INTRODUCTION

Bladder cancer (BC) is the 10th most common malignancy worldwide and a major global health concern. By 2020, it had accounted for approximately 573,000 new cases and 212,536 deaths annually [1]. The most prevalent subtype, accounting for over 90% of patients, is urothelial carcinoma (UC), which originates from the urothelium [2].

Urothelial BC (UBC) management depends primarily on the clinical stage. Metastatic UBC (mUBC) is an incurable disease that relies on systemic therapies involving chemotherapy, immunotherapy, or antibody-drug conjugates to improve survival and alleviate symptoms. The traditional reliance on platinum-based chemotherapy has demonstrated limited long-term efficacy and considerable side effects, prompting the development of new therapeutic approaches [3,4]. Over the last decade, significant advances in the molecular understanding of UBC have led to the identification of novel therapeutic targets, including fibroblast growth factor receptors (FGFRs) [4-6]. FGFR inhibitors (FGFRis) have emerged as a promising treatment strategy, particularly for patients with specific FGFR alterations [5-
In patients with actionable FGFR2 or FGFR3 genomic alterations, erdafitinib is considered after platinum-based treatments [7,10–12]. However, the contribution of FGFRis in mUBC remains limited owing to limited efficacy, and treatment-related toxicities. Erdafitinib is currently the only U.S. Food and Drug Administration (FDA)-approved FGFRi for FGFR2/3 altered, platinum-resistant patients with advanced/mUBC (a/mUBC); however, several other FGFRis are in the late stages of clinical development. This review explores the role of FGFRis in treating UBC, focusing on their mechanism of action, efficacy, and potential future directions.

**FGFR PATHWAY AND ITS ROLE IN BLADDER CANCER**

The FGFR pathway has emerged as an actionable pathway for the targeted therapy of a/mUBC. The FGFR family comprises 4 receptors (FGFR1–4). Aberrations in FGFR signaling, such as mutations, amplifications, and translocations, have been implicated in the pathogenesis of several cancers, including BC [6,13]. Furthermore, activating FGFR3 mutations are the most extensively studied FGFR genetic aberrations in BC [5,14,15]. Recent studies have shown that FGFR3 mutations such as point mutations (R248C, S249C, and Y373C) and gene fusions such as FGFR3-TACC3 occur in 60%–70% of low-grade papillary Ta tumors [16] and 20%–25% of muscle-invasive BC (MIBC) and metastatic UC cases [17–19]. FGFR3 activation triggers downstream signaling pathways, including the Ras/mitogen-activated protein kinase (Ras-MAPK) and the phosphoinositide 3-kinase/protein kinase B (PI3K-Akt) pathways, which are critical for cell growth and survival [20–23]. This activates the Ras-MAPK pathway [7,23,24]. The presence of FGFR3 mutations appears to identify a subgroup of patients with a favorable prognosis and is associated with the luminal subtype of BC [17,20,25]. The presence of FGFR3 alterations is a viable target for therapeutic intervention. FGFRis are used to treat metastatic UC of the bladder and upper urinary tract [21–23].

**FGFR INHIBITORS IN CLINICAL TRIALS**

Targeting FGFRs in UBC is a promising therapeutic strategy [6]. Notably, several FGFRis are currently under clinical development or have been approved for treating UBC (Table 1) [13]. Erdafitinib, an orally administered pan-FGFRis, has shown significant efficacy in patients with a/mUBC with FGFR alterations [13]. The BLC2001 study, an open-label phase II trial, enrolled patients with locally advanced and unresectable mUC. The inclusion criteria were at least one FGFR3 mutation or FGFR2/3 fusion identified from formalin-fixed, paraffin-embedded tumor samples using a custom reverse-transcriptase polymerase chain reaction (RT-PCR) assay developed by Qiagen as a

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FGFR, fibroblast growth factor receptor; mUC, metastatic urothelial carcinoma; 2L, second-line; 1L, first-line; ORR, overall response rate; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; DCR, disease control rate.
companion diagnostic test. Notably, all patients had a history of disease progression during or after at least one course of chemotherapy or within 12 months of neoadjuvant or adjuvant chemotherapy. In this study, erdafitinib achieved an overall response rate (ORR) of 40% with a median progression-free survival (PFS) of 5.5 months and overall survival (OS) of 13.8 months [13].

