

# Fibroblast Growth Factor Receptor

Subjects: [Oncology](#)

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Fibroblast growth factors (FGFs) are a family of 22 cell-signaling proteins of extracellular origin, generally released upon tissue injury, which act as systemic or locally circulating molecules capable of activating tyrosine-kinase receptors.

[Fibroblast growth factors](#)

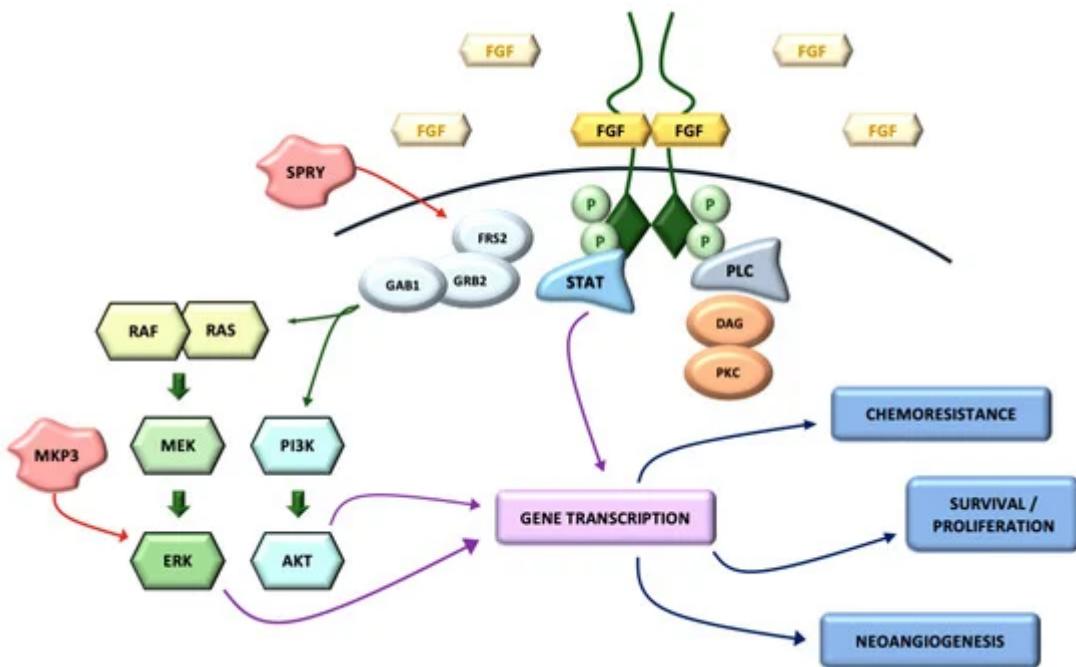
[Urothelial carcinoma](#)

## 1. Molecular Biology of Fibroblast Growth Factor Receptor (FGFR)

Fibroblast growth factors (FGFs) have been classified in seven subfamilies according to their phylogeny: five paracrine FGFs (FGF1, FGF4, FGF7, FGF9 and FGF8), an endocrine FGF (FGF15/19) and an intracellular subgroup (FGF11). These receptors have a beta-trefoil fold with a heparan sulfate binding-site that facilitates its sequestration close to the cell surface for binding to an FGF receptor (FGFR) [1].

FGFRs are encoded by four different genes (FGFR1–FGFR4) and are composed of three extracellular immunoglobulin-type domains (D1, D2 and D3), with D3 mediating heparan-sulfate binding and being primarily responsible for ligand specificity. The dimerization of the FGFR intracellular-domain precedes an autophosphorylation signal for the tyrosine-kinase domain that leads to the activation of several downstream transduction pathways [2].

Mainly, two different mechanisms have been described in the further transmission of the signal. The first one is the activation of RAS-dependent mitogen activated protein-kinase (MAPK) and Raf phosphorylation. The second one leads to cell activation through other signaling molecules, such as Shb, Src kinase and STATs (signal transducers and activators of transcription), amongst others. The whole FGF/FGFR pathway is strongly regulated by feedback mechanisms, such as SPRY (which down-regulates the activation of growth factor receptor-bound protein) and MKP3 (which attenuates MAPK signaling) [3] ([Figure 2](#)).



