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Review – Bladder Cancer

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FGFR Inhibition in Urothelial Carcinoma

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Abstract

Background and objective: The 2024 US Food and Drug Administration approval of erdafitinib for the treatment of metastatic urothelial carcinoma (mUC) with *FGFR3* alterations ushered in the era of targeted therapy for bladder cancer. In this review, we summarize the effects of FGFR pathway alterations in oncogenesis, clinical data supporting FGFR inhibitors in the management of bladder cancer, and the challenges that remain.
Methods: Original articles relevant to FGFR inhibitors in urothelial cancer between 1995 and 2024 were systematically identified in the PubMed and MEDLINE databases using the search terms "FGFR" and "bladder cancer". An international expert panel with extensive experience in FGFR inhibitor treatment was convened to synthesize a collaborative narrative review.
Key findings and limitations: Somatic *FGFR3* alterations are found in up to 70% of low-grade non–muscle-invasive bladder cancers; these activate downstream signaling cascades and culminate in cellular proliferation. Beyond a link to lower-grade/lower-stage tumors, there is little consistency regarding whether these alterations confer prognostic risks for cancer recurrence or progression. *FGFR3*-altered tumors have been linked to a non-inflamed tumor microenvironment, but paradoxically do not seem to impact the response to systemic immunotherapy. Several pan-FGFR inhibitors have been investigated in mUC. With the introduction of novel intravesical drug delivery systems, FGFR inhibitors are poised to transform the therapeutic landscape for early-stage UC.

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Conclusions and clinical implications: With deepening understanding of the biology of bladder cancer, novel diagnostics, and improved drug delivery methods, we posit that FGFR inhibition will lead the way in advancing precision treatment of bladder cancer.

ADVANCING PRACTICE

What does this study add?
Approval of erdafitinib for *FGFR3*-altered urothelial carcinoma represents the first success in targeted therapy for bladder cancer. Our narrative review summarizes key insights regarding FGFR-targeted therapies. Several pan-FGFR inhibitors have been investigated in metastatic urothelial cancer. With the introduction of novel intravesical drug delivery systems, FGFR inhibitors are poised to transform the therapeutic landscape for early-stage urothelial cancer.

Clinical Relevance
Over the past several years, the era of precision oncology has emerged with the advent of targeted therapies for various malignancies. Notably, therapies targeting activating FGFR alterations in urothelial carcinoma have gained significant attention. While erdafitinib, the first approved FGFR inhibitor for advanced urothelial carcinoma, has been a major focus, the research landscape surrounding FGFR alterations is extensive. This timely expert review summarizes the clinical and molecular associations of FGFR alterations, highlighting promising treatment paradigms that could be applied to earlier-stage urothelial carcinoma in the future. Associate Editor: Gianluca Giannarini M.D

Patient Summary
A class of drugs called FGFR inhibitors is approved for the treatment of advanced bladder cancer that does not respond to chemotherapy. These drugs may also be of benefit in patients with early-stage non–muscle-invasive bladder cancer. Our review summarizes evidence on the use of these drugs in bladder cancer.

1. Introduction

Targeted therapies against oncogenic driver mutations have been successful in the treatment of chronic myeloid leukemia harboring *BCR-ABL* fusions [1], $BRAF^{V600E}$-mutated melanoma [2], *EGFR*-mutated lung cancer [3], and breast cancers with *HER2* amplification [4], among others. In January 2024, the US Food and Drug Administration (FDA) approved erdafitinib for patients with locally advanced/metastatic urothelial carcinoma (mUC) with *FGFR3* alterations whose disease has progressed on or after one line of prior therapy, which opened the door to targeted treatments in bladder cancer. Much has been uncovered regarding the molecular characteristics of *FGFR3* mutants in UC, with important implications for therapeutic inhibition, impact on the tumor immune microenvironment, and potential resistance mechanisms. This review summarizes current knowledge regarding the properties and functions of wild-type (WT) and mutant *FGFR3*, the prognostic role of *FGFR3* mutation, various therapeutic targeting strategies, and clinical trial results in UC. In addition, we examine the evidence gathered on mechanisms underlying resistance to FGFR inhibitors and anticipate potential strategies for circumvention.

2. Methods

Relevant articles for this narrative review were identified via a systematic approach for articles published from 1995 to 2024. PubMed and MEDLINE were queried for keywords "FGFR" and "bladder cancer" with the Boolean AND operator, which yielded 267 articles. Articles eligible for inclusions were original articles, reviews, and meta-analyses published in English. Case reports and articles that were not peer-reviewed were excluded. Titles and abstracts were screened and reviewed independently by the lead author (R. L.) and second author (J.L.) for relevance. Reference lists in the pertinent articles were examined to augment the source material. Duplicates were filtered. The full text of relevant studies was reviewed, and evidence was collated and condensed by the first and second authors and a summary document circulated to all co-authors for consensus before drafting of the manuscript.

3. Results

FGFR1–4 are a family of highly conserved receptor tyrosine kinases (RTKs) consisting of an extracellular ligand-binding

