

REVIEW

Fibroblast Growth Factor Receptor Inhibitors as a Cancer Treatment: From a Biologic Rationale to Medical Perspectives

Maria Vittoria Dieci^{1,3,5}, Monica Arnedos^{1,3}, Fabrice Andre^{1,3,4}, and Jean Charles Soria^{2,3,4}

ABSTRACT

The fibroblast growth factor/fibroblast growth factor receptor (FGF/FGFR) signaling pathway plays a fundamental role in many physiologic processes, including embryogenesis, adult tissue homeostasis, and wound healing, by orchestrating angiogenesis. Ligand-independent and ligand-dependent activation have been implicated in a broad range of human malignancies and promote cancer progression in tumors driven by FGF/FGFR oncogenic mutations or amplifications, tumor neoangiogenesis, and targeted treatment resistance, thereby supporting a strong rationale for anti-FGF/FGFR agent development. Efforts are being pursued to develop selective approaches for use against this pathway by optimizing the management of emerging, class-specific toxicity profiles and correctly designing clinical trials to address these different issues.

Significance: FGF/FGFR pathway deregulations are increasingly recognized across different human cancers. Understanding the mechanisms at the basis of these alterations and their multiple roles in cancer promotion and drug resistance is a fundamental step for further implementation of targeted therapies and research strategies. *Cancer Discov*; 3(3); 264–79. ©2012 AACR.

INTRODUCTION

Fibroblast growth factors (FGF) that create signals by binding with FGF receptors (FGFR) play a critical role in many physiologic processes. Compelling evidence indicates that aberrant FGF signaling is also involved in the pathogenesis of many malignancies. A growing body of research indicates that the inhibition of the FGF pathway may present an effective therapeutic option for cancer.

This review will summarize the involvement of the FGF pathway in cancer progression, examine the current clinical data for FGFR inhibitors, and discuss the challenges associated with developing FGFR inhibitors.

FGFs AND FGFRs IN HUMAN PHYSIOLOGY

FGFs and FGFRs

The FGF ligand family contains 18 known components that can be divided into the following 2 categories: hormone-

Authors' Affiliations: ¹Breast Cancer Unit and ²Early Drug Development Unit (SITEP), Department of Medical Oncology; ³INSERM Unit U981, Gustave Roussy Institute, Villejuif; ⁴Paris Sud University, Orsay, France; and ⁵Department of Oncology, Hematology, and Respiratory Diseases, University Hospital, Modena, Italy

Corresponding Author: Fabrice Andre, Comité 050, Gustave Roussy Institute, 114 rue E Vaillant, 94800 Villejuif, France. Phone: 003-314-211-4371; Fax: 003-314-211-5274; E-mail: fandre@igr.fr

doi: 10.1158/2159-8290.CD-12-0362

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like FGFs (i.e., FGF19, 21, and 23) and canonical FGFs (i.e., FGF1–10, 16–18, and 20). The FGF-FGFR interaction is stabilized by the formation of a ternary complex that involves either cell surface heparan sulfate proteoglycans (HPSG) or Klotho proteins that further increase the specificity of the interaction in the case of hormonal FGFs (1).

Four of 5 identified FGFRs (i.e., FGFR1–4) are single-pass, transmembrane, tyrosine kinase receptors (Fig. 1). The extracellular domain contains 3 immunoglobulin (Ig)-like fragments (Ig-I, -II, and -III). Ig-I and the acid box are supposed to have a role in receptor autoinhibition, whereas Ig-II and Ig-III bind ligands and HPSGs (1). Alternative splicing of the second half of the Ig-III extracellular fragment of FGFR1, 2, or 3 may generate isoforms, that is, Ig-IIIb and Ig-IIIc, which are specifically expressed in the epithelium and mesenchyme, respectively, and differ in terms of ligand-binding specificity (2). The cytoplasmic portion of FGFR1–4 contains a tyrosine kinase domain and a COOH tail. A fifth receptor, FGFR1, also binds FGFs, but it lacks the tyrosine kinase domain; moreover, FGFR1 reportedly reduces cell growth and accelerates cell differentiation (3).

The specificity of the FGF-FGFR interaction is established through the different ligand-binding capacities of FGFRs as well as the alternative splicing of *FGFR* mRNA, and the tissue-specific expression of ligands, receptors, and cell-surface proteins.

FGF/FGFR Signaling

The binding of an FGF to an FGFR induces receptor dimerization, thereby enabling the intermolecular