**Figure 2.** FGFR signaling pathway.

In non-cancer cells, the activation of FGFRs leads to the stimulation of several intracellular signaling cascades that play crucial roles in embryonic development, metabolism and tissue repair. Due to the significant influences of FGF/FGFR pathway on cell growth, proliferation and differentiation, its dysregulation secondarily to different kinds of genetic aberrations (including receptor mutations, amplifications and chromosomal translocations) has an important oncogenic role, especially related to tumor progression and resistance to CT. Around 7.1% of all tumor types present genetic alterations in the FGF/FGFR axis, FGFR1 being the most frequently altered (49%), followed by FGFR3 and FGFR2—hence it is the third most frequently altered pathway after TP53 and KRAS [4].

Specifically, amplifications of *FGFR1* gene have been found in 9–10% of urothelial BC, followed by FGFR3 (3–5%) and FGFR2 (0.8%), and activating mutations of FGFR3 gene have been described in 38–66% of non-invasive BC and 15–20% of invasive BC. Interestingly, for therapeutic purposes, the presence of any FGFR mutation, fusion or overexpression seems to be associated with a higher sensitivity to FGFR inhibitors in pre-clinical models [5].

Amplification of FGFR represents around 66% of FGFR alterations, with FGFR1 being the most frequently amplified subtype. FGFR1 amplification seems to be much more represented in early than advanced-stage tumors, suggesting a possible role of FGFR1 amplification during the initial phase of oncogenesis, which may be clinically relevant for therapeutic purposes [6].

Missense mutations such as *FGFR3<sup>S249C</sup>* (21%), *FGFR3<sup>Y375C</sup>* (7%), *FGFR3<sup>R248C</sup>* (3%) and *FGFR3-TACC3* fusions (2%) are relatively common in NMIBC (20–50%) and not rare in MIBC (10%) [7], and they have been related to the aberrant formation of cys-mediated intermolecular bonds between mutant receptors and to the constitutive activation of the FGFR3 tyrosine-kinase [8][9].

Despite these genetic alterations having set the stage for the development of targeted therapies, the modest response rates observed in clinical trials, and the accumulating evidence related to other TKIs, suggest that primary or acquired resistance is an unavoidable concern related to the current FGFR inhibitors. The bypass activation of the same or similar downstream effectors is a known mechanism of both intrinsic and acquired resistance. For example, the activation of EGFR/HER3-dependent PI3K/Akt signaling has been described in urothelial tumors harboring driver FGFR3 mutations such as *FGFR3<sup>S249C</sup>* and *FGFR3-TACC3*, which are intrinsically resistant to FGFR3 inhibition, suggesting that EGFR-dependent PI3K signaling is a potential mechanism of resistance to FGFR inhibitors [10]. A second major cause of resistance to FGFR-targeted therapies is the emergence of secondary *FGFR* alterations. Gatekeeper mutations, including *FGFR1<sup>V561M</sup>*, *FGFR2<sup>V564F/L</sup>*, *FGFR3<sup>V555M</sup>* and *FGFR4<sup>V550E/L</sup>*, can either occur de novo or during treatment with targeted therapies, leading to amino acid substitutions for the valine residue located in the drug-binding pocket of the tyrosine-kinase domain that may alter the mode of drug-FGFR interactions [11]. Intratumor heterogeneity has been also considered involved in the antitumor responses to FGFR targeted therapies. The homogeneous overexpression of FGFR has been shown to confer malignant cells a high sensitivity to FGFR inhibitors, whereas a heterogeneous FGFR upregulation might entail the existence of resistant cell clones.

Further research is necessary to adequately monitor and identify the emergence of resistant tumor subclones with an activation of parallel pathways or secondary *FGFR* mutations, enabling the detection of treatment resistance and the stratification of patients to receive appropriate targeted therapies.

