# Fibroblast Growth Factor Inhibitors

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Fibroblast Growth Factor Inhibitors (FGFRis) are used for cancer treatment. Dysregulated activation of fibroblast growth factor receptor (FGFR) signaling enhances tumor proliferation, survival, invasion, angiogenesis, and immune evasion. The recent U.S. Food and Drug Administration approval of erdafitinib and the emergence of other potent and selective FGFR inhibitors have shifted the treatment paradigm for patients with a/m UBC harboring actionable FGFR2 or FGFR3 genomic alterations, who often have a minimal-to-modest response to ICIs. FGFRi–ICI combinations are therefore worth exploring, and their preliminary response rates and safety profiles are promising.

Keywords: urothelial bladder carcinoma ; precision medicine ; fibroblast growth factor receptor ; fibroblast growth factor inhibitor ; tumor microenvironment ; treatment resistance ; immune checkpoint inhibitors ; combination

## 1. Introduction

Patients with non-muscle invasive urothelial bladder cancer (NMI-UBC, carcinoma in situ, Ta, or T1), which accounts for approximately 75% of initial UBC diagnoses, demonstrate unexpectedly high recurrence rate and multifocality with disease progression to muscle-invasive UBC (MI-UBC), which has a much less favorable prognosis and occurs in 10–15% of patients diagnosed with NMI-UBC [1][2][3][4][5][6]. For patients who present with non-metastatic MI-UBC, consensus guidelines recommend radical cystectomy and urinary diversion combined with lymph node dissection following cisplatin-based neoadjuvant chemotherapy. However, according to the available scientific data, 50% of patients with MI-UBC develop distant metastasis despite radical cystectomy, and 5% of UBC patients are present with metastasis at diagnosis. Although approximately 50–70% of locally advanced or metastatic UBCs (a/m UBCs) patients respond to chemotherapy, unfortunately, in most cases, progression or recurrence occurs with conventional strategies, and limited benefit is seen in second-line and later setting [2][3][4][5]. The prognosis of patients affected by locally advanced or metastatic (a/m) UBC remains dismal, with a 5-year overall survival (OS) of approximately 10–15% [1][2][3][4][5][6].

Recently, the efficacy of immunotherapy using immune checkpoint inhibitors (ICIs) has been investigated in patients with a/m UBC [1][4][5][7][8]. Anti-programmed death-1 (PD-1) agents pembrolizumab and nivolumab, as well as anti-programmed death ligand-1 (PD-L1) agents avelumab and atezolizumab, have been approved by the USA Food and Drug Administration (FDA) for treating a/m UBC patients who do not respond to platinum-based chemotherapy and have demonstrated durable clinical benefits with reduced toxicity. However, only a subset of patients may respond to ICIs (objective response rate (ORR): 15–21%), and treatment options are limited for patients who do not respond to ICIs. For such patients, antibody-drug conjugates (ADCs) and targeted therapies/anti-angiogenesis agents, which are still under clinical trials, remain the only viable treatment strategies, while taxane-based or vinflunine chemotherapy has modest results but is still used in clinical practice [2][4][5][8].

Multi-platform, high-throughput next-generation sequencing (NGS) technology has enabled comprehensive assessment of the UBC landscape and significantly improved our understanding of its complex pathology, ushering in a new era of precision oncology [2][4][5][8][9][10]. Advances in genomic profiling, the development of targeted therapies, and the resurgence of ICI have led to the molecular subclassification of a/m UBC, and efforts are underway to define therapeutic strategies and associated predictive biomarkers. Receptor tyrosine kinases (RTKs), which transduce extracellular signals to a variety of intracellular signaling cascades [11][12], are classified into the epidermal growth factor receptor (EGFR) group (EGFR, HER2, MET, and RYK, among others), the fibroblast growth factor receptor (FGFR) group (FGFRs, colony-stimulating factor 1 receptor (CSF-1R) and vascular endothelial growth factor (VEGF) R2, among others.) , the insulin receptor (INSR) group (INSR, insulin-like growth factor 1 receptor (IGF1R), ALK, and ROS1, among others), the RAR-related orphan receptor (ROR) group (ROR1, ROR2, DDR2, and NTRK1, among others), and the EPH receptor (EPH) group (EPHA1, EPHB1, and PTK7, among others) [8][11][12][13][14][15][16]. The human FGFR family includes four highly conserved RTKs: FGFR1, FGFR2, FGFR3, and FGFR4, which are encoded by distinct genes.