THOR (NCT03390504) cohort 1 was a confirmatory, randomized, phase 3 study that evaluated whether erdafitinib provides a survival advantage over the investigator’s choice of chemotherapy (docetaxel or vinflunine) in 266 patients with advanced unresectable or metastatic UC who had progressed after 1 or 2 prior treatments, including a programmed death-ligand 1 (PD-L1) agent, and who exhibited an FGFR2 or FGFR3 mutation. Molecular eligibility was confirmed through central laboratory screening or historical local test results from tissue or blood. The local tests included next-generation sequencing, direct digital counting, and the Qiagen Therascreen FGFR Rotor­Gene Q RT­PCR assay. Tumors were required to exhibit one or more specific FGFR3 mutations (R248C, S249C, G370C, or Y373C) or one or more of the following fusions (translocations): FGFR2–BICC1, FGFR2–CASp7, FGFR3–TACC3_V1, FGFR3–TACC3_V3, or FGFR3–BAIAP2L1. The most prevalent alterations were the FGFR3 S249C mutations (47%), followed by the FGFR3 Y373C mutation (17%) and the FGFR3–TACC3_V1 fusion (10%) [13]. No changes were observed in FGFR2 alterations. The median follow-up was 15.9 months. The median OS was significantly longer with erdafitinib than with chemotherapy (12.1 months vs. 7.8 months; hazard ratio [HR], 0.64; 95% confidence interval [CI], 0.47–0.88; p=0.005). The median PFS was also longer with erdafitinib than with chemotherapy (5.6 months vs. 2.7 months; HR, 0.58; 95% CI, 0.44–0.78; p<0.001) [13]. An OS benefit was observed across all clinically relevant subgroups, including those with FGFR mutations or translocations. Erdafitinib improved the ORR (46% vs. 12%) and complete response (CR) rate (7% vs. 1%) than chemotherapy. Grade ≥3 toxicity rates were similar between the 2 treatment arms (46% each) [13]. For erdafitinib, grade ≥3 toxicities included palmar-plantar erythrodysesthesia (10%), stomatitis (8%), onycholysis (6%), hyperphosphatemia (5%), diarrhea (3%), central serous retinopathy (CSR; 2%), and eye disorders other than CSR (2%) [13].

Erdafitinib was also compared with pembrolizumab in an open-label phase III trial (THOR, cohort 2) of 351 patients with advanced unresectable or metastatic UC with an FGFR2 or FGFR3 mutation who had progressed after one prior therapy and were naïve to a PD-L1 inhibitor [14]. At a median follow-up of 33 months, erdafitinib demonstrated similar OS (median 11 months each; HR, 1.18; 95% CI, 0.92–1.51) relative to pembrolizumab [14]. Erdafitinib is approved by the FDA for adult patients with locally advanced or metastatic UC (a/mUC) with an FGFR3 alteration that has progressed on or after at least one line of systemic therapy [13,15]. It is not recommended for the treatment of patients who are eligible for and have not received prior programmed death-1 (PD-1) or PD-L1 inhibitor therapy.

Rogaratinib (BAY1163877) is an oral pan-FGFRi. The FORT-1 trial (NCT03410693) was a randomized, open-label, phase II/III study. Patients with a/mUC with ≥1 prior platinum-containing regimen were randomly assigned (1:1) to rogaratinib (800 mg orally twice daily, 3-week cycles; n=87) or chemotherapy (docetaxel 75 mg/m², paclitaxel 175 mg/m², or vinflunine 320 mg/m² intravenously once every 3 weeks; n=88). Patients were considered FGFR1/3 messenger RNA (mRNA)-positive with an RNAscope score of 3+ or 4+. Overall, 10.9% of the cohort had mutations in either PIK3 Catalytic Subunit Alpha (PIK3CA) or RAS. The primary endpoint was OS, with planned ORR analysis following phase II accrual. The trial did not confirm the feasibility of this approach as the ORRs were 20.7% for rogaratinib and 19.3% for chemotherapy, with no significant differences in OS or PFS. Safety data indicated that 43.0% of the rogaratinib group experienced grade 3 adverse events (AEs) compared with 39% of the chemotherapy group. Grade 4 AEs were reported in 4.7% of the rogaratinib group and 18.3% of the chemotherapy group [16]. Additionally, the trial’s secondary objective of clarifying the effect of PIK3CA or RAS mutations in response to FGFR inhibition was not met because of the small number of patients with these mutations.