### 3.2. Clinical Trials with FGFR inhibitors in urothelial carcinoma

Several compounds have been developed in recent years to inhibit FGFR. Some of them are non-selective multi-target inhibitors, and others are highly selective FGFR-TKIs, although other approaches, such as monoclonal antibodies and FGF-ligand traps, are also under research. [Table 2](#) shows the more relevant clinical trials targeting FGFR.

**Table 2.** Clinical trials of FGFR inhibitors.

Study Design (NCT Identifier and Code)	Study Phase	Experimental Treatment	Population	Estimated n	Primary Endpoint	Estimated Study Completion Date
BLC2001 (NCT02365597)	Phase II	Erdafitinib	mUC with FGFR3 mutation or FGFR2/3 fusion afterchemotherapy treatment	236	ORR	30 June 2022 (Recruiting)
NCT03390504	Phase III	Erdafitinib Pembrolizumab	mUC with FGFR alterations as second or third line of treatment	631	OS	5 November 2021 (Recruiting)

Study Design (NCT Identifier and Code)	Study Phase	Experimental Treatment	Population	Estimated n	Primary Endpoint	Estimated Study Completion Date
NORSE study (NCT03473743)	Phase I/II	Erdaftinib+cetrelimimab Erdaftinib+ (cis/carbo)platin	mUC with selected FGFR alterations	160	DLT	17 March 2023 (Recruiting)
NCT04172675	Phase II	Erdaftinib	NMIBC with FGFR mutations or fusions and recurred after BCG therapy	280	RFS	10 June 2026 (Recruiting)
NCT01004224	Phase I	Infiratinib	Solid tumors with FGFR alterations	208	DLP	8 October 2018 (Completed)
NCT04197986	Phase III	Infiratinib	UC with FGFR3 alterations as adjuvant treatment	218	OS	31 January 2025 (Recruiting)
NCT01976741	Phase I	Rogaratinib	Several solid tumors without/with FGFR alterations	168	DLP	11 March 2019 (Completed)
FORT-1 (NCT03410693)	Phase II/III	Rogaratinib	mUC with FGFR1/3 after platinum-based chemotherapy	172	ORR	27 October 2020 (Completed)
FORT-2 (NCT03473756)	Phase Ib/II	Rogaratinib+atezolizumab	UC with FGFR alterations as first line of treatment	210	DLP	4 September 2024 (Recruiting)
FIGHT-201 (NCT02872714)	Phase II	Pemigatinib	mUC with FGFR alterations	263	ORR	31 March 2021 (Active, no recruiting)
FIGHT-205 (NCT04003610)	Phase II	Pemigatinib+atezolizumab Pemigatinib	mUC with FGFR3 alteration and not eligible to cisplatin	6	PFS	31 January 2026 (Recruiting)
NCT02052778	Phase I	TAS 120	Tumors with FGF/FGFR alterations	386	DLT	29 May 2021 (Active, not recruiting)

Study Design (NCT Identifier and Code)	Study Phase	Experimental Treatment	Population	Estimated n	Primary Endpoint	Estimated Study Completion Date
NCT01948297	Phase I	Debio 1347-101	Tumors with FGFR 1, 2, 3 alterations	77	DLT	26 June 2020 (Terminated)
BISCAY (NCT02546661)	Phase I [12]	AZD4547 AZD4547+durvalumab	MIBC who progressed prior line of treatment	156	DLT	14 February 2022 (Active, not recruiting) [13]
NCT04045613	Phase I/II	Derazantinib Atezolizumab Derazantinib ± atezolizumab	mUC with FGFR alterations	306	ORR	Recruiting (May 2022)
NCT00790426	Phase II	Dovitinib [14]	UC	48	OS	April 2012 (Completed)
NCT01732107	Phase II [15]	Dovitinib	NMIBC with FGFR3 alterations	13	ORR	6 March 2017 (Completed)

Furthermore, the combination of FGFR inhibition and IT has been analyzed with different agents. The rationale for this strategy is based on different hypothesis. IT may enhance the antitumor effects of FGFR inhibitors and also prevent or delay the development of resistance. Urothelial carcinoma can be divided into T-cell-inflamed and non-T-cell-inflamed subtypes [16]. Non-T-cell-inflamed subtypes correlated with an absence of CD8+ T lymphocyte and resistance to IT, which produced a rationale for a combination of FGFR inhibitors and anti-PD-1/PD-L1 [17]. The aim of the combination of an FGFR inhibitor and an anti-PD-1/PD-L1, such as NORSE study, FORT-2 or FIGHT-205, is to prove that targeting FGFR makes it possible to turn an immunologically cold tumor into a hot tumor.