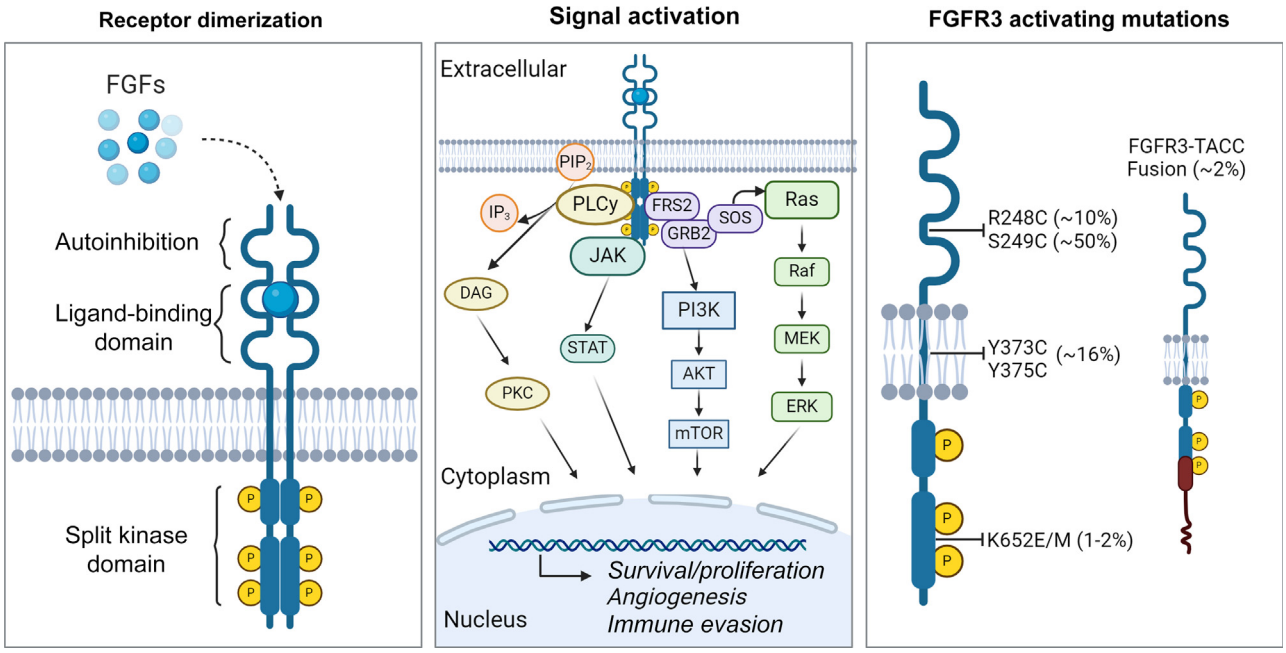

Fig. 1 – FGFR structure and function. The general structure of the FGFR family includes an extracellular domain with a ligand-binding pocket, a transmembrane domain, and an intracellular domain containing a split tyrosine kinase capable of phosphorylating the activation loop of a partner FGFR following receptor dimerization. Receptor activation leads to downstream signal cascades via multiple pathways, including Ras/Raf/MAP kinase, JAK/STAT, PLCγ, and PI3K/AKT, all of which are implicated in the regulation of cell proliferation. *FGFR3* is the most commonly altered *FGFR* gene in urothelial carcinoma, with several hotspot mutations. The majority of activating single-variant mutations involve cysteine substitution in the extracellular or transmembrane domain, which leads to receptor dimerization via the formation of disulfide bonds in the absence of ligand interaction. Mutations in the tyrosine kinase domain can lead to constitutive autophosphorylation. Similarly, *FGFR3* fusions (*FGFR3-TACC*) can lead to autophosphorylation and constitutive signaling.

domain, a transmembrane domain, and an intracellular tyrosine kinase domain (Fig. 1) [5]. FGFs and other ligands trigger receptor dimerization, leading to autophosphorylation of tyrosine residues on the activation loop of the intracellular domain, which in turn stimulates several downstream signaling cascades, including PLCγ, PI3K-AKT, and RAS-MAPK [6]. FGFR signaling is physiologically involved in embryonic development, metabolic homeostasis, endocrine function, and wound repair [7]. In cancer, FGFR dysregulation promotes the proliferation and survival of cancer cells and the development of resistance. As FGFR is not constitutively active in nonmalignant cells, they serve as optimal targets for inhibition in cancer treatment.

3.1. *FGFR alterations in UC*

Activating somatic alterations most commonly occur in the *FGFR3* gene in UC [8]. These mutations are found in up to 70% of low-grade, non–muscle-invasive bladder cancer (NMIBC) cases and in 10–15% of muscle-invasive bladder cancer (MIBC) cases [9]. *FGFR3* alterations have been observed in precancerous lesions such as urothelial hyperplasia and papilloma, and it is thought that they contribute to early oncogenesis [10]. The most common activating alterations are missense mutations, including $FGFR3^{S249C}$ (48.1%) and $FGFR3^{R248C}$ (9.2%) in the extracellular domain, and $FGFR3^{Y375C}$ (13.2%) in the transmembrane domain [11]. These missense mutations induce cysteine-mediated disulfide bond formation, which leads to ligand-independent dimerization and autoactivation. Gene fusion has also been observed, such as coupling between the C-terminus of *FGFR3* and *TACC3* (2%). This results in escape from microRNA targeting the 3′-untranslated region of *FGFR3*, followed by *TACC3*-mediated dimerization and activation of *FGFR3* [12].

A recent query of 1421 UC samples in the Memorial Sloan Kettering IMPACT database revealed that the prevalence of *FGFR3* alterations in UC was 27.5%. Altered *FGFR3* was found in 39% of NMIBC cases (biased towards T1 HG NMIBC), 14% of MIBC cases, 43% of localized upper tract UC (UTUC) cases, and 26% of metastatic tumors [13]. The most common co-altered genes were *PIK3CA* (28%) and *TSC1* (13%). Notably, in patients with paired primary and metastatic lesions, genomic profiling revealed 26% discordance for *FGFR3* alteration. The degree of intrapatient tumor heterogeneity underscores the importance of updated tumor biopsy and profiling immediately before initiation of therapy.

One significant loss-of-function mutation that co-occurs with *FGFR3* alterations is in *KDM6A*. Barrows et al [14] demonstrated an antagonistic relationship between the functions of *KDM6A* and *FGFR3* in urothelial cell differentiation: whereas *KDM6A* supported the transcription of genes essential for luminal cell fate and *FGFR3* activation was associated with lower levels of luminal gene expression. Phenotypically, *KDM6A* expression prevented *FGFR3*-driven increases in colony formation in vitro by blunting *FGFR3*-dependent gene expression. Although no causal relationship has been demonstrated, *KDM6A* loss may create a more plastic epigenetic background that globally supports the activation of *FGFR3* signaling and increases the likelihood of tumorigenesis.

Proteogenomic profiling revealed another attractive property of *FGFR3*-altered bladder tumors with therapeutic implications: their heightened sensitivity to apoptotic stimuli [15]. Proapoptotic effectors, such as initiator caspase-8, its effector, BID, and other apoptosis effectors (caspase-3, 6), were enriched in *FGFR3*-mutated tumors. In addition, FGFR3 overexpression was linked to accumulation of receptors for TRAIL and concomitant abrogation of inhibitors of apoptosis (c-FLIP), making such cells doubly sensitized to apoptotic signaling.

3.2. Impact on immunity and rationale for immune checkpoint inhibitor combinations

In addition to its interaction with other intracellular pathways, *FGFR3* overexpression has consequences that extend beyond the cancer cell and into the tumor microenvironment. Sweis et al [16] demonstrated a discrepancy in *FGFR3* alterations between noninflamed (*FGFR*-high) and inflamed (*FGFR*-low) bladder tumors from The Cancer Genome Atlas (TCGA). These results were corroborated in the UROMOL NMIBC cohort [17] and a smaller UTUC cohort, with upregulation of IFNγ-related genes (*BST2*, *MX2*, *IRF9*, and *GBP2*) on *FGFR3* knockdown proposed as a possible mechanism [18].