Pemigatinib (INCB054828) is a selective, reversible, and adenosine triphosphate-competitive inhibitor of FGFR1–3. The phase I/II FIGHT-101 study (NCT02393248) assessed the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of pemigatinib in various solid tumors,
including UC. Hyperphosphatemia was the most frequently reported adverse event, affecting 75% of participants. This open-label, single-arm, multicenter phase II study was conducted at 73 academic and community-based sites across 11 countries. Patients with mUC were stratified into 2 cohorts based on their tumor FGF/FGFR alteration status. In cohort A, the ORR was 17.8% (10.9%–26.7%) and 23.3% (15.5%–32.7%) for patients receiving a continuous dose and those on an intermittent dosing regimen, respectively [18,19].

Infigratinib (BGJ398) is an orally bioavailable, small-molecule inhibitor of FGFR1–3. This phase I trial aimed to evaluate the efficacy of infigratinib across various lines of therapy in patients with mUC. The trial enrolled 7 patients, of whom 1 (19.4%) received infigratinib as early-line therapy for mUC, primarily because they were ineligible for platinum-based chemotherapy. Overall, the ORR was 25.4% (95% CI, 15.5–37.5), and the disease control rate (DCR) was 64.2% (95% CI, 51.5%–75.5%). Notably, the ORR was higher in the first-line treatment setting (30.8%; 95% CI, 9.1%–61.4%) than in subsequent lines (24.1%; 95% CI, 13.5%–37.6%), suggesting potential benefits from earlier use. PFS and OS were similar in both groups. AEs were primarily mild and included hyperphosphatemia (46.3%), elevated creatinine levels (41.8%), and fatigue (37.3%). Ocular toxicity manifested as dry eyes and blurred vision in 16.4% and 10.4% of patients, respectively, with no grade 3 or higher AEs reported [24].

The other FGFRis are under investigation. These drugs have shown potential in early-phase clinical trials with promising safety profiles and preliminary efficacy in FGFR-mutant BC. A selective FGFR3 inhibitor, vofatamab, has been evaluated in combination with docetaxel in patients with metastatic UC [26]. The combination was well-tolerated and showed increased activity in tumors with FGFR3 alterations [26].

COMBINATION THERAPIES WITH FGFR INHIBITORS

Combining FGFRIs with other therapeutic modalities, such as immune checkpoint inhibitors (ICIs) and chemotherapy, is being explored to enhance treatment efficacy and overcome resistance [5,27-30]. Two significant break-throughs in the treatment of a/mUBC were the approval of ICIs and the FGFRi erdafitinib. There is conflicting data on FGFR alterations and responses to ICIs, with previous studies suggesting a lower response to ICIs in FGFR alteration [31,32]. FGFR alterations are associated with T-cell exhaustion in the UC immune microenvironment, potentially resulting in reduced T-cell-mediated antitumor immune responses [33]. Other previous work notes no difference in ORR in FGFR wild-type versus mutation, and FGFR knockdown upregulates interferon (IFN)-gamma response genes [32,34]. Thus, combining FGFR and PD-1/L1 inhibitors may be a logical therapeutic approach, with increased efficacy, reverse resistance, address heterogeneity, and target the microenvironment [28,31].

Notably, several trials randomizing patients between monotherapy and combination therapy are currently ongoing. Three compare FGFRi monotherapy with FGFRi-ICI combination (NORSE or NCT03473743, FIDES-02 or NCT04045613, and FIGHT-205 or NCT04003610), one compares ICI monotherapy with FGFRi-ICI combination (FORT-2 or NCT03473756), and another compares FGFRi, chemotherapy, and pembrolizumab monotherapy (THOR or NCT03390504) (Table 2).

The phase I/II NORSE trial is designed to assess the efficacy of erdafitinib alone or in combination with cetrelimab (an IgG4 anti-PD-1 inhibitor) in patients with a/mUC with FGFR2/3 alterations. These patients were cisplatin ineligible and enrolled as first-line therapy. The median follow-up time was 14.2 months. The ORR for erdafitinib + cetrelimab was 54.5%, with 6 CRs (13.6%) and 12 months OS of 68%. The ORR for erdafitinib alone was 44.2% with one CR and 12 months OS of 68% [35]. No dose-limiting toxicities were observed in any of the 15 enrolled patients. Ten patients experienced grade 3 AEs. The most frequent treatment-emergent AEs (any grade) were hyperphosphatemia (68.9% vs. 83.7%), stomatitis (59.1% vs. 72.1%), and diarrhea (45.5% vs. 48.8%) in the erdafitinib+cetrelimab and erdafitinib groups. Grade ≥3 treatment-related AEs occurred in 45.5 (erdaftinib+cetrelimab) and 46.5% (erdaftinib) of patients. One cetrelimab-related death secondary to pulmonary failure occurred in the erdafitinib+cetrelimab group [35]. (NCT03473743).