Gain-of-function coding mutations, gene fusion, and gene amplification are three major classes of FGFR alterations associated with the luminal-papillary subtype of a/m UBC [4][5][8][15][17][18]. In spite of the general association between FGFR alterations and favorable characteristics in NMI-UBC, there is no evidence to suggest that FGFR gene alterations correlate with a less aggressive phenotype once urothelial carcinoma advances. In fact, FGFR3 gene alterations are associated with less favorable outcomes in the context of chemotherapy for a/m UBC [15][17][19]. Erdafitinib, a tyrosine kinase inhibitor (TKI) of FGFR1–4, has shown significant benefits in patients with a/m UBC with FGFR alterations [20][21].

## 2. Monotherapy FGFR-Targeting Strategies for a/m UBC

As the role of FGF-FGFR signaling in a/m UBC has become clearer, a large number of potential and promising drugs targeting this signaling pathway have been developed. According to their mode of action, they can be divided into three categories: (a) small-molecule FGFR TKIs (non-selective and selective), (b) anti-FGFR antibodies, and (c) FGF ligand traps and DNA/RNA aptamers [4][5][8][11][15][17][22][23][24][25][26][27][28][29][30][31][32][33][34][35] (**Table 1**). As the FGFR TKIs may target other growth factor receptors because the binding pocket of ATP-competitive FGFRs shares a high degree of homology with other oncogenic RTKs, such as VEGFR and platelet-derived growth factor receptor (PDGFR), these TKIs can be divided into multi-kinase (non-selective) FGFRis and FGFR-specific TKIs (selective) [22][23][24][25][26][33].

**Table 1.** Representative FGFRi's as single anti-cancer agents.

| FGFRi | Mode of Action |
|---|---|
| **Dovitinib (TKI258)** | **Non-selective, ATP-competitive, FGFR1-3, VEGFR1-3, PDGFR-β, FLT3, KIT inhibitor** |
| **Brivanib (BMS-540125)** | **Non-selective, ATP-competitive, FGFR1, VEGFR1/2, PDGFR-β inhibitor** |
| **Nintedanib (BIBF1120)** | **Non-selective, ATP-competitive, FGFR1-3, VEGFR1-3, PDGFR-α/β, FLT3, KIT inhibitor** |
| **Lenvatinib (E7080)** | **Non-selective, ATP-competitive, FGFR1-4, VEGFR1-3, PDGFR-α/β, FLT1, KIT inhibitor** |
| **Erdafitinib (JNJ-42756493)** | **Selective, ATP-competitive, FGFR1-4 inhibitor** |
| **Rogaratinib (BAY1163877)** | |
| **Infigratinib (BGJ398)** | **Selective, ATP-competitive, FGFR1-3 inhibitor** |
| **Pemigatinib (INCB054828)** | |
| **Aprutumab ixadotin (BAY 1187982)** | **Antibody–drug conjugates (ADCs), a fully human anti-FGFR2 monoclonal antibody conjugated by lysine side chains to a non-cleavable linker and via this an innovative auristatin W derivative (a highly potent microtubule-disrupting agent)** |
| **Bemarituzumab (FPA144)** | **A human monoclonal antibody specific to the splice-variant FGFR2b that inhibits binding of the ligands FGF7, FGF10, and FGF22** |
| **MFGR1877S** | **A human monoclonal antibody that targets FGFR3 to prevent ligand binding, receptor-receptor association, and FGFR3 signaling** |
| **Vofatamab (B-701)** | **A fully human monoclonal antibody against FGFR3 that blocks activation of the wildtype and genetically activated receptor** |

