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**Fibroblast growth factor receptor signaling as therapeutic targets in gastric cancer**

Yashiro M *et al.* FGFR signaling in gastric cancer

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**Abstract**

Fibroblast growth factor receptors (FGFRs) regulate a variety of cellular functions, from embryogenesis to adult tissue homeostasis. FGFR signaling also plays significant roles in the proliferation, invasion, and survival of several types of tumor cells. FGFR-induced alterations, including gene amplification, chromosomal translocation, and mutations, have been shown to be associated with the tumor initiation and progression of gastric cancer, especially in diffuse-type cancers. Therefore, the FGFR signaling pathway might be one of the therapeutic targets in gastric cancer. This review aims to provide an overview of the role of FGFR signaling in tumorigenesis, tumor progression, proliferation, and chemoresistance. We also discuss the accumulating evidence that demonstrates the effectiveness of using clinical therapeutic agents to inhibit FGFR signaling for the treatment of gastric cancer.

**Key words:** Fibroblast growth factor receptor; Gastric cancer; Signaling pathway; Targeted therapy

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**Core tip:** Fibroblast growth factor receptor (FGFR) is one of the drivers signaling in the development of gastric cancer. The use of molecular agents as targets of the FGFRs pathway has currently been approved in experimental and clinical trials as a mono-targeted approach or in combination with chemotherapeutic agents. FGFRs might be a promising therapeutic target for the treatment of gastric cancer.

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**INTRODUCTION**

Gastric cancer is one of the most common malignancies in the world. Despite considerable improvements in clinical diagnostics and surgical skills, the prognosis of advanced gastric cancer with distant metastasis is still poor with a median overall survival of approximately less than 1 year[[1](#_ENREF_1),[2](#_ENREF_2)]. To date, the molecular heterogeneity underlining tumor initiation and progression has been elucidated[[3](#_ENREF_3)]. Following the understanding of gastric cancer biology, targeted therapies have been evaluated in experimental studies and transferred promptly to clinical trials. 'The use of molecular agents to target the signaling pathways of several receptors, such as epidermal growth factor receptor (EGFR), human epidermal growth factor 2 (HER2), and vascular endothelial growth factor receptor (VEGFR), has been approved for the treatment of gastric cancer as a mono-targeted approach or in combination with cytotoxic chemotherapeutic drugs[[4](#_ENREF_4)]. Fibroblast growth factor receptor (FGFR) signaling also plays an important role in the development of various types of malignancies, including gastric cancer through the regulation of many other signaling pathways[[5](#_ENREF_5)]. The *FGFR2* gene, also known as the *K-samII* gene, has been shown to be amplified and overexpressed in gastric cancer, preferentially in diffuse-type cancers[[6-9](#_ENREF_6)].

In this review, we discuss the genetic alterations induced by FGFR signaling and the role of FGFR signaling in gastric cancer. Subsequently, we review the possibility of a rational therapy through FGFR signaling inhibition.

**FGFR CONSTRUCTION AND SIGNALING PATHWAY**

The FGFR is a transmembrane tyrosine kinase receptor involved in signaling *via* interaction with members of the FGFR family (Figure 1). Four members of the FGFR family, FGFR1, FGFR2, FGFR3, and FGFR4, have been identified. These receptors are diverse depending on their ligand, binding affinity, and tissue distribution. FGFR consists of an extracellular domain, a transmembrane domain, and an intracellular domain[[10](#_ENREF_10)]. The extracellular ligand domain is composed of three immunoglobulin (Ig)-like domains: D1, D2, and D3. The FGFR family binds to their ligands, the fibroblast growth factors (FGFs), with high affinity[[11](#_ENREF_11)]. FGFR1, FGFR2, and FGFR3 are divided into types IIIb and IIIc based on the alternative splicing within the C-terminal half of the third Ig loop (D3) in the extracellular FGF binding domain. Exon 8 produces the IIIb isoform, whereas exon 9 produces the IIIc isoform. The IIIb isoform is mainly expressed in epithelial cells, while the IIIc isoform is preferentially expressed in mesenchymal cells.