The link between *FGFR3*-altered tumors and a noninflamed microenvironment is not fully explained by intrinsic tumor factors (eg, tumor mutational burden [8]) and several other mechanisms have been proposed. Analysis of a model in which tumorigenesis is induced by *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine demonstrated rapid tumor growth on a background of $FGFR3^{S249C}$ mutation, presumably because of suppression of neutrophil infiltration in early oncogenesis [19]. *FGFR3* alterations are also implicated in stimulation of serine synthesis in cancer cells, which leads to activation of the PI3K/Akt pathway in infiltrating macrophages and a shift to an immune-inert phenotype with lower production of the T-cell chemoattractant CXCL9 [20]. Inhibition of the PI3K pathway using duvelisib reversed the immunosuppressive macrophage phenotype, which synergized with FGFR3 inhibition to increase antitumor activity. Finally, FGFR3 expression also impacts the T-cell compartment within the tumor immune microenvironment. Activation of the FGFR3 pathway suppresses PD-L1 levels in tumor cells via increased ubiquitination, which provides a rationale for combination strategies using FGFR3 and PD-(L)1 inhibition [21]. Further support for this approach comes from emerging preclinical data demonstrating that inhibition of FGFR2 on T-regulatory cells on administration of erdafitinib led to an increase in antitumor activity associated with PD-1 inhibition in an FGFR3-driven transgenic murine model [22].

Evidence for the role of FGFR3 in creating an immunosuppressive microenvironment prompted several post hoc analyses of immune checkpoint inhibitor (ICI) trials in UC. The hypothesis was that the inert immune microenvironment associated with such tumors may impair treatment responses. In a combined analysis of IMVigor210 and CheckMate275, Wang et al [23] found that *FGFR3*-altered tumors were not associated with worse response to ICI therapy despite exhibiting decreased T-cell transcriptomic signature. The study suggested that lower T-cell infiltration may have been compensated by the attenuated immunosuppressive effect from TGFβ or EMT/stromal pathway signaling. A neoadjuvant study, in which tumors with high *FGFR3* effector activity and *FGFR3* long noncoding RNA were not associated with non-response despite being associated with suppressed immune activation recapitulated this finding [24]. By contrast, a post hoc biomarker analysis of the JAVELIN Bladder 100 trial found inferior survival for patients with *FGFR3*-altered tumors treated with avelumab in the switch maintenance setting [25]. Further analysis is required to confirm whether *FGFR3* alterations can be used to predict response to ICIs.

3.3. Prognostic role

Much effort has been dedicated to defining the prognostic role of *FGFR3* alterations in UC. Tumors with *FGFR3* alterations are typically of lower grade or stage, but there is little consistency on whether this confers a higher risk for recurrence or progression [26,27]. For low-grade NMIBC, conflicting data have demonstrated and association between *FGFR3* alterations and both lower [28] and higher [27] recurrence rates. For high-grade T1 NMIBC, some results showed no association with progression and survival [29], while others suggested favorable prognosis [30]. In a cohort of 263 patients with high-grade T1 NMIBC receiving intravesical bacillus Calmette-Guérin (BCG), there were no significant differences in recurrence, progression, or disease-specific survival between the *FGFR*-altered and WT groups [31].

Curiously, co-alterations between *FGFR3* and *TP53* were rare, typically occurring in <10% of the tumors profiled [29,30]. The lack of overlap between these two alterations suggests that they are critical drivers of divergent pathways of oncogenesis [32]. While this may imply better prognosis for *FGFR3*-altered tumors, the reality is likely to be more complex, with close interactions between many intertwining molecular pathways. Thus, the true prognostic power of *FGFR3* alterations needs to be defined within the context of other associated alterations and pathways.

3.4. Targeting of FGFR

Given the high prevalence of *FGFR* alterations in UC, especially in NMIBC, there has been growing interest in targeted FGFR inhibition (Table 1). Tyrosine kinase inhibitors (TKIs) are small-molecule inhibitors broadly categorized as selective or nonselective. First-generation nonselective TKIs block multiple phylogenetically related RTKs such as VEGFR, PDGFR. Owing to their structural homology, selective inhibitors may target several members or an entire family of RTKs (eg, FGFR1–4). There is general uncertainty about whether the original nonselective TKIs can sufficiently inhibit FGFR signaling, as dosing is limited by on-target toxicity such as hypertension and cardiovascular adverse events (AEs) induced by VEGFR inhibition [33]. Amongst the nonselective TKIs, only dovitinib (targeting VEGFR1–3, FGFR1–3, and PDGFRβ) has been tested in BCG-unresponsive NMIBC and exhibited modest efficacy (6-mo complete response [CR] rate 8%) despite an adequate biological concentration in the urothelium [34].

