utDNA) assays achieve 91.4% sensitivity and 95.1% specificity for detecting UC-associated FGFR3 or TERT mutations, outperforming cytology and enabling longitudinal genotyping without repeated cystoscopy (98). This high diagnostic accuracy underscores the utility of utDNA in capturing tumor-derived genetic material shed into the urine, thereby providing a more comprehensive representation of intratumoral and inter-lesional heterogeneity compared with single-site tissue biopsies. In the prospective TAR-210 trial, real-time utDNA screening for FGFR3 alterations increased trial-enrollment efficiency by 36% and permitted early identification of emergent FGFR3 gate-keeper mutations (99). By circumventing the spatial limitations of tissue biopsies, utDNA offers a non-invasive means to dynamically monitor clonal evolution and adapt therapeutic strategies in response to molecular changes. Analogously, plasma ctDNA panels that cover FGFR2/3, PIK3CA, TP53 and ERBB2 can be performed every 4-6 weeks; rising variant-allele frequencies precede radiological progression by a median of 4.2 months in patients receiving erdafitinib or enfortumab vedotin, providing a lead-time window for therapy adaptation (100). Thus, liquid biopsy platforms already allow dynamic patient selection and early resistance surveillance and are being integrated into adaptive trial designs such as the ULTRA-switch study (100).

6. Resistance mechanisms and overcoming therapeutic limitations

Resistance to FGFR inhibitors and ADCs in UC is multifactorial, driven by convergent pathways such as kinase switching, persistent downstream signaling and TME interactions (101,102) (Fig. 3). However, emerging strategies, including biomarker-guided combinations, next-generation ADCs and epigenetic modulation, hold promise for overcoming these barriers. Future studies must prioritize longitudinal biomarker validation and innovative trial designs to translate preclinical insights into clinical success.

Convergent resistance pathways between FGFR-TKIs and ADCs. Resistance to FGFR inhibitors (for example, erdafitinib) and ADCs (for example, EV) often involves compensatory activation of parallel signaling pathways (103,104). For instance, FGFR inhibition in metastatic UC induces upregulation of platelet-derived growth factor receptor (PDGFR), enabling tumor cells to bypass FGFR dependency via PDGF ligand stimulation (105). Preclinical studies in breast cancer models demonstrated that FGFR inhibitor pemigatinib triggers PDGFRα/β overexpression, reactivating MAPK/ERK signaling and promoting minimal residual disease (MRD) survival (106). Similarly, resistance to HER2-targeted ADCs (for example, disitamab vedotin) may involve MET or HER2 amplification, as observed in non-small cell lung cancer (NSCLC) EGFR-TKI resistance models (107). These findings highlight a shared mechanism of 'kinase switching' across targeted therapies.

Both FGFR inhibitors and ADCs face resistance due to sustained activation of downstream effectors. In FGFR3-altered UC, MEK/ERK and PI3K/AKT pathways remain active despite FGFR inhibition, driven by co-mutations (for example, TP53 and RB1) or epigenetic adaptations (108,109). For ADCs, resistance may arise from defective payload release or upregulation of anti-apoptotic proteins (for example, BCL-2) (110). For example, EV-resistant UC cell lines exhibit increased expression of multidrug resistance transporters, reducing monomethyl auristatin E cytotoxicity (104).

Tumor cells evade targeted therapies through EMT or lineage plasticity (111). FGFR inhibition in UC promotes EMT via STAT3 activation, enhancing metastatic potential (103). ADCs targeting NECTIN-4 or HER2 may similarly encounter resistance due to loss of target expression during phenotypic shifts (112,113). Additionally, stromal interactions in the TME play a pivotal role. Lung fibroblasts secrete PDGF-AA to support MRD survival in FGFR inhibitor-treated models, while cancer-associated fibroblasts shield tumor cells from ADCs penetration by secreting extracellular matrix components (114).

Novel strategies to circumvent resistance. Dual inhibition of FGFR and compensatory pathways (for example, PDGFR or PI3K) has shown promise (115,116). In preclinical UC models, combining erdafitinib with the DNA methyltransferase 1 inhibitor GSK3484862 delayed relapse by suppressing PDGFR upregulation and epigenetic plasticity (90). For ADCs, co-targeting HER2 and MET (for example, trastuzumab + savolitinib) is under investigation in NSCLC, with potential applicability to UC (90).