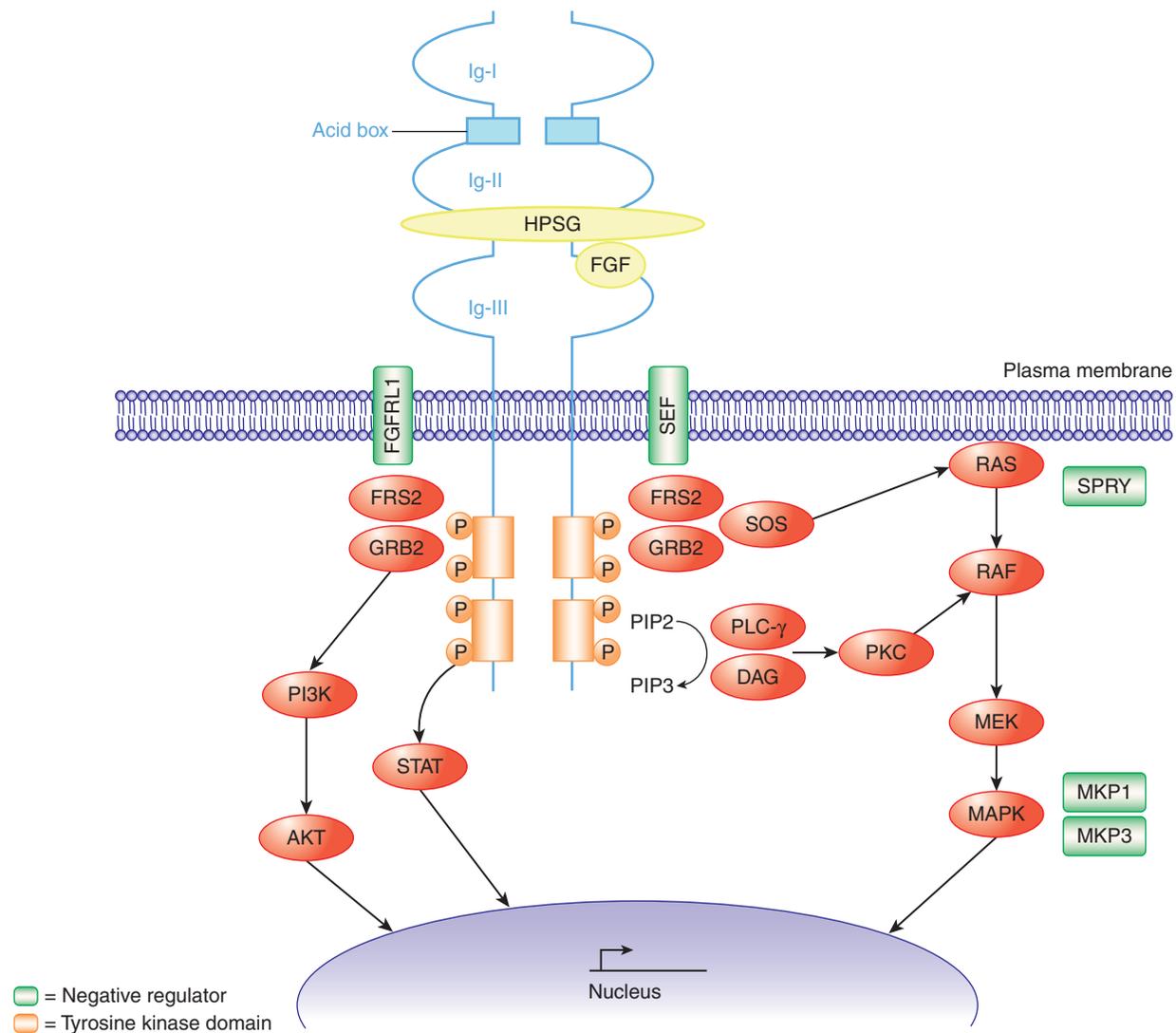


Figure 1. The FGFR structure and signaling network. FGFRs are single-pass transmembrane receptors with an extracellular domain comprising 3 Ig-like domains (Ig-I-III) and an intracellular tyrosine kinase domain. The ligand-receptor binding is stabilized by the interaction with HPSG, thus inducing receptor dimerization and transphosphorylation at several tyrosine residues in the intracellular portion of FGFR. Two main downstream pathways are shown. The first induces Ras-dependent MAPK signaling, and the second leads to PI3K/Akt activation, independently and in parallel with Ras. PLC- γ may also be activated, thus triggering PKC, which converges with the MAPK pathway. Other pathways may be switched on, such as the STAT-dependent pathway. Many negative regulators are able to attenuate signaling at different levels, including FGFR1, SEF, SPRY, and MAPK phosphatase 1 and 3 (MKP1 and MKP3) MEK, MAP-ERK kinase.

transphosphorylation of several tyrosine residues in the COOH terminal tail, kinase domains, and juxtamembrane region. The activated FGFR phosphorylates FGFR substrate 2 (FRS2) and recruits growth factor receptor-bound 2 (GRB2), finally resulting in the activation of RAS and the downstream RAS/mitogen-activated protein kinase (MAPK) pathway. Likewise, GRB2 activates phosphoinositide 3-kinase (PI3K)/AKT-dependent signaling. Operating independently from FRS2, phospholipase C- γ (PLC- γ) binds to a phosphotyrosine at the COOH tail and hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-triphosphate (PIP3) and diacylglycerol (DAG), thus activating protein kinase C (PKC), which converges with the MAPK pathway (Fig. 1; ref. 4).

Negative feedback loops involve the induction of MAPK phosphatase 3 (MAPK3), Sprouty (Spry) proteins, and “similar expression to FGF” (SEF) family members, which can attenuate the signal cascade at different levels. Moreover, following activation, the receptor is internalized and then degraded or recycled, partly depending on the extent of ubiquitination (4).

Biologic and Context-Dependent Responses

FGFRs/FGFs are key molecules involved in embryogenesis, tissue homeostasis, tissue repair, wound healing, and inflammation (5). The main effects of the FGFR pathway include proliferation, migration, and antiapoptotic signals. Proliferation is mainly achieved through the MAPK cascade, whereas antiapoptotic signals are mediated by PI3K/AKT with

STATEMENTS OF RELEVANCE

- FGF/FGFR oncogenic driver mutations/amplifications characterize rare tumor segments across various cancer types, and FGFR pathway activation may act as a resistance mechanism to targeted and antiangiogenic drugs.
- Data from phase I/II trials suggest that FGFR inhibitors exhibit antitumor activity and should be further advanced in the clinical development process.
- Targeting the FGF/FGFR pathway in human cancer represents an illustration of the current challenges in drug development: how to develop drugs in rare genomic segments; how to develop compounds that aim at reversing resistance to conventional agents; and how to better target the host, including angiogenesis.

cross-talk between both pathways (4). However, in specific cellular contexts, FGF signaling may induce growth arrest and cell differentiation according to the cell type-specific expression of FGFs, FGFRs, and adaptor molecules.