Therefore, a phase Ib/II clinical trial (NORSE study) evaluated erdafitinib in combination with cetrelimab, a PD-1 inhibitor, in 15 patients with mUC and FGFR2/3 alterations after progression to at least one line of treatment. The combination of erdafitinib (8 mg with uptitration to 9 mg) with cetrelimab was deemed safe for further evaluation [18]. In the seven patients treated with the recommended phase II dose, ORR was 71%. This combination is further being evaluated in a randomized phase II clinical trial in combination with platin-based CT (NCT03473743). However, in high risk, BCG refractory NMIBC with FGFR gene alterations, erdafitinib is being compared with intravesical CT (NCT 04172675).

Infiratinib (BGJ398) is an oral, selective, ATP-competitive FGFR 1–3 TKI. A phase I clinical trial evaluated the safety and antitumor activity of infiratinib in 132 patients with solid tumors [19]. Thirty-three mUC patients with activating FGFR3 mutations or fusions received BGJ398 125 mg on a once-a-day, 3 weeks on/1 week off regimen. Median treatment duration was 13.3 weeks. ORR was 35% [20]. This drug is under development in other UC settings, such as in the perioperative context and in upper urothelial tract (a promising response has been identified in a phase I trial [21]). A phase III clinical trial is currently evaluating infiratinib in patients with UC in the bladder and upper tract in the adjuvant setting (NCT04197986) [22].

Rogaratinib is an oral and selective FGFRs 1–4 TKI that inhibits the auto-phosphorylation of FGFR. A phase I trial tested rogaratinib in patients with advanced solid tumors who were FGFR mRNA-positive. In the mUC cohort, the ORR was 20.8%, with one patient achieving a complete response, and the disease control rate (DCR) was 68.1% [23].

The FORT-1 study evaluated the efficacy of rogaratinib in comparison with CT in patients with mUC who received prior platin-based CT [24]. Patients were included according to FGFR 1 and 3 mRNA expression, analyzed centrally by *in situ* hybridization from archival tumor tissue; 175 patients were randomized in the study—87 to the rogaratinib arm and 88 to the chemotherapy arm. The ORRs were 19.5% and 19.3% (1-sided  $p = 0.56$ ), and mPFS values were 2.7 (95% CI, 1.6–4.2) vs. 2.9 (95% CI, 2.6–4.2) months for rogaratinib and CT, respectively. In the exploratory analysis directed at patients with FGFR3 DNA mutations or fusions, ORR was 52.4% for rogaratinib—higher compared to CT's 26.7%. Considering these results, the study terminated early.

FORT-2 is a phase Ib/II study that evaluates the safety and efficacy of rogaratinib in combination with atezolizumab, an anti PD-L1, as a first-line treatment in cisplatin–ineligible patients with mUC and FGFR mRNA overexpression. The ORR was 44%, with a DCR of 68% and the duration of response was not reached. The most common treatment-emergent events were diarrhea (58%), hyperphosphatemia (45%) and urinary tract infection (36%). The presence of resistance gene mutations was analyzed, and three patients with detectable mutations in PI3K had no objective response [25].

Pemigatinib is another potent and competitive oral inhibitor of the kinase activity of FGFRs 1, 2 and 3. There was a phase II clinical trial (FIGHT-201) with mUC patients who progressed on one or several lines of therapy or were platinum ineligible [26]. Sixty-four patients with some FGFR3 mutation or fusion were assigned to cohort A, and 36 patients with other FGF/FGFR genetic mutations were assigned to cohort B and received pemigatinib. ORR was 25% (95% CI, 14–40%). The efficacy of pemigatinib in combination with pembrolizumab was compared with the standard of care (CT or IT) in patients with cisplatin-ineligible UC in a phase II randomized study (FIGHT-205, NCT04003610).