Table 1 – FGFR inhibitors tested in urothelial cancer

Inhibitor	Mechanism	Target	Binding site	Delivery	Primary cancer trials	Clinical trial	FDA approval	Most common grade ≥3 AEs	Clinically notable AEs (any grade)	References
Second generation (FGFR selective)										
Erdafitinib (JNJ-42756493)	TKI RTI	FGFR1–4	ATPc	Oral	UC	Phase 3	UC	Overall 45.9% PPE (9.6%), STM (8.1%), anemia (7.4%), HPP (5.2%)	HPP (80%), PPE (51.1%), nail disorders (66.7%), SRD (5.2%), RPED (1.5%)	[35,43]
Rogaratinib (BAY1163877)	TKI RTI	FGFR1–4	ATPc	Oral	UC	Phase 2/3	Under review	Overall 47.7% Asthenia (9.3%), lipase ↑ (8.2%), diarrhea (4.7%), anemia (3.5%)	HPP (45.3%), PPE (NR), nail disorders (NR), retinal disorder grade >2 (7.0%)	Collin 2018 [41]
Infigratinib (BGJ398)	TKI RTI	FGFR1–3	ATPc	Oral	UC/CGC	Phase 1/3 (discontinued)	CGC	Overall 68.7% Lipase ↑ (10.4%), PPE (7.5%), anemia (7.5%), HPO (7.5%), hyponatremia (6.0%)	HPP (46.3), PPE (11.9%), dry eye/blurred vision (26.8%), central serous retinopathy and RPED (17%)	[39] Javale 2021
Pemigatinib (INCB054828)	TKI RTI	FGFR1–3	ATPc	Oral	UC	Phase 2	CGC	Overall 36.5% STM (8.8%), anemia (8.1%), UTI (7.3%), asthenia (4.6%)	HPP (53.5%), NTX (40%), dry eye (26.9%), SRD (13.1%), HPO (8.5%), vitreous detachment (2.3%)	Lui 2020 [54]
Fexagratinib (AZD4547)	TKI RTI	FGFR1–3	ATPc	Oral	Lung, breast	Phase 2 (breast)	No	Overall 41.0% Mucositis (14.0%), AST ↑ (8.0%), PPE (6.0%), ALT ↑ (6.0%)	HPP (50.0%), NTX (26.0%), dry rye (22.0%), RPED (21.2%), HPO (8.0%)	Chae 2020 Coombes 2022
Tasurgratinib (E7090)	TKI type V	FGFR1–3	ATPc	Oral	CGC	Phase 2 (CGC)	No [a]	N/A	N/A	Miyano 2016 Koyama 2020
Derazantinib (ARQ 087)	TKI	FGFR1–3	ATPc	Oral	UC/CGC	Phase 2	No	N/A	Retinal events (16.0%), NTX (6.1%), STM (4.0%), PPE (0%)	Hall 2016 Necchi 2023
LY2874455	TKI RTI	FGFR1–4	ATPc	Oral	Gastric/ NSCLC	Phase 1	No	N/A	N/A	Michael 2017 Dehghanian 2021
Futibatinib (TAS-120)	TKI IRTI	FGFR1–4	KD P-loop	Oral	CGC	Phase 2	No	HPP, AST ↑, STM, fatigue	N/A	Goyal 2023
Third generation (FGFR subtype–specific)										
TYRA-300	TKI	FGFR3	KD GMR	Oral	UC	Phase 1	No	N/A	N/A	Starrett 2022
LOXO-435	TKI	FGFR3	KD GMR	Oral	UC	Phase 1	No	N/A	N/A	Iyer 2023
LY3076226	ADC	FGFR3	ECR	Systemic	UC	Phase 1	No	N/A	N/A	Kollmannsberger 2021
Vofatamab (B-701)	mAb	FGFR3	LBD	Systemic	UC	Phase 2	No	N/A	N/A	Necchi 2019 Siefker-Radtke 2023
MFGR1877S	mAb	FGFR3	LBD	Systemic	STs	Phase 1	No	N/A	N/A	O'Donnell 2012
First generation (nonselective TKIs)										
Dovitinib (TKI258)	TKI RTI	VEGFR1–3 FGFR1–3 PDGFRA/B	ATPc	Oral	RCC	Phase 3 (aRCC)	No [b]	Hypertriglyceridemia (14%), fatigue (10%), HTN (8%), diarrhea (7%)	N/A	[34] Motzer 2014

Table 1 (*continued*)

Inhibitor	Mechanism	Target	Binding site	Delivery	Primary cancer trials	Clinical trial	FDA approval	Most common grade ≥3 AEs	Clinically notable AEs (any grade)	References
Lucitanib (E3810)	TKI	VEGFR1–3 FGFR1–3 PDGFRA/B	ATPc	Oral	Breast, lung, FGFR1-amplified STs	Phase 2	No	Overall 78.9% HTN (57.9%), proteinuria (15.8%), TMA (14.5%), diarrhea (5.3%)	N/A	[33]
Ponatinib (AP24534)	TKI type II	ABL VEGFR FGFR1 c-SRC	ATPc	Oral	Biliary, FGFR-aberrant advanced STs	Phase 3 (CML)	CML	Thrombocytopenia (32%), neutropenia (14%), anemia (6%), lipase ↑ (10%)	N/A	Cortes 2013

↑ = elevation; ADC = antibody-drug conjugate; ATPc = ATP-competitive; aRCC = advanced RCC; CGC = cholangiocarcinoma; CML = chronic myeloid leukemia; ECR = extracellular receptor; FDA = US Food and Drug Administration; GMR = gatekeeper mutation–resistant; HPO = hypophosphatemia; HPP = hyperphosphatemia; HTN = hypertension; IRTI = irreversible type I; KD = kinase domain; LBD = ligand-binding domain; mAb = monoclonal antibody; N/A = not applicable; NR = not reported; NSCLC = non–small-cell lung cancer; NTX = nail toxicity; PPE = palmar-plantar erythrodysesthesia; RCC = renal cell carcinoma; RPED = retinal pigment epithelial detachment; RTI = reversible type I; SRD = serous retinal detachment; STM = stomatitis; STs = solid tumors; TKI = tyrosine kinase inhibitor; TMA = thrombotic microangiopathy; UC = urothelial carcinoma; UTI = urinary tract infection.

[a] Under review in Japan for biliary cancers.

[b] Under review for third-line treatment of aRCC.

Second-generation inhibitors specific to the FGFR kinase domains have a lower rate of toxic effects as they are not constitutively active in nonmalignant cells. Several orally bioavailable FGFR inhibitors are currently in clinical development. Of these, erdafitinib (JNJ-42756493) is the only one approved by the FDA for use in patients with locally advanced/mUC. As of September 2023, the European Medicines Agency (EMA) accepted and reviewed a marketing authorization for a similar indication. Erdafitinib is a pan-FGFR1–4 inhibitor, with a half-maximal inhibitory concentration ranging between 1.2 and 5.7 nmol/l [35]. Preclinical studies consistently showed that erdafitinib decreased phosphorylation of FGFR and its downstream effectors, leading to inhibition of cellular proliferation in *FGFR*-altered tumor cell lines [35]. Similar small-molecule inhibitors of FGFR include rogaratinib (BAY1163877), pemigatinib (INCB054828), and infigratinib (BGJ398). Third-generation FGFR3-specific inhibitors are now in preclinical development. Preclinical and preliminary clinical safety have also been demonstrated for other modalities of FGFR inhibition (Table 1). Whether these alternative inhibition strategies will provide greater efficacy or lower toxicity remains to be seen.

In practice, the efficacy of FGFR inhibition has been variable in clinical trials, with overall response rates lower than predicted by preclinical studies, and occasional responses in those without detectable alterations. In part, the wide-ranging responses may be because of varying levels of cellular addiction to FGFR signaling. As demonstrated in lung cancer [36], differing levels of FGFR signaling activate different downstream pathways, leading to variable sensitivity to inhibition. Furthermore, signaling above a critical threshold may lead to cross-talk with other RTK pathways, further convoluting the effects of FGFR inhibition. Finally, other co-alterations found in specific tumors may compensate for FGFR signaling blockade by activating redundant pathways. The complexity of RTK signaling and their cascading downstream effects contribute to the unpredictability of FGFR inhibition and underscore the importance of patient selection.