FGF and Angiogenesis

Embryogenesis, angiogenesis, and wound healing were the first fields in which FGF/FGFR proliferation and migration signals were shown to play a fundamental role. Both FGF1 and FGF2 drive potent angiogenic signals according to the results of various preclinical assays. FGF1 and FGF2 directly promote endothelial cell proliferation, migration, vessel formation, and maturation (6). Indirectly, FGFs can synergize with the VEGF and platelet-derived growth factor (PDGF) pathways. For instance, in one preclinical microvascular endothelial cell model, the angiogenic response occurred faster when both FGF2 and VEGF were added, as compared with the addition of either factor alone (7).

FGF SIGNALING AND CANCER PROGRESSION

FGF signaling is deregulated in many cancer types. Strong evidence supports the relevance of FGFR activation in carcinogenesis, as seen by the results of a screen of 921 base substitution somatic mutations found in the coding exons of 518 protein kinase genes from 210 different human cancers. In this analysis, the FGF signaling pathway showed the highest enrichment for kinases containing nonsynonymous mutations (8).

The FGF/FGFR alterations that are found in cancer may result either in constitutive ligand-independent FGFR activation or in aberrant ligand-dependent signaling. FGFR pathway activation can generally be involved in the following 3 mechanisms that lead to cancer progression: oncogenesis, neoangiogenesis, and drug resistance.

Activating FGFR Genomic Alterations

Table 1 summarizes the main activating FGFR genomic alterations found in human cancers. These major oncogenic aberrations have features that make them potentially good

therapeutic targets for specific cancers, and the details of these targets are discussed subsequently.

FGFR1

The most convincing evidence for the involvement of FGFR signaling in cancer progression is provided by the hematologic field. For example, the 8p11 myeloproliferative syndrome is an aggressive neoplasm characterized by rapid acute leukemic transformation. To date, almost 70 cases have been reported, and either a translocation or an insertion at the 8p11 locus harboring the *FGFR1* gene has been linked to the disease. The permanently activated fusion proteins consist of an N-terminal portion with a dimerization domain and the C-terminal portion that houses the FGFR1 tyrosine kinase domain (18). The most common translocation is t(8;13)(p11;q12) and involves ZNF198. Preclinical evidence shows that FGFR inhibitors are able to reduce growth and induce apoptosis in cell lines harboring *FGFR1* gene rearrangements (37).

The *FGFR1* gene also frequently exhibits alterations in other diseases. Indeed, the amplification of the chromosomal region 8p11-12, which includes the gene encoding FGFR1, has been detected in 8% to 10% of breast cancers, that is, mainly in estrogen receptor (ER)-positive cases. Moreover, this finding has been related to higher *FGFR1* mRNA levels (10, 38) and poorer prognosis (39, 40). As the 8p11-12 amplicon contains other potential oncogenic sections, the role of *FGFR1* as an oncogenic driver cannot be established with certainty. Nevertheless, *FGFR1*-amplified breast cancer cells seem to have an oncogenic connection to FGFR1 signaling, as evidenced by their high sensitivity to FGFR1 tyrosine kinase inhibitors (TKI; ref. 41). More recently, reports have indicated that *FGFR1* is amplified in 20% of squamous non-small cell lung cancers (NSCLC). Interestingly, preclinical studies have shown that *FGFR1*-amplified NSCLCs are extremely sensitive to FGFR inhibition by PD173074 (9).

FGFR2

FGFR2-activating mutations have been described in 12% of endometrial carcinomas. Notably, endometrial cancer cell lines harboring *FGFR2* mutations showed high sensitivity to PD173074 (22).

Approximately 10% of cases of gastric cancer also exhibit *FGFR2* amplification and mutations (20). This genomic segment is the current target of clinical development for AZ4547 (clinicaltrials.gov, NCT01457846). Moreover, *FGFR2* amplification can be detected in 4% of triple-negative breast cancers. Treatment with PD173074 induced apoptosis in *FGFR2*-amplified triple-negative breast cancer cell lines, partly owing to inhibition of PI3K/AKT signaling (21). These observations could gain further relevance in the light of recent research accomplishments in the field of triple-negative breast cancer classification. Among the 5 different subtypes of triple-negative breast cancers described in the article by Lehman and colleagues (42), the mesenchymal and mesenchymal-like subtypes were enriched in epithelial-mesenchymal transition and growth factor pathways. Among them, the expression of components of the FGF pathway was also identified.

Table 1. Activating genetic alterations in FGFR and related cancer types

Gene	Alteration	Cancer type (incidence, if known; reference)
FGFR1	Amplification	Squamous NSCLC (20%; ref. 9) Breast cancer (10%; ref. 10) Ovarian cancer (~5%; ref. 11) Bladder cancer (3%; ref. 12) Others: oral squamous cell carcinoma, esophageal squamous carcinoma, prostate cancer (13–15)
	Mutation	Melanoma (rare), glioblastoma (16, 17)
	Translocation	8p11 myeloproliferative syndrome, chronic myeloid leukemia (rare; refs. 18, 19)
FGFR2	Amplification	Gastric cancer (10%; ref. 20) Breast cancer (4% of triple-negative cases; ref. 21)
	Mutation	Endometrial cancer (12%; ref. 22) Squamous NSLC (5%; ref. 8) Gastric cancer (rare; ref. 23)
	Germline SNP	Second intron SNP: breast cancer susceptibility (24)
FGFR3	Amplification	Bladder cancer (25) Salivary adenoid cystic cancer (26)
	Mutation	Bladder cancer (50–60% non-muscle invasive; 10–15% muscle invasive; ref. 27) Cervical cancer (5%; ref. 28) Myeloma (5% of the translocated cases; ref. 29) Prostate cancer (3%; ref. 30) Spermatocytic seminoma (7%; ref. 31) Colorectal cancer (23) Oral squamous cancer (32)
	Translocation	Myeloma (15%–20%; ref. 33) Peripheral T-cell lymphoma (rare; ref. 34)
	Mutation	Rhabdomyosarcoma (7%–8%; ref. 35)
	Germline SNP	Coding SNP: poor prognosis in many cancer types (36)

Interestingly, cell models for these specific subtypes were sensitive to PI3K inhibition.