FGF ligands are a family of 22 structurally related proteins that are further divided into subfamilies according to their sequence homology. The secreted-type ligands of the FGF family, including FGF1-10 and FGF16-23, bind to multiple FGFRs to transduce signals in target cells. The FGF-FGFR complex comprises two receptor molecules, two FGFs, and a heparan sulfate proteoglycan. Alternative splicing of D3 in the ligand binding domain mediates the ligand specificity. The IIIb isoform preferentially binds secreted FGF ligands from adjacent mesenchyme such as FGF7, FGF10, and FGF22; the IIIc isoform usually binds ligands secreted from the adjacent epithelium.

A major downstream signaling route of the FGFR family is *via* the Ras-Raf-mitogen-activated-protein-kinase (MAPK) pathway. Activation of Ras initiates a multistep phosphorylation cascade that leads to the activation of such MAPK as extracellular signal-regulated kinase 1 (ERK1) and ERK2. ERK1 and 2 regulate the transcription of molecules linked to cell proliferation, survival, and transformation[[12](#_ENREF_12)]. Another important cascade in FGFR signaling is phosphatidylinositol 3-kinase (PI3K) and the downstream protein-serine/threonine kinase Akt; the latter transduces signals triggering a cascade of responses that promote cell growth and proliferation, survival, and motility[[13](#_ENREF_13)]. Taken together, the activation of FGFR results in the activation of protein kinase C, the activators of transcription (STAT), and inositol-triphospate (IP3)-mediated Ca2+ release[[11](#_ENREF_11)]. FGF signaling cascades also interact with Notch, Wnt, Hedgehog, and bone morphogenetic protein (BMP) signaling cascades to maintain the homeostasis among stem and progenitor cells[[14](#_ENREF_14)]. These FGFR signaling pathways have been shown to mediate not only a variety of fundamental diverse cellular behaviors including embryogenesis and adult tissue homeostasis[[11](#_ENREF_11)], but also oncogenesis, such as mitogenesis, differentiation, cell proliferation, angiogenesis, and invasion. The aberrant regulation of this pathway has been implicated in anti-apoptosis, drug resistance, and epithelial-to-mesenchymal transition (EMT).

**FGFR ALTERATIONS IN GASTRIC CANCER**

Genetic modification or overexpression of FGFRs has been associated with the tumor initiation and progression of several types of malignancies due to gene amplification, translocation, and mutations leading to enhanced kinase activity[[7](#_ENREF_7),[11](#_ENREF_11),[15](#_ENREF_15),[16](#_ENREF_16)]. *FGFR* gene abnormalities have been reported in various cancers[[17-19](#_ENREF_17)], including non-small cell lung cancer (*FGFR1* amplification or *FGFR2* mutation), breast cancer (*FGFR1* and *2* amplification), squamous cell carcinoma (*FGFR1* amplification), gastric cancer (*FGFR2* amplification), bladder cancer (*FGFR3* mutation or gene translocation), endometrial carcinoma (*FGFR2* mutation), glioblastoma (*FGFR3* gene translocation), and rhabdomyosarcoma (*FGFR4*-activating mutation).

In gastric cancer, *FGFR2* amplification has been reported to occur in 2 to 9% of patients and more frequently in patients with diffuse-subtype cancers[[20-24](#_ENREF_20)]. FGFR2 is identical to the product of the *K-samII* gene[[25](#_ENREF_25),[26](#_ENREF_26)], which is cloned from a diffuse-type gastric cancer cell line, KATO-III[[25](#_ENREF_25),[27](#_ENREF_27)], A previous paper has asserted that *FGFR2* amplification in gastric cancer cell lines is dependent on the overexpressed and activated FGFR2 receptor for cell growth. Interestingly, *FGFR2*-amplified cell lines contain elevated EGFR, HER2, and ErbB3 phosphorylation that are regulated by FGFR2 kinase activity[[23](#_ENREF_23)]. Meanwhile, a recent paper has revealed that aberrations in the FGFR2-ErbB3-PI3 kinase pathway are found in diffuse-type gastric cancers, while intestinal-type gastric cancer has an activated ErbB2 oncogenic pathway[[28](#_ENREF_28)], *FGFR2* amplification has been found to be associated with a higher pT stage, a higher pN stage, and lymph node metastasis, as well as related to poor overall survival[[9](#_ENREF_9),[21](#_ENREF_21),[22](#_ENREF_22),[29](#_ENREF_29)]. Interestingly, cancer genomic profiling studies have shown that while the amplification of the *FGFR2* gene is prompted in the primary diffuse-gastric tumor, the *FGFR2* locus is not amplified in the metastatic tumor[[30](#_ENREF_30)].