The phase Ib/II FORT-2 trial (NCT03473756) investigated Ho Kyung Seo, et al: FGFR-Targeted Therapies for Bladder Cancer
the safety, tolerability, and efficacy of rogaratinib combined with atezolizumab as first-line treatment in cisplatin-ineligible patients with a/mUC. These patients exhibit FGFR1/3 mRNA overexpression, as detected through RNA in situ hybridization of archival tissues using an RNAscope. Preliminary results presented at the American Society of Clinical Oncology 2020 congress revealed an ORR of 54% and a DCR of 83% among the 26 patients treated. These findings suggest that the combination of rogaratinib and atezolizumab may overcome some limitations of the FORT-1 trial [36].

Another interesting phase II trial, FIGHT-205 (NCT04003610), investigated pemigatinib alone versus pemigatinib plus pembrolizumab versus the standard of care in patients with cisplatin-ineligible mUC. Unfortunately, the study was terminated after enrolling only 7 patients. Additionally, a phase II combination trial of futibatinib plus pembrozilumab (NCT04601857) is currently enrolling patients and has shown promising preliminary safety and tolerability data.

The FIDES-02 (NCT04045613) trial is designed to explore whether the combination of derazantinib, an oral multi-tyrosine kinase inhibitor (TKI) that targets FGFR1–4 genomic alterations, with the ICI, atezolizumab offers superior clinical outcomes compared with FGFRi monotherapy in patients with a/mUC with FGFR2 or FGFR3 alterations. However, the FIDES-02 data fail to support the development of derazantinib in metastatic UC [38].

The FIERCE-22 (NCT03123055) trial is a single-arm, phase Ib/II study evaluating vofatamab (a fully human monoclonal antibody against FGFR3 that blocks the activation of both the wild-type and genetically activated receptors, 25 mg/kg), followed by a vofatamab-pembrolizumab combination. The study enrolled patients with advanced, platinum-resistant UBC, regardless of the FGFR status. In a preliminary report, 28 patients were enrolled in the phase II segment (FGFR altered: n=8, wild-type: n=20), with an
ORR of 40% [39]. Responses were similar between FGFR-altered (43%) and wild-type (40%) cohorts [39]. Notably, the translational analysis revealed that the luminal molecular subtype was associated with a higher response rate, the p53-like molecular subtype with poorer survival, and lead-in vofatamab monotherapy-induced inflammatory pathway alterations.

The phase III LEAP-011 trial investigates the combination of lenvatinib and pembrolizumab as front-line treatment. Lenvatinib, a multi-TKI that inhibits vascular endothelial growth factor receptor-1–3, FGFR1–4, platelet-derived growth factor receptor alpha, CD117 and stem cell factor receptor, and rearranged during transfection is a potent angiogenesis inhibitor and an effective immunomodulator [40–43]. The dual inhibitory activity of lenvatinib against both VEGF and FGF induces broad-spectrum antitumor activity due to its antiangiogenic effects [42,44]. These antiangiogenic effects convert the immunosuppressive status of the tumor microenvironment to a pro-tumor milieu and lead to the priming of increased IFN-gamma production by cytotoxic T cells [45,46]. Lenvatinib shows more potent antitumor activity when combined with PD-1 blockade because of decreased tumor-associated macrophage numbers [47]. The combination of lenvatinib and pembrolizumab is being investigated as a front-line treatment in the phase III LEAP-011 trial (NCT03898180), which is evaluating the combination in cisplatin-unfit patients with PD-L1 combined positive score ≥10 or in patients deemed ineligible for any platinum-based regimen, regardless of PD-L1 expression [48].

**SIDE EFFECTS OF FGFR INHIBITORS**

Erdafitinib, has now been approved for the treatment of a/m UC that harbor certain FGFR mutations. Despite their efficacy, FGFRis are associated with several toxicities that can impact the patient’s quality of life and lead to dose reduction, interruption, or discontinuation of therapy.