Bispecific ADCs (for example, targeting HER2 and TROP2) or payload modifications (for example, TOP1 inhibitors) may overcome resistance by broadening target engagement or enhancing cytotoxicity (117). Erdafitinib intravesical delivery systems (TAR-210) improve local efficacy while reducing systemic toxicity, achieving 82%

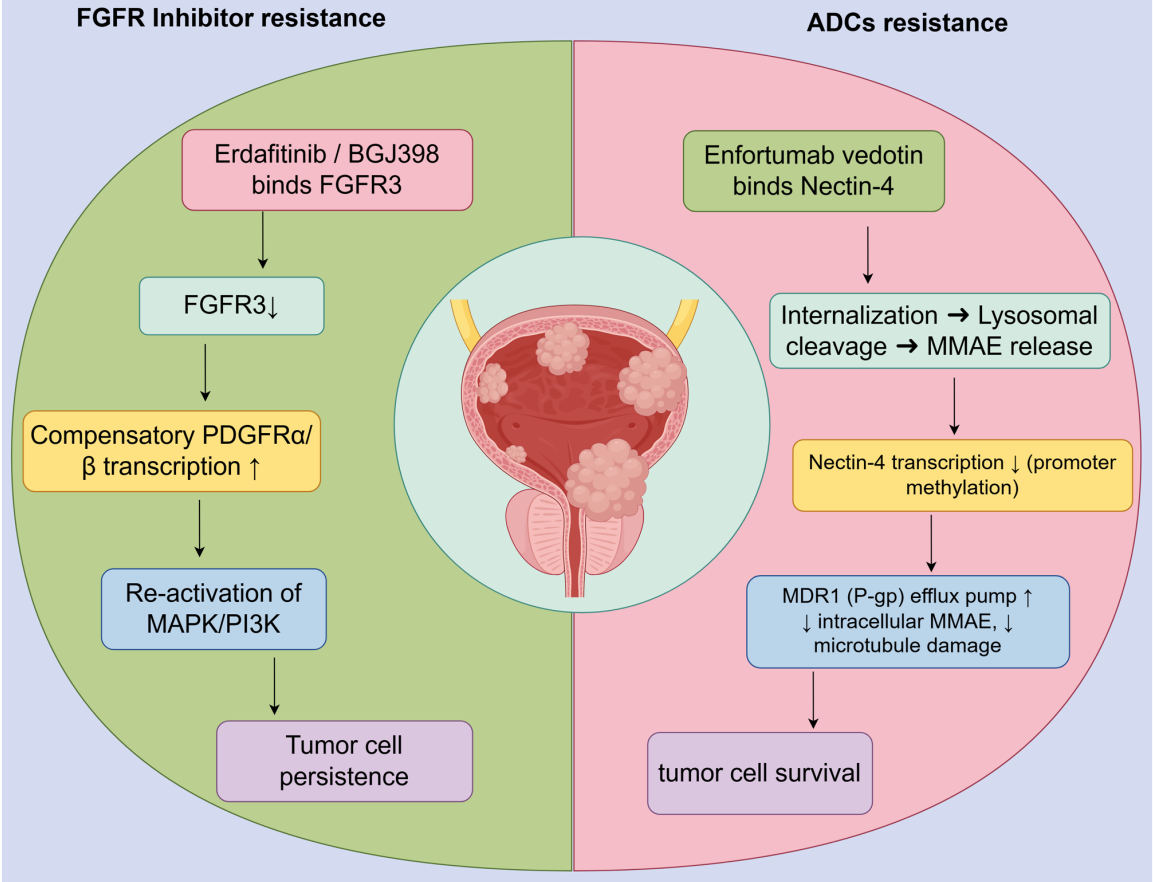

Figure 3. Schematic of convergent resistance pathways and novel overcoming strategies for FGFR inhibitors and ADCs in UC. This figure illustrates the shared and target-specific resistance mechanisms to FGFR-TKIs and ADCs in UC, alongside emerging therapeutic strategies to circumvent resistance. The image was designed using Figdraw.com. FGFR, fibroblast growth factor receptor; ADCs, antibody-drug conjugates; UC, urothelial carcinoma.

recurrence-free survival in FGFR3-altered NMIBC (99). Similarly, FGFR3-specific degraders (for example, PROTACs) are emerging to address kinase domain mutations (118).