## 3. Conclusions and Perspectives

FGFRis exert their antitumor activities through direct effects on tumor cells harboring FGFR alterations and through indirect effects on the TME, including the regulation of angiogenesis, immune evasion, and paracrine tumor proliferation, independent of FGFR alterations [35]. Therapeutic applications of FGFRis mark an important milestone for precision medicine in the treatment of a/m UBC. Erdafitinib was approved by FDA for use in later-line settings based on clinical activity in heavily pre-treated FGFR2/3-altered a/m UBC patients [21]. Although only approximately 20% of patients are eligible for erdafitinib, combination regimens may extend the benefit of these therapies to a larger population of patients. Since FGFR alterations may be associated with ICI resistance, FGFRi–ICI combinations may be attractive due to the potential immune-modulatory effects of FGFRis and based on the presumed non-cross-resistance of these therapeutic classes. The adverse events (AEs) related to FGFRis or ICIs as monotherapies are largely non-overlapping and can often be mitigated for both therapeutic classes with education, prompt reporting of signs/symptoms, and aggressive management (**Table 2**).

**Table 2.** Combinations of FGFRi + ICI: rationale and its applications.

| Category | Rationale for Treatment Synergism between FGFRi and ICI in a/m UBC |
|---|---|
| Tumor infiltrating NK/NKT/cytotoxic CD8+ T cells | Immune effector cells involved in cancer cell elimination |
| Tumor infiltrating dendritic cells/MDSCs/M2-TAMs/Treg | Defective immune modifiers contributing to tumor immune evasion |
| MDSCs | Directly interact with tumor cells and promote cancer cell stemness<br>Lead to immune evasion in the TME by activating M2-TAMs/Treg cells and inhibiting NK/cytotoxic CD8+ T cells |
| M2-TAMs | Express immunosuppressive paracrine factors, such as IL-10, TGFβ, and ARG1 |
| Endothelial progenitor cell-like MDSCs/M2-TAM subset | Promote tumor angiogenesis |
| Dendritic cell-specific C-type lectin TAMs | Contribute increased levels of Treg cells/cytotoxic CD8+ T cells with an impaired cytolytic activity (reduced levels of the cytotoxins perforin, granzyme B, and IFN-γ) |
| Treg cells | Suppress antitumor immune activity through release of inhibitory cytokines (TGFβ, IL-10) and cell–cell contact via immune checkpoint molecules (CTLA-4, LAG3)<br>Induce apoptosis of cytotoxic CD8+ T cells through cytolysis via perforin or granzyme, IL-2 consumption and ATP deprivation through CD38 hydrolyzing ATP to ADP and AMP |
| Immune exclusion phenotype caused by FGFR 3 mutations | Caused by the sequestration of cytotoxic CD8+ T cells in TME due to increased deposition of fibronectin and collagen in the extracellular matrix |
| ICIs | Target negative regulating cell receptors on immune cells, predominantly T cells, leading to reactivation of those cells and promotion of a durable antitumor response<br>Seem to be less effective on UBC TCGA luminal I subtype with attenuated CD8+ cytolytic activity, lower expression of PD-L1 in both tumor cells and immune cells |
| FGFRis | Reverse the TME from immunologically cold tumors into hot tumors by enhancing T cell recruitment by normalizing tumor blood vessels<br>Target immune suppressive cells in TME such as MDSCs/M2-TAMs/CAFs in direct or indirect manners |

Despite the enthusiasm, combination FGFRi–ICI trials are mostly in the early phases of clinical development, and current clinical practice should still follow a sequential approach. To move forward with FGFRi–ICI combinations, reliable and predictive biomarkers for assessing FGFRi–ICI combinations are urgently needed to quantify the complex interplay of FGFR signaling and the immune components in the TME.

The results of ongoing trials will delineate the optimal role and sequence of FGFRi or FGFRi-based combination regimens for treating a/m UBC.

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