Hyperphosphatemia is an AE of FGFRis, owing to the role of FGFR pathways in phosphate homeostasis, involving feedback mechanisms with FGF 23, 1,25-dihydroxyvitamin D, and parathyroid hormone (Fig. 1) [13,15,49]. Hyperphosphatemia occurs in over 60% of patients treated with FGFRis, presenting early after treatment initiation (average, 15–20 days) [13]. It is generally mild (grade 1 or 2) but can lead to complications such as soft tissue mineralization, cutaneous calcifications, calcinosis, and nonuremic calciphylaxis [13]. Management typically includes: a low phosphate diet to reduce phosphate intake, using phosphate binders in the gastrointestinal tract, such as sevelamer, and reducing or interrupting the dose of FGFRis to control serum phosphate levels [50].

Acute kidney injury (AKI) is another significant AE associated with FGFRis; 6% of patients treated with erdafitinib experience AKI, with 2% having a grade ≥3 AKI [13]. A case report involving rogaratinib showed renal biopsy findings of acute tubular necrosis that improved upon discontinuation of the drug and did not recur when reintroduced at a lower dose [51]. Management strategies include regular renal function assessment through serum creatinine and urine output measurements, hydration, and dose modification.

FGFRis are also associated with a serous retinopathy (foci
of subretinal fluid) to that seen with the MEK inhibitors [52,53]. Dry eyes and eyelash trichomegaly, including corneal epithelial lesions, have also been reported with this class of agents [13,54,55], as are corneal epithelial lesions [56]. In the phase II BLC2001 trial, ocular toxicity from erdafitinib resulting in a visual field defect was reported in 25% of patients, with a median time to first onset of 50 days [13]. Grade 3 symptoms, defined as those involving the central field of vision causing vision worse than 20/40 or >3 lines of worsening from baseline, were reported in 3% of patients. Dry eye symptoms occurred in 28% of patients during treatment, and grade 3 symptoms occurred in 6%. Ocular symptoms resolved in 13% of the patients and were ongoing at a study cutoff in 13% [13]. The United States Prescribing Information for erdafitinib recommends that all patients receive prophylactic use of ocular demulcents, undergo monthly ophthalmologic examinations, and the drug should be withheld in cases of serous retinal toxicity with reevaluation within 2 weeks. Dose-modification guidelines are recommended for patients with adverse ocular reactions.

Dermatologic toxicities associated with FGFRis include hand-foot skin reaction, stomatitis, xerostomia, nail changes (paronychia and onychomadesis), and alopecia [54]. These drugs have been associated with diarrhea in approximately half of treated patients and are severe in <5% of patients.

**FGFR-TARGETED THERAPIES FOR NON-NMIBC**

FGFR3 alteration, prevalent in 50%–80% of non-muscle-invasive bladder cancer (NMIBC), is much more frequent than in MIBC [57,58]. However, all systemic therapies developed to date exhibit toxicity profiles that are not acceptable for most patients with NMIBC, who, despite recurrent localized disease, usually have a long-life expectancy. However, in the highest-risk group of patients with NMIBC, including those who have failed the bacillus Calmette-Guérin (BCG) therapy, systemic therapy may be considered an alternative to radical cystectomy (RC).

The THOR-2 trial (clinical trial number NCT04172675), a multi-cohort phase 2 study, was designed to assess erdafitinib, which has already been approved for advanced cases of FGFR3/2 alterations after platinum chemotherapy failure in patients with NMIBC [59]. Cohort 1 assessed whether erdafitinib improved recurrence-free survival (RFS) compared with intravesical chemotherapy in patients with recurrent, BCG-treated, papillary-only, high-risk NMIBC harboring select FGFR3/2 alterations who refused or were ineligible for RC. Seventy-three patients were randomized in 2:1 to erdafitinib or chemotherapy groups. The median follow-up period for RFS was 13.4 months in both groups [59]. Median RFS was not achieved for erdafitinib (95% CI, 16.9 months–not estimable) and was 11.6 months (95% CI, 6.4–20.1 months) for chemotherapy, with an estimated HR of 0.28 (95% CI, 0.1–0.6; p = 0.0008) [59]. In this population, the safety results were generally consistent with the known profiles for erdafitinib and chemotherapy. These promising results indicate that erdafitinib may be a viable treatment for patients with NMIBC, especially in cases where surgical options are limited or infeasible. Cohorts 2 and 3 were exploratory, enrolled patients with BCG-unresponsive carcinoma in situ (CIS) with/without papillary disease and patients with intermediate-risk NMIBC, respectively. Cohort 2 included patients with histologically confirmed BCG-unresponsive HR-NMIBC and FGFR3/2 alterations who presented with CIS and refused or were ineligible for RC. In this cohort, patients received continuous oral erdafitinib 6 mg once daily without up-titration in a 28-day cycle. Treatment with erdafitinib was discontinued if no CR was observed within 3 months. The exploratory efficacy endpoints were CR rates at cycle 3 day 1 (C3D1) and cycle 6 day 1 (C6D1) disease evaluation, and safety was a key secondary endpoint. Ten patients with a median age of 72 years (range, 52–83 years) were treated with erdafitinib. Notably, 90% of the patients had CIS, whereas one patient with Ta was missed. Patients received erdafitinib for a median duration of 5.9 months (range, 1.1–17.0 months). Of the 10 enrolled patients, the CR rates at the first (C3D1) and second (C6D1) evaluations were 100% (9/9 evaluable patients) and 75% (6/8 evaluable patients), respectively. Grade ≥3 treatment-related event (TRAE) rates were 80% (9/11 evaluable patients) and 66% (10/15 evaluable patients), respectively. Grade ≥3 treatment-related TRAEs, including dry mouth, stomatitis, nail disorder, onychomadesis, AKI, chronic kidney disease, sepsis, and hypotension, occurred in 3 patients (30%). One patient (10%) developed serious treatment-related TRAEs, including dry mouth, hypotension, pneumonitis, AKI, and sepsis, and 1 (10%) discontinued
MECHANISMS OF RESISTANCE AND FUTURE DIRECTIONS