Several papers have presented the role of FGFR4 in gastric cancer. The FGFR4 expression rate in gastric cancer specimens is 38% to 44%, and it has been associated with lymph node metastasis and poor prognosis. Silencing FGFR4 expression in gastric cancer cells results in decreased growth and an increased rate of apoptosis, which is correlated with Caspase 3 and Bcl-xL activity[[31](#_ENREF_31),[32](#_ENREF_32)]. One report has recently asserted that the co-expression of several FGFRs might be a useful prognostic factor. Patients with gastric cancer, who have elevated levels of FGFR1, FGFR2, or FGFR4, have a significantly shorter life expectancy. Furthermore, the co-overexpression of all three FGFRs results in a poorer disease-specific survival, compared to the expression of none or only one of the FGFRs, and serves as an independent prognostic factor[[33](#_ENREF_33)]. Diagnostic detection of tumors with FGFR genetic alterations in the primary and secondary lesions could be useful for selecting patients for FGFR-targeted therapies.

**FUNCTIONAL ROLE OF FGFR IN GASTRIC CANCER**

FGFR2 mRNA is amplified in scirrhous gastric cancer cells, and ligand FGF7, also designated as keratinocyte growth factor (KGF), is produced by gastric fibroblasts. KGF secreted by fibroblasts has a pivotal role in the development of scirrhous gastric cancer with *K-*samII amplification in a paracrine manner[[27](#_ENREF_27)]. Scirrhous-type gastric cancer, also designated as linitis plastica, is diffuse and biologically aggressive, typically infiltrating into the gastric wall with a high frequency of peritoneal metastasis. The proliferative and infiltrative ability of scirrhous gastric cancer cells is closely correlated with the growth factors produced by organ-specific fibroblasts[[34](#_ENREF_34)]. We previously reported that the conditioned medium derived from gastric fibroblasts stimulates the growth of gastric cancer cells, which are mediated by FGF7/FGFR2 signaling.

EMT is a critical process in cancer progression that provides cancer cells with the ability to escape from the primary foci, invade stromal tissues, and metastasize to secondary regions due to decreased cell-cell adhesion. Most EMT processes are regulated by extracellular matrix (ECM) components and soluble growth factors. Among these, FGF/FGFRs signaling is positively associated with EMT[[11](#_ENREF_11)]. The FGF/FGFRs signaling pathway has been shown to be associated with WNT signaling, which results in the regulation of cellular phenotype and migration, and subsequently leads to EMT. Twist-related protein 1 (Twist1), a transcriptional factor, has been reported to have an important role in cell lineage determination and differentiation. One paper has asserted that Twist1 prompts the expression of FGFR2 in gastric cancer cell lines, and that FGFR2 mediates Twist 1-induced invasion and EMT, suggesting that the dual inhibition of these factors can become a novel tool for the targeted therapy of gastric cancer[[35](#_ENREF_35)].

**EXPERIMENTAL STUDIES TARGETING FGFR SIGNALING IN GASTRIC CANCER**

In ToGA trials, trastuzumab, an anti-HER2 targeting antibody, prolonged the overall survival of patients with HER2-positive gastric tumor when combined with conventional chemotherapy[[36](#_ENREF_36)]. However, considering the low expression rate (6%-23%) of HER2 and the modest effect of the ToGA trial (only 2.7 months of prolonged survival) in gastric cancer patients, the development of a novel targeted therapy with higher potency is still required. In contrast, therapies targeting VEGFR and EGFR have failed to translate their preclinical efficacy into improved patient outcomes in several trials for gastric cancer[[37-39](#_ENREF_37)]. As FGFRs have an important role in the progression of gastric cancer, as mentioned previously, their use as a therapeutic candidate for the development of targeted anticancer agents should attract substantial attention. In this section, relevant literatures will be reviewed to identify the current and future roles of the FGFR family as a potential targeted signaling pathway for gastric cancer treatment (Table 1 and Figure 2). Preclinical studies have established that the inhibition of the FGFRs pathway, alone or in combination with other signaling or chemotherapy, reveals the antitumor activity in gastric cancer *in vitro* and *in vivo*.