Furthermore, genome-wide association studies identified *FGFR2* as a breast cancer susceptibility gene; indeed, several single nucleotide polymorphisms (SNP) in *FGFR2* were found to be highly associated with breast cancer risk (24).

FGFR3

Mutations in *FGFR3* are found in approximately 50% of cases of bladder cancers, and the most common are extracellular domain mutations that lead to constitutive receptor activation (27). Actions intended to target *FGFR3* reduced cell proliferation and tumor growth in both bladder cancer cells and mouse models (43). In human bladder cancer, *FGFR3* mutations are strongly related to low-grade, non-muscle-invasive tumors and good prognosis (44).

About 15% to 20% of patients with multiple myeloma harbor the chromosomal translocation t(4;14), which brings *FGFR3* and the adjacent multiple myeloma SET domain (*MMSET*) gene under the control of the Ig heavy chain promoter, thereby leading to the aberrant expression of *FGFR3* and *MMSET* (33). The relative transforming contributions of *FGFR3* and *MMSET* are still unclear; however, dependence on *FGFR3* signaling has been shown in t(4;14) cell lines and mouse models (45).

FGFR4

Some cases of rhabdomyosarcoma (7%–8%) may harbor *FGFR4*-activating mutations. *FGFR4* overexpression has also been frequently observed and correlated to advanced stages and poorer outcomes (35).

Autocrine/Paracrine Signaling

An increased availability of FGFs can promote cancer, as shown in several mouse models (4). High FGF levels may be derived from the upregulation of FGF expression in cancer or stromal cells and the enhanced release of FGFs from the extracellular matrix (46).

Much evidence supports the carcinogenic and metastatic role of stromal-epithelial interplay involving FGFR signaling in prostate cancer. Indeed, according to previous studies, multiple FGFs, including FGF1 and 2 and FGF6–9, are upregulated in this disease, whereas *FGFR1* is expressed in 40% of poorly differentiated localized prostate cancers (46). The stromal expression and release of various FGFs are related to angiogenic and tumor-promoting effects. More specifically, studies in transgenic mice have linked *FGFR1* activation and FGF8 epithelial overexpression to epithelial-mesenchymal transition and the induction of prostatic adenocarcinomas (47). A humanized monoclonal anti-FGF8 antibody and selective FGFR TKIs, such as AZ8010,

displayed *in vivo* antitumor activity against prostate cancer cell lines (46, 48).

FGF2 has also been shown to induce epithelial-mesenchymal transition in NSCLC cell lines (49). The inhibition of FGFR signaling through antisense RNA, naturalizing FGF2 antibodies, or TKIs led to the *in vitro* inhibition of cellular proliferation and tumor growth (50).

Finally, autocrine loops of FGF2 have also been reported in triple-negative breast cancers. This autocrine loop occurred mainly in basal-like B cells (showing mesenchymal-like features) and was associated with high sensitivity to FGFR inhibitors in preclinical models (51).

Overall, these data suggest that autocrine/paracrine loops of FGF could be involved in epithelial-mesenchymal transition and cancer progression in at least 3 common cancers.

FGF and Tumor Neoangiogenesis

FGFs have also been implicated in tumor neoangiogenesis. FGFs exert their angiogenic functions on endothelial cells in both a paracrine fashion and via autocrine release from capillary endothelial cells (4). Overexpression of a soluble FGFR led to an impairment in the maintenance of tumor angiogenesis and a decrease in tumor vessel density. Conversely, the inhibition of the VEGF pathway affected the initiation phases of tumor angiogenesis (52). Other compelling evidence comes from a preclinical study in which antisense-oriented FGF2 or FGFR1 cDNAs were delivered in preclinical models of melanomas. Intratumoral angiogenesis blockage caused the cessation of tumor growth (53). Studies on ovarian cancer revealed that FGF1 overexpression is correlated with both microvessel tumor density and poorer overall survival (OS). Moreover, both ovarian cancer cells and endothelial cells showed increased survival and motility when treated with exogenous FGF1 (54).

Evidence for synergism between FGFs and other angiogenic pathways in tumor angiogenesis has also been reported. For example, the simultaneous expression of VEGF and FGF2 rapidly increased tumor growth, blood vessel density, and permeability in xenograft models. The inhibition of FGF2 expression resulted in a significant decrease in tumor volume concomitant with a decrease in vessel density, whereas VEGF inhibition led to impaired pericyte organization and permeability (55).

As FGFR and VEGF receptor (VEGFR) pathways are integrated in tumor neoangiogenesis through complementary and, in part, overlapping functions, the upregulation of FGFs/FGFRs may also serve as a mechanism of resistance to anti-VEGF therapy. In the preclinical setting, murine pancreatic neuroendocrine tumor models initially responding to anti-VEGF treatment showed a higher expression of *FGF2* at the time of progression, as compared with that of stable tumors (56). A TKI that inhibited both VEGFR and FGFR presented antitumor activity in a model of anti-VEGF failure (57). In agreement with these observations, reports have indicated that FGF2 is higher in patients with colorectal cancer after the failure of bevacizumab-containing regimens and in glioblastoma patients after treatment with a VEGFR TKI (6).

FGF and Drug Resistance

A significant amount of cross-talk between FGF and oncogenic pathways could explain emerging data that indicate a role for FGF/FGFR in the mediation of resistance to targeted and endocrine therapies. As recently shown, the sensitivity of cancer cells to TKIs can be impaired by the increased availability of growth factor ligands. More specifically, when testing different growth factors on a series of kinase-addicted cancer cell lines that are sensitive to specific TKIs, hepatocyte growth factor, FGFs, and neuregulin seem to confer drug resistance to most of the cells (58). Interestingly, the secretion of these ligands may come from tumor stroma (59). These data suggest that FGF released by stromal cells can be involved in the resistance to targeted therapy. This assumption constitutes the rationale for evaluating dovitinib in patients with imatinib-resistant gastrointestinal stromal tumors (GIST; clinicaltrials.gov; NCT01478373, NCT01440959).