The numerous compounds that have been developed over the years to inhibit FGFRs have highlighted the diligent efforts of the scientific community to translate preclinical results into clinical practice. However, challenges, such as target selectivity and treatment-related AEs, have hampered the introduction of a valid therapeutic option. In addition, resistance mechanisms often emerge, leading to treatment failure. Therefore, understanding these mechanisms, such as secondary mutations in the FGFR gene or activation of alternative signaling pathways, is crucial for developing next-generation FGFRis [63]. Combination therapies such as ICIs or traditional chemotherapy may enhance efficacy and overcome resistance (Table 2). In addition, addressing the variability in response rates and identifying predictive biomarkers to determine which patients will benefit the most from these therapies is crucial.

Liquid biopsy is an innovative diagnostic technique that analyzes biomarkers in body fluids like blood, saliva, or urine to detect and monitor diseases, particularly cancers [64-66]. This technology captures circulating tumor cells, ctDNA, microRNAs, and other biomolecules, offering a noninvasive alternative to traditional tissue biopsies [67-69]. Research has underscored the potential of liquid biopsy in identifying FGFR alterations. In previous studies, the analysis of gene alterations was based on the primary tumor prior to treatment [13,70]. However, due to tumor evolution, the primary and metastatic tumors may possess different mutation statuses, which may not accurately reflect the tumor characteristics at the time of FGFR inhibitor administration [71]. This discrepancy can lead to a reduced predictive value for the effectiveness of FGFR inhibitors. Therefore, additional analysis of recurrent or metastatic tumors just before treatment is necessary. Since tissue sampling via biopsy of the metastatic site can be challenging, liquid biopsy utilizing blood CTCs, cfDNA, or exosomes can serve as a viable alternative.

The treatment landscape for a/mUC has changed dramatically changed in recent years. Based on the outstanding results of the EV-302 trial, the National Comprehensive Cancer Network recommends the combination of enfortumab vedotin (EV) with pembrolizumab as the primary systemic treatment for patients with a/mUC, irrespective of their eligibility for cisplatin. After progression on first-line treatments, such as the combination of EV with pembrolizumab, the role of erdafitinib should be elucidated in earlier settings.
going research is aimed at addressing these challenges and optimizing the use of FGFRis in clinical practice. PROOF 302 (NCT04197986), a randomized, double-blind, placebo-controlled phase III trial, was proposed in approximately 218 patients from 120 centers worldwide as an adjuvant therapy with infrafatinib (BGJ398) in patients with MIBC. Unfortunately, this trial was stopped early by the sponsor; however, genomic analysis provides insights into the prevalence of FGFR3 alterations, and the assessment of the primary and secondary endpoints is ongoing.

CONCLUSION

FGFRis represent a significant advancement in a/mUBC treatment, particularly for patients with FGFR2/3 genetic alterations. Ongoing research and clinical trials will further elucidate their roles and integration into current treatment paradigms. The future of UBC therapy lies in personalized medicine, where molecular profiling guides the use of targeted treatments, such as FGFRis, to improve patient outcomes.

NOTES

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