The difficulty of target identification is further complicated by the limitation of biopsy materials for next-generation sequencing (NGS) and obfuscated by the well-described effect of clonal evolution that leads to spatiotemporal heterogeneity [13,37]. Thus, targeted approaches may best suit localized disease settings with relative molecular homogeneity. In addition, liquid biopsies that capture the entire genomic spectrum of the disease, rather than limited to location-specific biopsies, holds promise for proper patient selection. Evidence in support of these approaches is beginning to emerge.

3.5. *Clinical trial results*

Table 2 summarizes completed and ongoing clinical trials of FGFR inhibitors in UC. Infigratinib was tested for efficacy in UC, supported by the 75% disease control rate (DCR) observed in eight patients with UC in a phase 1 basket trial [38]. In a subsequent phase 2 study involving a cohort of 67 platinum-ineligible patients with heavily pretreated

Table 2 – Clinical trials evaluating FGFR inhibitors for treatment of urothelial carcinoma

Trial	Design	Status/ published	Cohort	Phase	Stage	Screening	Inhibitor	Delivery	FGFR target	CMP	Tx arm (*n*)	ORR (CR/PR)	mPFS, mo (95% CI)	mOS mo (95% CI)	Reference
HCRN 12-157 NCT01732107 Phase 2	OL	Completed 2017	BCG-u ≥2 prior IVS Tx	2	NMIBC	FGFR3	Dovitinib	Oral	NS	SA	13	8% (6 mo)	NR	NR	Hahn
NCT01004224 Phase 1	OL	Completed 2018	Prior CTx or CTx-ineligible	1	Adv/ Met	FGFR1–3	Infigratinib	Oral	1–3	SA	67	25.4% (1.5/23.9)	3.8 (3.1–5.4)	7.8 (5.7–11.6)	[39]
BLC2001 NCT02365597 Phase 2	OL	Completed 2019	Prior CTx ± ICI	2	Adv/ Met	FGFR2/3	Erdafitinib	Oral	Pan	SA	99	40% (3/37)	5.5 (4.2–6.0)	13.8 (9.8–NR)	[42]
NCT02529553 Phase 1	OL	Completed 2021	76% ≥3 prior Tx	1	Adv/ Met	FGFR3	LY3076226	Systemic	FGFR3	SA	3	0%	N/A	N/A	Kollmannsberger
FORT-1 NCT03410693	OL/RS	Completed 2022	Prior CTx	2/3	Adv/ Met	FGFR1/3	Rogaratinib	Oral	Pan	Doce/ Pax/Vin	87	20.7% (2.3/18.4)	2.7 (1.6–4.6)	8.3 (6.5–NR)	[41]
THOR cohort 1 NCT03390504	RS	Completed 2023	Prior ICI ± CTx	3	Adv/ Met	FGFR2/3	Erdafitinib	Oral	Pan	Doce/ Vin	136	45.6% (6.6/39.0)	5.6 (4.4–5.7)	12.1 (10.3–16.4)	[43]
THOR cohort 2 NCT03390504	RS	Completed 2023	CTx + ICI naïve	3	Adv/ Met	FGFR2/3	Erdafitinib	Oral	Pan	Pembro	175	40.0% (6.3/33.7)	4.4 (4.-–5.5)	10.9 (9.2–12.6)	Siefker-Radtke
THOR2 NCT04172675	OL	Completed 2023	BCG-u	2	NMIBC	FGFR2/3	Erdafitinib	Oral	Pan	IVS MMC/ Gem	49	N/A	NR [d] (16.9–NR)	N/A	[44]
FIGHT-201 NCT02872714	OL	Completed 2023	Prior CTx or CPI	2	Adv/ Met	FGFR3	Pemigatinib	Oral	1–3	SA	204 CD 101 ID 103	CD 17.8% (0/17.8) ID 23.3% (3.9/19.4)	CD 4.0 (3.5–4.2) ID. 4.3 (3.9–6.1)	CD 6.8 (5.3–9.1) ID 8.9 (7.5–15.2)	[54]
FIDES-02 NCT04045613	OL	Completed 2023 [a]	≥2 prior Tx	1b/2	Adv/ Met	FGFR1–3	Derazantinib	Oral	1–3	SA	49	8.2% (0/8.2)	6.9 (NR)	Range 0.3–21.4	Necchi
NCI-MATCH cohort H NCT02465060	OL	ANR 2020 [a]	Tx per molecular subgroup	1b/2	Any ST	FGF1–3	Fexagratinib (AZD4547)	Oral	Pan	SA	48	8% (0/8)	3.4 (NR)	NR	Chae
FORT-2 NCT03473756	OL	ANR 2021 [a]	CPI, no prior Tx within 12 mo	1b/2	Adv/ Met	FGFR1/3	Rogaratinib + Atezo	Oral + systemic	Pan	SA	26	55% (13/42)	N/A	N/A	Rosenberg
NORSE NCT03473743	RS	ANR 2023 [a]	CPI, no prior Tx within 12 mo	2	Adv/ Met	FGFR1–3	Erdafitinib ± Cetre	Oral + systemic	Pan	± Cetre	87 E 43 E+C 44	E: 44.2% (2.3/41.7) E+C: 54.5% (13.6/40.9)	E: 5.6 (4.3–7.4) E+C: 11.0 (5.5–13.6)	N/A	Siefker-Radtke
TAR-210 cohort 3 NCT05316155	OL	AR 2023 [a]	Recurrent IR LG Ta/T1, VTL	1	IR NMIBC	FGFR2/3	Erdafitinib	IVS	Pan	SA	15	87% (87/0)	NR [d] (2.96–NR)	N/A	Vilaseca
NCT04963153	OL	AR –	ICI + prior CTx or CPI	1b/2	Adv/ Met	FGFR2/3	Erdafitinib + EV	Oral + systemic	Pan	SA	30 [b]	N/A	N/A	N/A	[56]
TAR-210 NCT05316155	OL	AR –	4 cohorts	1	NMIBC/ MIBC	FGFR2/3	Erdafitinib	IVS	Pan	SA	112 [c]	N/A	N/A	N/A	
NEOWIN EudraCT2022-002586-15	OL	AR –	NATx for CPI	2	MIBC	FGFR1-3	Erdafitinib ± Cetre	Oral + systemic	Pan	± Cetre	90 [b]	N/A	N/A	N/A	