Interestingly, in a mouse model of cervical carcinogenesis, using imatinib to target stromal PDGF receptor (PDGFR) resulted in reduced proliferation and angiogenesis via suppression of the expression of FGF2 and FGF7 by cancer-associated fibroblasts. Thus, PDGF ligands expressed by cancer epithelial cells stimulated PDGFR-expressing stroma to upregulate FGFs, thereby promoting angiogenesis and epithelial proliferation. Given this cross-talk, one mechanism of resistance to imatinib might involve upregulation of the FGF pathway (60).

In addition to FGF expression, FGFRs can also be involved in resistance to conventional therapies. First of all, a previous study showed that *FGFR1* overexpression/amplification mediates resistance to 4-hydroxytamoxifen, and the effect was reversed by the inhibition of *FGFR1* via siRNA (40).

More recently, EGF receptor (EGFR) inhibitors have been shown to induce transcriptional de-repression of *FGFR2* and *FGFR3* expression in NSCLC cell lines, thereby suggesting a novel mechanism for acquired resistance to anti-EGFR agents (61). Other reports have also suggested that FGFR3 activation mediates resistance to cetuximab in wild-type squamous tumor cells with *KRAS* mutations and to vemurafenib in BRAF V600E melanoma cells (62, 63).

In total, the data reported to date highlight a critical role for the FGFR pathway in human cancer. Altered FGF/FGFR function may not only promote cancer progression by directly stimulating cancer cell proliferation and survival but also play a major role in tumor neoangiogenesis. This proangiogenic effect is relevant *per se* to tumor growth and progression because it represents the key mechanism that sustains cancer cells, and it has also implications for the resistance to available antiangiogenic treatments. Finally, interesting recent data indicate that the FGFR pathway is a potential driver of resistance to various targeted drugs. Therefore, anti-FGF/FGFR agents can be used to affect tumor progression in cancers driven by FGF/FGFR-activating alterations, target angiogenesis as a fundamental process in cancer cell survival, and revert acquired resistance to antiangiogenic or other targeted agents. The fact that this strong rationale comprises at least 3 major issues represents a challenge for drug development and has implications for

current and future clinical research. Each of these 3 goals requires specifically designed clinical trials that differ in terms of patient selection, clinical setting, and treatment to be tested. For example, trials targeting *FGFR* mutations as oncogenic drivers should preferably be focused on patients harboring the specific mutations. Trials addressing the angiogenic issue may include patients who acquired resistance to other antiangiogenic treatments and should plan the evaluation of potential markers of resistance involving the FGF/FGFR pathway. The neoadjuvant setting could allow researchers to directly test the antiangiogenic properties of an FGF/FGFR blockade using an *in vivo* study. Finally, trials that investigate the ability of anti-FGFR drugs to overcome resistance to other targeted treatments should test drug combinations or sequential schedules and should select patients on the basis of their previous treatments.

ANTI-FGFR DRUGS: STATE OF THE ART

A large effort to develop FGF/FGFR inhibitors as anticancer treatments is under way. The most clinically advanced anti-FGFR drugs are small-molecule TKIs, but different approaches are also under development, including monoclonal anti-FGFR antibodies and FGF-trapping molecules. Those anti-FGFR drugs that have entered the clinical phases of development are reported in Table 2.

Small-Molecule TKIs

Several TKIs targeting the ATP-binding site of the intracellular tyrosine kinase domain of FGFRs are in clinical development (Table 2). Overall, FGFR inhibitors can be classified into 2 different families. The first class is represented by “multitarget” TKIs that include FGFR in their panel of targets (i.e., nonselective FGFR TKIs). These compounds usually also target VEGFRs and usually present modest but significant bioactivity against the FGFR family. The second class includes highly selective and highly bioactive FGFR inhibitors (i.e., selective FGFR TKIs). For the purpose of this review, we will focus on those compounds exhibiting an IC_{50} less than 200 nmol/L against at least one of the FGFRs. Those compounds that have entered the clinical phases of development are discussed subsequently.

Drugs and Phase I Data

Nonselective FGFR TKIs

TKI258 (i.e., dovitinib) is a potent TKI that shows biochemical IC_{50} values less than 20 nmol/L for VEGFR1, 2, and 3; PDGFR- β ; FGFR1 and 3; Fms-like tyrosine kinase receptor 3 (FLT-3); KIT; RET; neurotrophic tyrosine kinase receptor type 1 (TrkA); and colony-stimulating factor 1 (CSF-1). Dovitinib can potentially show antitumor activity through the direct inhibition of FGFR and PDGFR; moreover, dovitinib shows antiangiogenic activity through the inhibition of FGFR, VEGFR, and PDGFR (64). A phase I dose-escalating trial of orally administered dovitinib studied 35 patients with advanced solid tumors. The most frequent drug-related adverse events were gastrointestinal disorders and fatigue. Cardiovascular events were seen in 5 patients (14%); the specific cardiovascular issues that were experienced by the

panel are as follows: grade 2 left ventricular ejection fraction decline in 2 patients, grade 3 asymptomatic elevation in cardiac troponin I in 1 patient, and hypertension in 2 patients (grade 2 and grade 3). One melanoma patient had a partial response (PR) to the treatment, and 2 patients achieved stable disease (SD) status for more than 6 months. Interestingly, 5 of 14 evaluable patients had a modulation of phosphorylated extracellular signal-regulated kinase (ERK) levels in peripheral blood mononuclear cells (76). Forty-seven previously treated patients with advanced melanoma were included in a phase I/II dose-escalation study evaluating dovitinib. The most frequent grade 3 and/or grade 4 adverse events were fatigue (27.7%), diarrhea (10.6%), upper abdominal pain (8.5%), dehydration (8.5%), and nausea (8.5%). Grade 3 and/or grade 4 hypertension was also reported in 2 patients (4.3%). Efficacy data showed only limited activity, as SD in 12 patients was the best observed tumor response. An increase in plasma FGF23, VEGF, and placental growth factor levels and a decrease in soluble VEGFR2 were observed during the first cycle of treatment. As the modulation of plasma FGF23 has been shown to act as a surrogate pharmacodynamic biomarker of FGFR1 inhibition, the results of the pharmacodynamic studies were consistent with FGFR and VEGFR inhibition (77).