***FGFR tyrosine kinase inhibitor***

FGFR tyrosine kinase inhibitors (TKIs) demonstrate their therapeutic effectiveness on cancer cells *in vitro* and *in vivo*[[40](#_ENREF_40),[41](#_ENREF_41)]. Most of the FGFR TKIs include Ki23057[[42](#_ENREF_42)], dovitinib, S49076[[43](#_ENREF_43)], Pazopanib[[44](#_ENREF_44)], foretinib[[45-47](#_ENREF_45)], and Dovitinib (TKI258)[[20](#_ENREF_20),[48](#_ENREF_48),[49](#_ENREF_49)], are not specific to FGFRs along with other kinases. Although the multi-kinase inhibitor compounds successfully inhibit the proliferation of FGFRs-amplified gastric cancer cells following the attenuation of multiple serine/threonine and tyrosine kinases, it is not clear whether specific FGFR2 inhibition alone is sufficient. AZD4547 [N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2Hpyrazol- 3-yl]-4-(3,5 diemthylpiperazin-1-yl) benzamide] is a selective ATP-competitive receptor tyrosine kinase inhibitor that interrupts recombinant FGFR1-3 activities. A previous paper has shown that AZD4547 application results in tumor growth inhibition in *FGFR2*-amplified gastric tumor xenografts and the induction of apoptosis by impairing the downstream signaling of FGFR2[[50](#_ENREF_50)]. As a selective FGFR1-3 inhibitor, PD173074 has been evaluated for its anti-tumor efficacy in gastric cancer cell lines[[23](#_ENREF_23)]. FGFR2 inhibition by PD173074 has displayed potent and selective growth inhibition in *FGFR2*-amplified gastric cancer cell lines. Interestingly, the inhibition of ErbB3 has also inhibited growth in *FGFR2*-amplified cell lines. Inhibitors of FGFR2 or ErbB3 signaling may have therapeutic efficacy in the subset of gastric cancers containing *FGFR2* amplification. LY2874455 is an orally bioavailable, FGFR-dominant kinase inhibitor lacking significant activity against VEGFR2 *in vivo*. This molecule is effective on all FGFRs equally. LY2874455 is more potent at inhibiting the growth of gastric cancer cells with increased FGFR-signaling activity *in vitro* and *in vivo*. These results demonstrate the potential of FGFR inhibitors as attractive molecular targeted agents for patients for whom anti-VEGF/VEGFR therapies have been inactive[[51](#_ENREF_51)].

***FGFRs antibodies***

As mentioned above, small molecule antagonists of FGFRs demonstrate significant efficacy for the treatment of gastric cancer. Highly specific monoclonal antibody against FGFR2 generated from mouse melanoma cells (GAL-FR21 and -22) has been found to strongly depress the growth of xenografts from two gastric cancer cell lines, OCUM-2M and SNU-16[[52](#_ENREF_52)]. These results suggest that the anti-FGFR2 antibody would be an attractive clinical candidate for gastric cancer therapy[[52](#_ENREF_52)]. At the same time, GP369, an FGFR2-IIIb-specific antibody, has exhibited anti-proliferative activity against gastric cancers driven by *FGFR2* overexpression[[53](#_ENREF_53)].

FPA144, an FGFR2b-specific antibody, is developed to treat patients with gastric cancers bearing an amplification of the *FGFR2* gene (*J Clin Oncol* 2014;32 suppl; abstr e15074). FPA144 is glycol-engineered for enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), a process in which cells of the immune system kill the tumor cell recognized by the antibody. FPA144 may act to prevent the binding of FGFs, such as FGF7, FGF10, and FGF22, to FGFR2b, as well as inhibit their ability to promote the growth of tumor cells. FP-1039, also known as GSK3052230, is a protein drug designed to intervene in the FGF signaling through FGFR1 that stimulates cancer cell growth and angiogenesis. FP-1039 can bind to FGF ligands circulating in the extracellular space, preventing these signaling proteins from reaching FGFR1 on the surface of tumor cells. A phase IB trial to evaluate FP-1039 in combination with paclitaxel and carboplatin, or docetaxel in subjects with solid tumor, is ongoing (NCT01868022).