TAS-120 is a selective irreversible inhibitor for FGFR 1–4. A phase I study treated 134 patients with different advanced solid tumors and FGFR aberrations. Twenty-one mUC patients were included. In the dose-escalation phase, a 20 mg per day oral dose of TAS-120 was considered safe and exhibited clinical activity in various tumors, which need to be confirmed [27].

Debio-1347 is a small oral molecule that selectively inhibits the ATP binding site of FGFR1–3. A phase I clinical trial evaluated the safety and antitumor activity of debio-1347 in 58 patients with solid tumors with FGFR 1–3 alterations; 10% of patients had mUC [28].

Dovitinib is a small multikinase inhibitor that binds to FGFR3, inhibiting its phosphorylation. A phase II trial was prematurely closed because the ORR was 0% in FGFR3-mutated and FGFR3 wild-type patients [29]. Dovitinib in patients with localized UC did not show a clinical benefit in a phase II trial [30].

Derazantinib is a potent ATP competitive multikinase inhibitor of FGFR 1–3 and the colony stimulating factor 1 receptor (CSF1R) kinase. FIDES-02 is a clinical trial that is evaluating the safety and antitumor activity of single-agent derazantinib or in combination with atezolizumab in patients with mUC and FGFR aberrations (NCT04045613).

Recently, the BISCAY study (NCT02546661), characterized as an ambitious study on prospectively adapting the treatment based on genetic alterations, did not achieve a significant benefit for the patients included. Thus, in patients with FGFR, homologous repair gene or mTOR alterations, the study failed to significantly improve the ORR of 27.6% with durvalumab alone compared to AZD4547+durvalumab (ORR = 28.6%), olaparib+durvalumab (ORR = 35.7%) or vistusertib+durvalumab (ORR = 24.1%) [31].

In general, FGFR inhibitors share some adverse events (AEs) which are most easily manageable, but that require close physical examination monitoring, ophthalmic evaluation and early supportive therapy when required (Table 3) [32].

**Table 3.** Most common FGFR inhibitor-associated adverse events (AEs).

Drug	AEs Any Grade (%)	AEs Grade 3/4 (%)
Erdafitinib	Hyperphosphatemia (77%) Stomatitis (58%) Diarrhea (51%) Dry mouth (46%) Central serous retinopathy (27%) Onycholysis (18%)	Hyponatremia (11%) Stomatitis (10%) Asthenia (7%) Nail dystrophy (6%) Hand-foot syndrome (5%)
Infigratinib	Hyperphosphatemia (46.3%) Increase in serum creatinine (41.8%) Constipation (37.3%) Fatigue (37.3%) Anemia (35.8%)	Hyperlipasemia (10.4%) Fatigue (7.5%) Anemia (7.5%) Hand-foot syndrome (7.5%) Hypophosphatemia (7.5%)
Rogaratinib	Hyperphosphatemia (60%) Diarrhea (49%) Decreased appetite (36%) Fatigue (24%)	Fatigue (9%) Anemia (6%) Urinary tract infection (8%) Hyperlipasemia (8%)

Drug	AEs Any Grade (%)	AEs Grade 3/4 (%)
Pemigatinib	Nausea (28%) Urinary tract infection (11%) Diarrhea (40%) Alopecia (32%) Fatigue (29%)	Urinary tract infection (7%) Fatigue (6%)
Debio-1347	Constipation (28%) Dry mouth (28%) Hyperphosphatemia (76%) Diarrhea (41%) Nausea (40%) Fatigue (40%) Constipation (38%) Decreased appetite (33%) Nail changes (31%)	Hyperphosphatemia (21%) Anemia (12%) Dyspnea (5%) ALT increased (3%) Stomatitis (3%)

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