Table 2 (*continued*)

Trial	Design	Status/ published	Cohort	Phase	Stage	Screening	Inhibitor	Delivery	FGFR target	CMP	Tx arm (*n*)	ORR (CR/PR)	mPFS, mo (95% CI)	mOS mo (95% CI)	Reference
SURF301 NCT05544552	OL	AR –	*FGFR3* mutation, no pFGFRi	1/2	Adv/ Met	FGFR3	TYRA-300	Oral	FGFR3	SA	310 [c]	N/A	N/A	N/A	
LOXO-FG3-22001 NCT05614739	OL	AR –	*FGFR3* alteration, pFGFRi allowed	1	Adv/ Met	FGFR3	LOXO-435	Oral	FGFR3	SA	180 [c]	N/A	N/A	N/A	
PROOF-302 NCT04197986	RS	Terminated 2023 [a]	Prior NAC or CPI	3	MIBC/ UTUC	FGFR3	Infigratinib	Oral	1–3	Placebo	218 [b]	N/A	N/A	N/A	Grivas
FIGHT-205 NCT04003610	ROL	Terminated 2022 [a]	CPI	2	Adv/ Met	FGFR3	Pemigatinib + Pembro	Oral + systemic	1–3	Gem/ CBP	372 [b]	N/A	N/A	N/A	Galsky
FIERCE-21 NCT02401542	ROL	Terminated 2019 [a]	Prior CTx	2	Adv/ Met	FGFR3	Vofatamab ± Doce	Systemic	FGFR3	± Doce	55 [c] (211 [b])	12.7%	N/A	N/A	Necchi
FIERCE-22 NCT03123055	OL	Terminated 2019 [a]	Prior Ctx	1b/2	Adv/ Met	FGFR3	Vofatamab + Pembro	Systemic	FGFR3	SA	35 [c] (48 [b])	30%	N/A	N/A	Siefker-Radtke
NERA NCT05564416	ROL	Withdrawn –	CPI	2	MIBC	FGFR2/3	Erdafitinib ± Atezo	Oral + systemic	Pan	± Atezo	44 [b]	–	–	–	

Adv/Met = advanced/metastatic disease; Atezo = atezolizumab; ANR = active, not recruiting; AR = active, recruiting; BCG-u - bacillus Calmette-Guérin–unresponsive; CBP = carboplatin; CD = once daily continuously; Cetre = cetrelimab; CI = confidence interval; CMP = comparison; CPI = cisplatin-ineligible; CR = complete response; CTx = chemotherapy; Doce = docetaxel; E/E+C = erdafitinib/erdafitinib + cetrelimab; EV = enfortumab vedotin; Gem = gemcitabine; ICI = immune checkpoint inhibitor; ID = once daily intermittently; IR = intermediate risk; IVS = intravesical; LG = low grade; MMC = mitomycin C; N/A = not applicable; NAC = neoadjuvant CTx; MIBC = muscle-invasive bladder cancer; mOS = median overall survival; mPFS = median progression-free survival; NATx = neoadjuvant Tx; NMIBC = non–muscle-invasive bladder cancer; NR = not reached; NS = nonselective; OL = open label; ORR = objective response rate; Pax = paclitaxel; Pembro = pembrolizumab; pFGFRi = prior FGFR inhibitor; PR = partial response; ROL = randomized OL; RS = randomized study; SA = single arm; ST = solid tumor; Tx = treatment; UTUC = upper tract urothelial carcinoma; Vin = vinflunine; VTL = visible target lesion.

[a] Abstract.
[b] Planned.
[c] Enrolled.
[d] Recurrence-free survival.

advanced UC [39], the objective response rate (ORR) was 25.4% and 38.8% of patients had stable disease, yielding a DCR of 64.2%. More than two-thirds of the patients experienced grade ≥3 AEs, the most common of which was hyperphosphatemia. Biomarker analysis revealed that only 68% of the patients had matching *FGFR3* alterations in plasma cell-free DNA and tumor tissue. In 22% of the patients, no circulating tumor DNA (ctDNA) was found. A decrease in *FGFR3* ctDNA levels in longitudinal on-treatment samples correlated with better cancer control. Finally, gatekeeper mutations (V443L, V443M, and L496V) thought to confer treatment resistance were found in ctDNA from four patients during treatment, pointing to a possible resistance mechanism. These results led to initiation of the phase 3 PROOF 302 trial investigating disease-free survival rates in patients with high-risk muscle-invasive UTUC or MIBC and susceptible *FGFR3* alterations receiving oral infigratinib [40]. Disappointingly, the study was terminated early because of poor accrual.

Rogaratinib, an oral pan-*FGFR* inhibitor, was compared to chemotherapy in the phase 2/3 FORT-1 trial [41]. A total of 165 patients with *FGFR1/3* mRNA–positive, locally advanced/mUC with at least one prior platinum-containing regimen were randomized to rogaratinib or chemotherapy (docetaxel, paclitaxel, or vinflunine). There was no significant difference in either overall survival (OS; median 8.3 vs 9.8 mo; hazard ratio [HR] 1.11; $p = 0.67$) or the ORR (20.7% vs 19.3%; $p = 0.48$). The incidence of grade ≥3 toxicity was also similar between the treatment arms. A post hoc analysis revealed that only 21/87 patients with high *FGFR1/3* mRNA levels treated with rogaratinib actually had an *FGFR3* DNA alteration. However, the ORR was much higher in this subgroup (52.4%), suggesting that DNA alterations should be used for patient selection.

This approach was taken in the open-label phase 2 BLC2001 trial investigating the efficacy of erdafitinib in a similar cohort of patients with advanced UC following disease progression on or after chemotherapy [42]. Overall, 99 heavily pretreated patients with high-risk disease received a median of five cycles of oral erdafitinib. The ORR was 40% (3% CR; 37% partial response) in the overall cohort, and 59% in the group with previous ICI therapy, yielding progression-free survival (PFS) of 5.5 mo and OS of 13.8 mo. This was the first success for targeted therapy in UC and led to accelerated FDA approval of erdafitinib in 2019. Thereafter, the enhanced efficacy of erdafitinib in *FGFR3/2*-altered disease was validated in a phase 3 study comparing erdafitinib to chemotherapy (THOR-1) [43]. This trial enrolled 266 patients with advanced/mUC that progressed following previous treatments including ICIs. Erdafitinib-treated patients had longer OS (12.1 vs 7.8 mo; HR 0.64; $p = 0.005$) and PFS (5.6 vs 2.7 mo; HR 0.58; $p < 0.001$) and a higher ORR (45.6% vs 11.5%). The toxicity profile was similar to that in previous studies, with grade 3/4 treatment-related AE incidence of 45.9% and one treatment-related death. The most common grade ≥3 toxicities were hand-foot syndrome, stomatitis, onycholysis, and hyperphosphatemia. Central serous retinopathy was seen in 23 patients, with clinical resolution in the majority of patients. These confirmatory results led to full FDA approval in 2024 and acceptance of the marketing authorization application by the EMA.