***RNA interference-based therapeutics***

RNA interferenceis a recent potent technology for the treatment of malignancies. Small interfering RNA (siRNA) plays an integral role in RNA silencing therapy due to its stability and lower toxicity. A recent study has examined the effect of FGFR-targeting siRNA on the proliferation of gastric cancer cell lines[[54](#_ENREF_54)]. Treatment with siRNA has been shown to result in reduced proliferation and enhanced apoptosis, which accompany the reduction of VEGFR expression and the increase of apoptosis-related proteins. Some microRNAs (miR-133b) may contribute to the regulation of FGFR1 in gastric carcinomas such that FGFR1 expression is inversely correlated with miR-133b expression, suggesting that miR-133b might act as a novel tumor suppressor mechanism in gastric cancer cases[[55](#_ENREF_55)].

***Chemoresistance***

The development of drug resistant clones is one of the most serious challenges in the field of clinical oncology[[56](#_ENREF_56)]. FGF family has been shown to be associated with drug resistance in some type of cancer cells to which a variety of conventional chemotherapy has been applied[[57-59](#_ENREF_57)]. We previously reported that the combination of Ki23057 and 5-FU or S1 shows synergistic anti-tumor effects on diffuse-type gastric cancer cells by decreasing dihydropyrimidine dehydrogenase expression and increasing p21 expression[[34](#_ENREF_34)]. Accordingly, we explored the effects of Ki23057, combined with various known cytotoxic agents such as irinotecan, paclitaxel, etoposide, oxaliplatin, and gemcitabine, respectively, in cultures of a gastric cancer cell line and its drug-resistant clones[[60](#_ENREF_60)]. FGFR2 inhibitor could be the therapeutic agent for treating drug-resistant gastric cancer cells. In terms of the clinical trials of FGFRs inhibitors, rationally designed combination trials would be needed to abrogate the resistance to FGFRs targeted therapy and further improve clinical outcomes.

**CLINICAL THERAPEUTIC TRIALS AGAINST FGFR SIGNALING IN GASTRIC CANCER**

According to the positive results from preclinical experiments, several FGFRs inhibitors are being tested in clinical trials in patients with gastric cancer. To date, five trials are ongoing, as displayed in Table 2. A phase I expansion cohort study of AZD4547 for the treatment of advanced gastric and gastroesophageal cancer was conducted. All patients included were selected prospectively for *FGFR2* amplification using the fluorescent *in situ* hybridization (FISH) analysis of archival or fresh tumors. Preliminary analysis showed that one partial response was observed in a patient with a tumor that had clusters of *FGFR* gene amplification and that four patients had a stable disease (three with high *FGFR* amplification and one with clusters) ([2014 ASCO Annual Meeting](http://meetinglibrary.asco.org/VMTracks/2014%20ASCO%20Annual%20Meeting)). A phase II study, comparing AZD4547 with paclitaxel in the second-line setting for patients with *FGFR* polysomy or amplification, is ongoing (NCT01457846, SHINE trial). A phase II trial of dovitinib monotherapy, as a salvage treatment in patients with metastatic or unresectable gastric cancer harboring *FGFR2* amplification after failure of first- or second-line chemotherapy, is ongoing ([NCT01719549](http://mct.aacrjournals.org/external-ref?link_type=CLINTRIALGOV&access_num=NCT01402401)). An open labeled phase I/II trial of docetaxel plus dovitinib, as the second-line chemotherapy for patients with metastatic or unresectable gastric cancer after failure of first-line chemotherapy, is currently underway (NCT01921673). FGFR inhibitor TAS-120 selectively and irreversibly binds to and inhibits FGFR. A phase II trial studying the efficacy of TAS-120 monotherapy in patients with advanced solid tumors or multiple myeloma with FGF/FGFR-related abnormalities is ongoing (NCT02052778). A phase I open label, dose-finding study evaluating the safety and pharmacokinetics of FPA144, an FGFR2b-specific antibody, is currently underway for patients with advanced solid tumors with *FGFR2b* overexpression and *FGFR2* amplification (NCT02318329).