E3810 is a potent novel dual inhibitor of VEGFRs and FGFRs and shows activity in the low-nanomolar range for VEGFR1–3, FGFR1, FGFR2, and CSF-1R (66). E3810 is currently being tested in a phase I trial with patients with advanced solid tumors. Data from the dose-escalation phase are available. The dose-limiting toxicity (DLT) was glomerular thrombotic microangiopathy. Common side effects included hypertension, proteinuria, and hypothyroidism. Three patients achieved a SD beyond 1 year; 9 patients progressed, and 5 were withdrawn owing to adverse side effects. Two of these latter patients showed signs of clinical activity. Twenty-seven patients were recruited in the ongoing expansion phase, 5 of whom have an *FGFR1*-amplified cancer. All these patients are receiving treatment; 2 have confirmed PR, whereas one has achieved SD at course 4 (78).

BIBF1120 (nintedanib) is an orally available indolinone derivative that shows the capability of potently blocking VEGFR, PDGFR, and FGFR. The highest activity is against VEGFR1, 2, and 3 and FGFR2. It also targets SRC, LYN, LCK, and FLT-3 (65). In a phase I dose-escalating study, 61 patients with advanced cancers were investigated after treatment with first, once- and, then, twice-daily dosing schedules of BIBF1120. The most frequently reported drug-related adverse events were gastrointestinal events (i.e., nausea, vomiting, and diarrhea). Early signs of efficacy were observed, including one complete response in a patient with renal cell cancer and 2 PRs in a patient with renal cell cancer and a patient with colorectal cancer (79). In another open-label, phase I dose-escalation trial of BIBF1120 in Japanese patients with advanced NSCLC, SD for 2 or more treatment courses was reported in 76% of patients ($n = 16$; ref. 80). In both phase I studies, the observed DLTs were hepatic enzyme elevations (79, 80).

AP24534 (ponatinib) is an oral multikinase inhibitor that is predominantly active against BCR-ABL and is currently

Table 2. Ongoing clinical evaluation of anti-FGFR drugs with $IC_{50} < 100$ nmol against at least one FGFR (Continued on following page)

Compound	Targets and IC_{50} , nmol/L (if available)										Clinical development	Company	
	FGFR1	FGFR2	FGFR3	FGFR4	VEGFR1	VEGFR2	VEGFR3	PDGFR- α	PDGFR- β	Others [IC_{50} , nmol/L]			
Multitargeted TKIs													
TKI258 (dovitinib; ref. 64)	8		9		10	13		8	200	27	FLT-3 [1] KIT [2]	Phase III (RCC)	Novartis
BIBF1120 (nintedanib; ref. 65)	69	37	108	610	34	21		13	59	65	LCK [16] FLT-3 [26] SRC [156] LYN [195]	Phase III (NSCLC, ovarian)	Boehringer-Ingelheim
E3810 (66)	17.5	82.5	237.5	>1,000	7	25		10	175	525	CSF-1 [5] KIT [456]	Phase I (solid tumors)	Ethical Oncology of Science
E7080 (lenvatinib; ref. 67)	46				22	4		5.2	51	39	KIT [100]	Phase III (thyroid)	Eisai
BMS582664 (briwanib; ref. 68)	148	125	68		380	25		10		>6,000		Phase III (HCC, CRC)	Bristol-Myers Squibb
ENMD-2076 (69)	93	71	500			58		16	56.4		FLT-3 [2] RET [10.4] SRC [20.2] CSF-1 [24.8] Aurora A [14] Aurora B [350] KIT [120]	Phase II (breast, ovarian)	Entremed

Table 2. Ongoing clinical evaluation of anti-FGFR drugs with IC₅₀ < 100 nmol against at least one FGFR (Cont'd)

Compound	Targets and IC ₅₀ , nmol/L (if available)											Clinical development	Company
	FGFR1	FGFR2	FGFR3	FGFR4	VEGFR1	VEGFR2	VEGFR3	PDGFR- α	PDGFR- β	Others [IC ₅₀ , nmol/L]			
TSU68 (orantinib; ref. 70)	1.2 μ mol/L					2.1 μ mol/L				0.008 μ mol/L		Phase III (HCC)	Taiho Pharma- ceutical
AP24534 (ponatinib; ref. 71)	2	2	18	8		1.5		1.1		ABL [0.7] SRC [5.4] LYN [0.24] KIT [12.5]		Phase II (ALL, CML)	Ariad
Selective TKIs													
AZD4547 (72)	0.2	2.5	1.8	165		24				IGFR [581]		Phase II (breast, gastric)	AstraZeneca
BGJ398 (73)	0.9	1.4	1	60								Phase I (solid tumors)	Novartis
LY2874455 (74)	2.8	2.6	6.4	6		7 ^a						Phase I (solid tumors)	Eli Lilly
Monoclonal antibodies													
MGFR18775 [clinicaltrials. gov]												Phase I (MM, solid tumors)	Genentech
FGF traps													
HGS1036/FP- 1039 (75)										FGF1 FGF2 FGF4		Phase I (solid tumors)	Human Genomic Sciences

^aSix- to 9-fold cellular and *in vivo* selectivity on inhibition of FGF- over VEGF-mediated target signaling in mice.