FGFR inhibitors may synergize with ICIs by modulating the TME (119). Erdafitinib increases T-cell infiltration and reduces myeloid-derived suppressor cells in UC models, suggesting enhanced immunogenicity (119). Clinical trials evaluating erdafitinib + pembrolizumab (NCT05316155) are underway, with preliminary data showing durable responses in PD-L1-low populations. Furthermore, histone deacetylase (HDAC) inhibitors reverse resistance-associated epigenetic silencing (120). For example, low-dose decitabine restored FGFR3 expression in erdafitinib-resistant UC cells, re-sensitizing them to therapy. Metabolic reprogramming (for example, valine restriction) combined with HDAC6 inhibitors has shown efficacy in enhancing DNA damage in preclinical models, offering a novel combinatorial approach (120).

In addition, longitudinal assessment of resistance mutations via utDNA enables real-time adaptation of therapy (100). The UI Seek assay, which detects FGFR3/TERT mutations and methylation markers in urine, demonstrated 91.37% sensitivity and 95.09% specificity for UC diagnosis, outperforming traditional cytology (98). In the TAR-210 trial, utDNA-based FGFR3 screening improved patient enrollment by 36%, highlighting its utility in guiding adaptive therapies (121). Longitudinal ctDNA monitoring is being integrated into adaptive trial designs. The ULTRA-ctDNA sub-study (NCT05538680) will trigger crossover to alternative targeted agents or combination regimens as soon as emergent FGFR3 secondary mutations or PI3K/AKT pathway alterations are detected, aiming to prevent clinical relapse rather than merely documenting it post hoc.

Clinical translation of resistance data is now beginning to shape sequencing algorithms. In the multicenter real-world APOLLO study (n=184), patients who progressed on erdafitinib were systematically re-biopsied; 62% of cases acquired PIK3CA or PTEN loss-of-function alterations that were absent at baseline. Subsequent treatment with everolimus plus paclitaxel in these molecularly selected patients yielded a 34% ORR and 8.1-month median PFS, whereas non-selected historical controls achieved only 12% and 4.0 months, respectively (49). Similarly, longitudinal ctDNA surveillance during EV therapy revealed that emergent NECTIN-4 loss or TUBB3 mutations predicted resistance within 4-6 weeks; early addition of taxane-based chemotherapy at the time of molecular progression doubled median time-to-next-treatment compared with waiting for radiological progression (7.3 vs. 3.5 months, HR 0.48, P=0.02) (67).

Consequently, an adaptive 'biomarker-triggered' sequence is being evaluated prospectively in the ULTRA-switch trial (NCT05538680): Upon detection of FGFR3 gatekeeper or PI3K/AKT pathway mutations, patients crossover from

erdafitinib to a PI3Kβ inhibitor plus paclitaxel, while NECTIN-4 loss triggers EV-to-taxane switch. Early safety run-in data (n=42) show a 71% clinical benefit rate without additive toxicity, supporting the feasibility of real-time molecular triage.

7. Challenges and future directions

Resistance to targeted therapies poses a significant challenge in the treatment of UC. With respect to FGFR inhibitors, the mechanisms of resistance include secondary gene mutations and compensatory signaling pathway activation (122). For example, studies have found that FGFR gene mutations can lead to reduced inhibitor binding affinity of the inhibitors to the target, thereby causing resistance. Additionally, the activation of other signaling pathways, such as the EGFR pathway, can compensate for the inhibition of the FGFR pathway, promoting tumor cell survival and proliferation (122,123). Similar resistance mechanisms have been observed in the use of ADCs. Secondary gene mutations can alter the structure of the target antigen, reducing the binding ability of the ADCs (124). Moreover, the upregulation of drug efflux pump expression can decrease the intracellular concentration of the cytotoxic drugs, leading to resistance (124).