**CONCLUSION AND FUTURE PERSPECTIVES**

The activating FGFR signaling in *FGFR*-amplified or *FGFR*-overexpressed tumors is an attractive therapeutic target for gastric cancer. Novel FGFR inhibitors have recently been developed, and some of them are undergoing clinical trials for treating gastric cancers associated with aberrant FGFR signaling. Combination therapy of FGFR inhibitors and conventional cytotoxic agents may provide a synergistic anti-tumor effect and the possibility of overcoming chemoresistance in gastric cancer.

Although several evidences have shown the effectiveness of FGFR therapeutics, no clinical FGFR inhibitor has been approved. The main hurdle facing the effective usage of FGFR-targeted agents for cancer treatment is the development of a predictive biomarker that would allow optimal patient selection. There is a need for the establishment of biomarker-based patient selection, as it would most likely benefit FGFR-targeted therapy. Secondly, there are insufficient data to identify any one of the FGFR-targeted therapies as superior to the others. A recent high-resolution genomic analysis has presented a comprehensive survey of the genomic alterations in gastric cancer; this has revealed several promising targets for subtype-specific therapies [[20](#_ENREF_20)]. RTK/Ras signaling are frequently altered and mutually exclusive to one another in gastric cancer. *FGFR2* is amplified at frequencies comparable to *ERBB2*, and *KRAS* amplification is a prevalent event in gastric cancer[[61](#_ENREF_61)]. Classifying gastric cancer patients with signature genomic alterations may facilitate patient allocations to the most appropriate clinical trials. Whereas several obstacles may exist and must wait to be overcome, we believe that FGFR-targeted therapy can be a promising candidate for the development of future therapies for patients with certain subtypes of gastric cancer.

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**Figure 1 The fiblobrast growth factor structure and signaling network.** The Fibroblast growth factor (FGF)–FGFR complex consists of two receptor molecules, two FGFs, and a heparan sulfate proteoglycan (HSPG). The HSPG stabilizes and sequesters the FGFs. The FGFR comprises three extracellular Ig-like domains (D1-3), a transmembrane helix, and an intracellular split tyrosine kinase domain. D1 and D3 are separated by an acidic box. Ligand specificity of FGFR is regulated by alternative splicing within the C-terminal half of the third Ig loop (D3) in the ligand binding domain. Ligand binding and FGFR dimerization trigger the kinase domain phosphorylation, which leads to the docking of adapter residues and the activation of downstream pathways. Ligand-stimulated FGFRs phosphorylate the FGFR-associated cytosolic docking protein, FRS2. FRS2 activates SOS and GRB2, which in turn activate the Ras-Raf-MAPK pathway. A different complex involves GAB1, which activates the PI3K-Akt pathway. PLCγ hydrolyzes PIP2 to IP3 and DAG. PIP3 produces calcium. DAG also activates PKC, which results in the activation of the MAPK pathway by phosphorylating Raf. HSPG: Heparan sulfate proteoglycan; DAG: Diacylglycerol; FRS2α: FGFR substrate 2α; GRB2: Growth factor receptor-bound 2; IP3: Inositol triphosphate; PI3K: Phosphoinositide 3-kinase; PIP: 2-phosphatidylinositol-4,5-biphosphate; PKC: Protein kinase C; SOS: Son of sevenless; GAB1: GRB2-associated binding protein 1; PLCγ: Phospholipase Cγ.



**Figure 2** **Fiblobrast growth factor receptor-targeted therapeutics.** Fibroblast growth factor receptors (FGFRs)-targeted tyrosine kinase inhibitors are small molecule ATP-competitive agents that bind to the ATP-binding site of the intracellular tyrosine kinase domain of FGFRs. Monoclonal antibody targets the extracellular domain of the FGFR and blocks ligand binding. RNA interference suppresses the expression of various genes. FGFR: Fiblobrast growth factor receptor.