Abbreviations: ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; CRC, colorectal cancer; FLT-3, Fms-like tyrosine kinase receptor 3; HCC, hepatocellular carcinoma; IGFR, insulin-like growth factor receptor; MM, multiple myeloma; RCC, renal cell carcinoma; STS, soft tissue sarcoma.

being investigated in a phase II study in patients with chronic myelogenous leukemia and BCR-ABL-positive acute lymphoblastic leukemia (clinicaltrials.gov; NCT01207440, NCT01641107). Furthermore, it has been shown to be a potent pan-FGFR inhibitor in preclinical assays. Remarkably, it was able to inhibit *in vitro* cell proliferation and signaling in various cell lines characterized either by *FGFR* amplifications or activating mutations (81). These recent data highlight the rationale to investigate ponatinib as a potential treatment for FGFR-driven solid tumors as well.

In addition to these leading compounds, other inhibitors, such as BMS582664 (brivanib; ref. 82), E7080 (lenvatinib; refs. 67, 83), ENMD-2076 (69), and TSU-68 (orantinib; ref. 70), have shown some anti-FGFR activity but are mainly active against VEGF receptors or other kinases (Table 2).

Overall, phase I studies have suggested that nonselective FGFR inhibitors can be used in the treatment of patients with cancer. Several of these phase I/II studies have reported bioactivity against FGFR at the doses recommended for the phase II studies. Although these drugs are bioactive against FGFR *in vivo*, their main toxicity profile remains related to VEGFR inhibition.

Selective Anti-FGFR TKIs

Recently, some selective anti-FGFR TKIs have been developed. The preclinical evaluation of potent FGFR TKIs has suggested that tissue calcification could be a safety issue that must be addressed in the drug development process. This specific toxicity occurs as a consequence of hyperphosphatemia, which is caused by the blockage of FGF23 signaling (4). The following 3 selective FGFR TKIs have entered the clinical phases of evaluation.

AZD4547 is a highly active pan-FGFR selective inhibitor. Activity against VEGFR2 is approximately 120-fold lower than that against FGFR1. AZD4547 suppresses FGFR signaling and growth in tumor cell lines owing to deregulated FGFR expression. In a representative FGFR3-driven human tumor xenograft model, the oral administration of AZD4547 was well tolerated and resulted in potent antitumor activity (72). AZD4547 is currently being evaluated in a phase I clinical trial. A second expansion phase will include patients with *FGFR1*- and/or *FGFR2*-amplified cancers (clinicaltrials.gov; NCT00979134). A randomized, double-blind phase IIA study will assess the safety and efficacy of AZD4547 when taken in combination with exemestane versus the administration of exemestane alone in patients with ER-positive breast cancer with *FGFR1* polysomy or amplification (clinicaltrials.gov; NCT01202591). Finally, another phase II randomized study is testing AZD4547 monotherapy versus paclitaxel in patients with advanced gastric carcinoma or gastroesophageal junction cancers with *FGFR2* polysomy or amplification (clinicaltrials.gov; NCT01457846).

BGJ398 is another selective inhibitor of FGFR1-3 (73). A phase I trial is currently recruiting patients with advanced solid tumors showing *FGFR1* or *FGFR2* amplification or *FGFR3* mutation. Preliminary data from the first 26 patients (including 13 patients with *FGFR1*-amplified cancers) are available. Adverse events were generally considered grade 1 to 2 and included diarrhea, fatigue, and nausea. Dose-dependent hyperphosphatemia was observed and could be

managed with phosphate binders and diuretics. One patient with *FGFR1*-amplified lung cancer achieved a 33% reduction in the target lesions at 8 weeks, which was also confirmed at 12 weeks (84).

LY287445 is a selective pan-FGFR inhibitor (i.e., against FGFR1-4). *In vivo* assays showed that LY287445 is much more potent (i.e., 6- to 9-fold) at inhibiting FGFR than VEGFR signaling. LY287445 was active against cancer cells and xenograft models harboring specific activating FGFR alterations. Furthermore, LY287445 did not show VEGFR2-mediated toxicity at efficacious doses (74). Currently, this molecule is being clinically tested in a phase I trial (clinicaltrials.gov; NCT01212107).

Overall, some main considerations may arise from these early-phase data. First, proof of an effective inhibition of FGFR by TKIs in patients with cancer has been produced. As previously mentioned, in phase I trials of the nonselective FGFR inhibitor dovitinib, both a modulation of phosphorylated ERK levels in peripheral blood cells and an increase in circulating FGF23 have been observed.

However, the toxicity profiles of multiple-targeted TKIs and selective TKIs are clearly different. All the nonselective compounds showed toxicities related to VEGFR inhibition, such as hypertension, cardiovascular events, and proteinuria. Notably, the incidence of drug-related hypertension reached 33.8% in the phase I study of brivanib (82). Moreover, the other most commonly reported adverse events include toxicities that are shared with other targeted agents, including gastrointestinal disorders and skin reactions. Conversely, selective FGFR inhibitors show a different and "FGFR-specific" toxicity profile, including hyperphosphatemia. These considerations have 2 major implications. First, this toxicity profile will matter when combinations are developed. One could argue that the "FGFR-specific" safety profile of AZD4547, BGJ398, and LY287445 could give them an advantage. Indeed, given their broad toxicity profile, developing multikinase inhibitors with other compounds could be more challenging. Second, new toxicities are emerging for the selective anti-FGFR class of drugs, the most evident of which is hyperphosphatemia and tissue calcification as a consequence of the blockage of FGF23 signaling. Very preliminary data from clinical settings suggest that this toxicity may also represent an issue in humans. In the BGJ398 phase I trial, hyperphosphatemia was reported as controllable by the use of phosphate binders and diuretics (73). Then, the next step will be to develop specific and adequate toxicity management protocols and strategies. One of the major issues with this drug class will be the long-term toxicity related to the potent inhibition of FGFR.