In another phase 3 study, erdafitinib was compared to pembrolizumab in ICI-naïve patients with mUC with *FGFR3/2* alterations whose disease progressed on one prior line of treatment in THOR-1 cohort 2; the hypothesis was that these patients may have an attenuated response to immunotherapy because of poor baseline immune infiltration [16]. However, there was no statistically significant difference in median OS (10.9 vs 11.1 mo; HR 1.18; $p = 0.18$). Although the ORR was higher in the erdafitinib arm (40.0% vs 21.6%; RR 1.85), the median duration of response was much longer in the pembrolizumab arm(14.4 vs. 4.3 mo). These results corroborated the post hoc analysis results reported by Wang et al [23] for the IMVigor210 and CheckMate275 studies, which showed no differences in response to ICI or survival between the *FGFR3*-altered and WT groups.

With the proof of concept established in mUC, investigations of oral erdafitinib were initiated in NMIBC. In THOR-2 cohort 1, patients with BCG-exposed, papillary-only high-grade NMIBC with *FGFR3/2* alterations were randomized to receive erdafitinib (6 mg) or intravesical chemotherapy [44]. Despite a clear efficacy signal (recurrence-free survival 16.9 vs 11.6 mo; HR 0.28; $p < 0.001$), the trial was terminated because of slow accrual. Despite the reduced dosing, erdafitinib caused unacceptable toxicity, leading to treatment discontinuation in 29% of patients, which is higher than the rate previously reported for advanced/mUC. The promising antitumor activity of erdafitinib but lower tolerance for AEs in localized disease suggest that local delivery mechanisms could enhance the efficacy and bypass systemic toxicity.

TAR-210 is a novel intravesical system designed to provide local, sustained release of erdafitinib within the bladder for which a remarkable benefit/risk profile has been demonstrated. At the 2023 European Society for Medical Oncology meeting, results for the initial 11 patients with BCG-exposed high-risk NMIBC and 15 patients with intermediate-risk NMIBC enrolled in the phase 1 study (NCT05316155) were reported: the recurrence-free survival rate was 82% and the CR rate was 87% in the two cohorts [45]. Notably, only a single treatment-related serious AE (pyelonephritis) occurred, with no dose-limiting toxicity. Other on-target serious AEs of interest seen with oral erdafitinib, such as hyperphosphatemia and central serous retinopathy, were not observed. These promising preliminary results prompted launch of the phase 3 MoonRISe-1 trial, which is comparing intravesical TAR-210 versus investigator choice of single-agent intravesical chemotherapy in patients with intermediate-risk NMIBC, in April 2024 (NCT06319820).

4. Discussion

If the impressive preliminary efficacy/toxicity profile can be recapitulated in the pivotal phase 3 trial, intravesical TAR-210 will be poised to disrupt the current treatment landscape for intermediate-risk NMIBC [46]. However, accumulating experience with other TKI therapies suggests that acquired resistance to FGFR inhibitors should be antici-