**Table 1 Recent preclinical studies of flobrast growth factor receptor-targeted therapy in gastric cancer**

|  |  |  |
| --- | --- | --- |
| **FGFRs targeted therapeutics (Campany)** | **Study (Ref.)** | **Main results** |
| **Multikinase inhibitors** |
| Ki23057 (KIRIN Brewery) | Nakamura K *et al*[[42](#_ENREF_42)] | Ki23057 significantly inhibited the proliferation and induced apoptosis in scirrhous gastric cancer lines. |
| Dovitinib(Novartis) | Deng N *et al*[[20](#_ENREF_20)] | Dovitinib specifically inhibited cell proliferation and induced apoptosis in gastric cancer cells with potent amplification of FGFR1. |
| S49076 | Burbridge F *et al*[[43](#_ENREF_43)] | S49076 impaired the growth of MET- and FGFR2-dependent gastric cancer cells and showed good synergistic inhibition of MET and FGFR2 *in vivo* medel. |
| Foretinib([GlaxoSmithKline](http://en.wikipedia.org/wiki/GlaxoSmithKline)) | Kataoka Y *et al*[[47](#_ENREF_47)] | Foretinib inhibits the cell growth of gastric cancer cell lines by inhibiting not only MET but also FGFR kinase. |
| **FGFRs specific inhibitors** |
| AZD4547 (AstraZeneca) | Xie L *et al*[[50](#_ENREF_50)] | AZD4547 application resulted in tumor growth inhibition in FGFR2-amplified gastric tumor xenograft and induction of apoptosis by impairing downstream signaling of FGFR2. |
| PD173074 | Kunii K *et al*[[23](#_ENREF_23)] | FGFR2 inhibition by PD173074 disolayed potent and selective growth inhibition in FGFR2-amplified gastric cancer cell lines. |
| *LY2874455* (Eli Lilly and Company) | Zhao G *et al*[[51](#_ENREF_51)] | LY2874455 is more potent at inhibiting the growth of gastric cancer cells with an increased FGFRs-signaling activity without high blood pressure. |
| **RNA based therapy** |
| siRNA | Zhou D *et al*[[54](#_ENREF_54)] | Treatment with siRNA resulted in reduced proliferation and prompted apoptosis, which accompanied the reduction of VEGFR expression and increase of apoptosis-related proteins. |
| miR 133b | Wen D *et al*[[55](#_ENREF_55)] | Some micro RNAs (miR 133b) may contribute to the regulation of FGFR-1 receptor in gastric carcinomas such that FGFR1 expression is inversely correlated with miR- 133b expression. |
|  |  |  |
| **FGFRs antibodies** |
| Gal-FR21, 22 and 23 | Zhao W *et al*[[52](#_ENREF_52)] | Highly specific monoclonal antibodies against FGFR2 strongly depressed growth of xenografts from 2 gastric cancer cell lines, OCUM-2M and SNU-16. |
| GP369 | Bai A*. et al*[[53](#_ENREF_53)] | GP369, an FGFR2-IIIb-specificantibody, exhibited anti-proliferative activity against gastric cancers driven FGFR2 overexpression. |

FGFR: Flobrast growth factor receptor; VEGFR: Vascular endothelial growth factor receptor.

**Table 2 Clinical trials of fiblobrast growth factor receptor 2-targeted therapy in gastric cancer**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Trial** | **Study design** | **FGFRs status** | **Regimen** | **Response rate** | **Status** |
| NCT01457846 | Phase I/1st | FGFR2amplification FISH + | AZD4547 | 38.5%(contained SD) | Conducted |
| SHINE | Phase II/1st | FGFR2amplification FISH + | AZD4547paclitaxel |  | Computed accural |
| NCT01719549 | Phase II/2nd | FGFR2 amplification | dovitinib |  | Ongoing |
| NCT01921673 | Phase I/II/2nd | FGFR2 amplification | dovitinib, docetaxel |  | Ongoing |
| NCT02052778 | Phase I/II/2nd | FGF/FGFR-Related Abnormalities | TAS-120 |  | Ongoing |
| NCT02318329 | Phase I/1st | FGFR2b overexpression and FGFR2 amplification | FPA144 |  | Ongoing |

FGFR: Fiblobrast growth factor receptor; FISH: Fluorescence *in situ* hybridization; SD: Stable disease.