To overcome these resistance mechanisms, several strategies are being explored. Combination therapies represent a promising approach. For instance, combining FGFR inhibitors with immunotherapy or chemotherapy may enhance therapeutic efficacy (125). Preclinical studies have shown that the combination of FGFR inhibitors and anti-PD-1 antibodies can synergistically inhibit tumor growth by alleviating immunosuppression in the TME (125,126). The development of next-generation drugs is also crucial. Researchers are working on designing FGFR inhibitors with higher selectivity and affinity to overcome resistance caused by secondary mutations. Furthermore, the use of ctDNA analysis may help in identifying resistance mechanisms and guiding treatment adjustments in a timely manner (127).

Managing the AEs associated with targeted therapies is essential for improving patient quality of life and treatment adherence. FGFR inhibitors are commonly associated with ocular toxicity and hyperphosphatemia. Ocular toxicity can manifest as macular edema, serous retinopathy and blurred vision. Regular ophthalmologic examinations are recommended for early detection and management of these side effects early (128). Hyperphosphatemia can usually be managed through dietary adjustments and the use of phosphate binders. ADCs, on the other hand, can cause peripheral neuropathy and myelosuppression. Peripheral neuropathy may require dose adjustments or the use of neuroprotective agents. Myelosuppression necessitates regular monitoring of blood cell counts and appropriate supportive care. It is crucial to establish standardized management protocols for these AEs to ensure the safe and effective use of targeted therapies in clinical practice (129).

Determining the optimal sequence of targeted therapies, immunotherapy and chemotherapy in UC treatment strategies remains an area of active research. Factors influencing treatment sequence decisions include tumor molecular tumor characteristics, patient performance status and prior treatment history (130). For example, patients with FGFR alterations may benefit from the use of FGFR inhibitors as first-line therapy. However, the optimal timing for introducing immunotherapy or chemotherapy in combination with targeted therapies remains unclear. Further studies are needed to investigate the interactions between different treatment modalities and their impact on patient outcomes. Clinical trials evaluating various treatment sequences are ongoing, and their results will provide valuable insights into the best approaches for optimizing treatment strategies for UC.

Combining targeted therapies with immunotherapy or other treatments offers exciting prospects for UC therapy. Preclinical and early clinical studies have demonstrated that such combinations can increase antitumor activity. For instance, combining FGFR inhibitors with ICIs may improve immune cell infiltration and function in the TME (130). However, combination therapies also present challenges, such as increased toxicity and trial design complexity. Careful consideration of the potential side effects and the development of effective toxicity management strategies are necessary to ensure the safety of combination therapies. Additionally, the design of clinical trials must account for the interactions between different drugs and their pharmacokinetic and pharmacodynamic characteristics. Despite these challenges, the potential benefits of combination therapies make them a promising direction for future research in UC treatment.

As our understanding of the molecular biology of UC continues to deepen, new therapeutic targets and drugs are emerging. In addition to the currently established targets such as FGFR and TROP2, other molecules such as MET, AXL and Wnt/β-catenin are gaining attention. MET amplification and mutations have been identified in a subset of patients with UC and are associated with poor prognosis. Inhibitors targeting MET are being developed and have shown initial promise in preclinical studies. AXL overexpression is linked to tumor progression and resistance to therapy. Drugs targeting AXL may provide new treatment options for patients with UC. The Wnt/β-catenin pathway plays a role in tumor cell proliferation and survival. Modulating this pathway may offer another avenue for therapeutic intervention. These novel targets and drugs, along with advancements in genomics and molecular biology technologies, are expected to further expand the therapeutic landscape for UC and to improve treatment outcomes for patients.

8. Conclusion

Significant advancements in biomarker-driven approaches and targeted therapies for UC have been made, offering new treatment options and hope for patients. However, challenges such as biomarker heterogeneity, resistance mechanisms, and the need for optimized treatment strategies remain. Future research should focus on improving biomarker validation, developing novel combination therapies, and designing innovative clinical trials to enhance the efficacy and precision of targeted treatments in UC.

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Authors' contributions

JD and YX made significant contributions to the conception of the manuscript, wrote the first version of the manuscript and prepared figures. TZ, HS and WL reviewed the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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