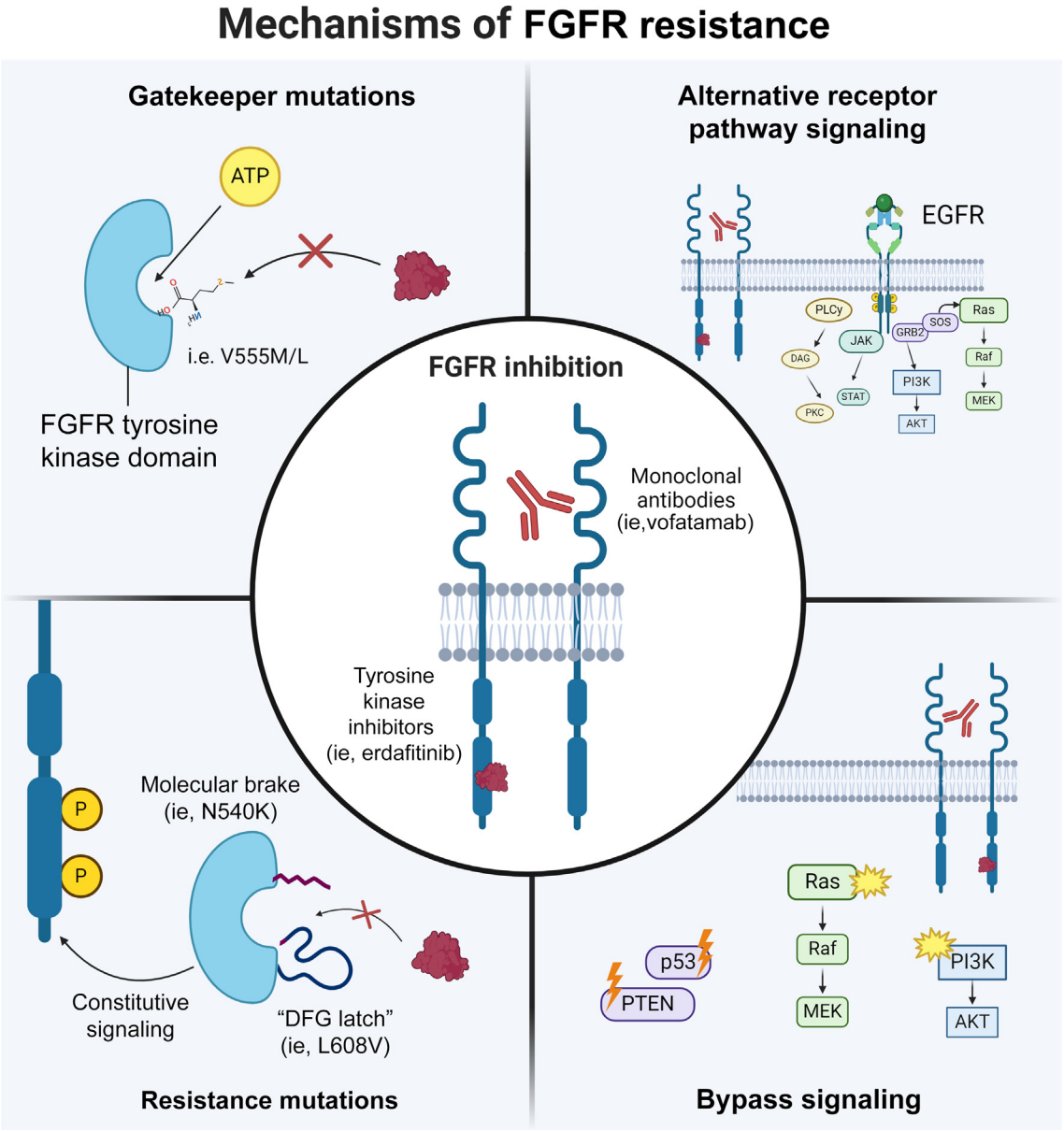

Fig. 2 – Mechanisms of resistance to FGFR inhibitors. Current FGFR inhibitors include small-molecule inhibitors targeting the tyrosine kinase domain and monoclonal antibodies to the extracellular domain. Multiple mechanisms of resistance exist. Gatekeeper mutations may lead to steric hindrance of the ATP-binding pocket and block small-molecule inhibitor binding. Tumor cells may switch from reliance on FGFR pathway signaling to other redundant cell proliferation pathways (eg, EGFR) to overcome FGFR inhibition. Reliance on an extracellular signal can be bypassed via constitutive activation of intracellular signaling molecules (Ras, PI3K) or loss of regulatory proteins (PTEN, p53). Additional single-nucleotide variations leading to resistance include mutations to the DFG latch, which alter the positioning of a constitutive amino acid required for binding of certain small-molecule inhibitors, and mutations that disrupt the molecular brake that autoinhibits FGFR activity.

pated. Fortunately, much has been gleaned about the mechanisms of resistance from the growing body of evidence from preclinical studies and correlative data from FGFR inhibitor trials (Fig. 2).

Using a small hairpin RNA library, Wang et al [47] screened for inhibitors that sensitize UC to FGFR inhibition in vitro. They found inhibition of components of the PI3K, EGFR, MET, and ERBB3 pathways abrogated potential compensatory resistance mechanisms following FGFR suppression. Other studies have confirmed the critical role of these pathways in rescuing FGFR inhibition [48–51]. For EGFR, two distinct mechanisms were identified, one in which FGFR3 signaling through the MAPK pathway was supplemented by EGFR, and another dominated by EGFR signaling via repression of FGFR3, with EGFR inhibition salvaged by delayed upregulation of FGFR3 expression [49]. These discoveries highlight the heterogeneity among tumor cells and suggest that dual inhibition of FGFR3 and EGFR may lead to enhanced antitumor efficacy.

In addition, multiple mechanisms of resistance involving point mutations in *FGFR3* have been described. Gatekeeper mutations can lead to substitution of bulky amino acid residues that create steric hindrance and block access to the ATP-binding domain (V555M/L and V553/L) while simulta-

neously strengthening the hydrophobic spine of the kinase to increase baseline activity of the receptor [49,50,52,53]. Mutations that change the molecular conformation of the DFG latch alter the binding site of many FGFR3 inhibitors and thus attenuate their potency. In addition, mutations such as N540K disengage the natural molecular brake, leading to a constitutive increase in enzyme activity (Fig. 2).

With the increasing clinical use of FGFR inhibitors, translational data that can define genomic patterns of resistance are accumulating. ctDNA from 36 patients treated with pemigatinib in the FIGHT-201 trial was used to identify acquired *FGFR3* mutations (four gatekeeper, two molecular brake) [54]. Similarly, genomic profiling at the time of progression in 19 patients treated with FGFR inhibitors revealed seven patients with gatekeeper mutations, five of which were absent at baseline, suggesting resistance via clonal evolution [55]. This was substantiated by functional studies in which each of the gatekeeper mutations was introduced to a pre-existing *FGFR3:TACC3* fusion cell line and led to a measurable increase in erdafitinib resistance. In the same cohort, 11 of the 19 patients had co-alterations within the PI3K pathway at the time of progression, including five with *PIK3CA* alteration [55]. Dual treatment with erdafitinib and pictilisib (PI3K inhibitor) in a patient-derived xenograft model resulted in synergistic tumor suppression. Lastly, analysis of FIGHT-201 trial samples revealed new oncogenic mutations in *TP53*, *FGFR3*, and *AKT1* before or at the time of clinical progression [13].

The convergence of preclinical and translational data for *FGFR3* gatekeeper mutations and alternative RTK activation supports combined TKI therapy and the development of next-generation FGFR inhibitors that might overcome these impediments. Two FGFR3 inhibitors (LOXO-435, TYRA-300) with reported efficacy against gatekeeper mutations are already under investigation. Furthermore, combining FGFR inhibitors with antibody-drug conjugates may result in higher efficacy [56]. Detection of mutations associated with treatment resistance in localized disease may be possible via more frequent and accurate monitoring using urinary ctDNA [57]. Increasingly accurate early detection of resistance mutations occurring at minimal variant allele frequencies may support administration of salvage agents. In addition, the TARIS platform for sustained intravesical drug delivery is not limited to erdafitinib, as evidenced by promising results from five SunRISe trials using TAR-200, a similar intravesical device that elutes gemcitabine. With such a dynamic delivery system, multiple drugs may be administered via the intravesical route to bypass potential systemic toxicity. Coupled with the development of diagnostic urinary ctDNA biomarkers and an ever-expanding understanding of the biology of bladder cancer, we are indeed turning the page to precision medicine as the next chapter in the management of NMIBC.

5. Conclusions

Although FGFR inhibitors are approved for advanced UC refractory to chemotherapy, they may provide a significant therapeutic benefit in patients with early-stage NMIBC. With an increasing understanding of the molecular underpinnings of FGFR-driven molecular oncogenesis and novel drug delivery platforms, we are at the dawn of precision oncology in bladder cancer.

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Acquisition of data: Li, Linscott.
Analysis and interpretation of data: Li, Linscott, Catto, Daneshmand, Faltas, Kamat, Meeks, Necchi, Pradere, Ross, van der Heijden, van Rhijn, Loriot.
Drafting of the manuscript: Li, Linscott, Loriot.
Critical revision of the manuscript for important intellectual content: Li, Linscott, Catto, Daneshmand, Faltas, Kamat, Meeks, Necchi, Pradere, Ross, van der Heijden, van Rhijn, Loriot.
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