Phase II Data

Targeting FGFR as an Oncogenic Driver

A 2-step phase II study evaluated dovitinib in patients with previously treated, metastatic, HER2-negative breast cancer. Patients were stratified into 4 groups according to *FGFR1* and hormone receptor (HR) status. Antitumor activity was observed in the *FGFR1*-amplified/HR-positive subset (25% had nonconfirmed PR and/or SD \geq 4 weeks). Moreover,

biomarker analysis suggested that coamplification of *FGFR1* and *FGFR3* might identify a small subgroup of dovitinib-sensitive patients (85). These observations were used as the rationale behind the design of an ongoing multicenter, randomized phase II trial of fulvestrant with and without dovitinib for postmenopausal, HER2-negative/HR-positive advanced breast cancer patients who saw cancer progression after endocrine therapy. Prospective molecular screening is expected to enrich the *FGFR1*, *FGFR2*, or *FGFR3* amplification (clinicaltrials.gov; NCT01528345).

Similarly, dovitinib is also being evaluated in the treatment of patients with bladder and endometrial cancer (clinicaltrials.gov; NCT00790426 and NCT01379534, respectively). The trial in endometrial cancer will study patients with *FGFR2* mutations, whereas the one in bladder cancers will retrospectively assess the predictive value of *FGFR3* mutations.

Targeting Angiogenesis

Anti-VEGFR TKIs have become the keystone for the treatment of renal cell carcinoma. Dovitinib has been evaluated in a phase II trial that studied 59 patients with metastatic renal cell carcinoma who did not improve after prior treatment with a VEGFR-TKI and/or an mTOR inhibitor or other therapies. The best overall responses were as follows: PR (3.4%), SD ≥ 2 months (49.2%), SD ≥ 4 months (27.1%), and progressive disease (PD; 18.6%). Median progression-free survival (PFS) and OS were 5.5 and 11.8 months, respectively (86). Dovitinib is currently under evaluation in a phase III trial versus sorafenib as a third-line treatment for patients whose cancers progressed on a prior VEGFR-TKI and prior mTOR inhibitor treatment (clinicaltrials.gov; NCT01223027).

According to a recent study, bevacizumab is highly effective in the treatment of advanced ovarian cancer (87), thus opening the field for other antiangiogenic strategies to be tested in this setting. In a phase II study, 83 patients at high risk for early recurrence after achieving a response to chemotherapy for relapsed ovarian cancer were randomized to either BIBF1120 maintenance or a placebo. Thirty-six-week PFS rates were 16.3% and 5.0% in the BIBF1120 and placebo groups, respectively ($P = 0.06$; ref. 88). Currently, a randomized phase III trial is evaluating carboplatin and paclitaxel in combination with BIBF1120 versus a placebo followed by maintenance with BIBF1120 or the placebo as the first-line treatment for advanced ovarian cancer (clinicaltrials.gov; NCT01015118).

Overcoming Drug Resistance

In a recently published phase II study, 33 patients with metastatic gastrointestinal tumors who had undergone a failed treatment regimen of imatinib and sunitinib were treated with regorafenib, a potent inhibitor of several tyrosine kinases, including VEGFR1, VEGFR2, VEGFR3, PDGFR- β , FGFR1, TIE2, c-KIT, RET, and intracellular signaling kinases. The clinical benefit rate was 75% due to 4 PRs and 22 instances of SD more than 16 weeks; moreover, the median PFS was 10 months (89). Preclinical studies have suggested a potential role for FGF pathway activation in the resistance to imatinib

(60). Although this drug shows only marginal activity against FGFRs, we must consider the thought that FGFR inhibition may have contributed to these results. Dovitinib is under evaluation in phase II trials in patients with GIST resistant to imatinib and sunitinib (clinicaltrials.gov; NCT01478373, NCT01440959).

Other studies designed to investigate FGF inhibition as a means to overcome drug resistance are currently ongoing. For example, a phase II study is randomizing postmenopausal, endocrine-resistant, HER2-negative/HR-positive breast cancer patients to groups receiving dovitinib or the placebo in combination with fulvestrant (clinicaltrials.gov; NCT01528345). Another phase III trial is evaluating the combined use of brivanib and cetuximab as a second- or third-line therapy for patients who have *KRAS*-wild type colorectal cancers and have received chemotherapy (clinicaltrials.gov; NCT00640471).

Monoclonal Antibodies

Several monoclonal antibodies against FGFRs have been assessed in preclinical studies, and these studies have shown an antiproliferative effect on bladder cancer cells, t(4;14) myelomas, and mouse xenograft models of *FGFR2*-amplified gastric cancer and breast cancer (4). However, the evaluation of a single-chain, anti-FGFR1-IIIc was stopped at the preclinical phase after it was shown to induce severe anorexia in rodents and monkey models (90). In another example, MGFR1877S, an anti-FGFR3 antibody, is currently being evaluated in 2 phase I trials, that is, one including patients with advanced solid tumor and the other recruiting patients with t(4;14) myeloma (clinicaltrials.gov; NCT01363024, NCT01122875).

FGF-Ligand Traps

FP-1039 consists of the extracellular domain of an FGFR1-IIIc splice isoform fused to the crystallizable fragment region of human IgG. This compound is supposed to hamper the activity of multiple FGFs. Indeed, it has shown antiangiogenic and antitumoral efficacy in preclinical *in vivo* studies (75). A phase I study in advanced cancers is under way (clinicaltrials.gov; NCT00687505), but a phase II study that would have assessed FP-1039 efficacy in patients with *FGFR2*-mutant endometrial cancer has been withdrawn before the enrollment phase. The study was deemed infeasible because the original assumption was that at least 5% of patients who were screened would qualify, but after 70 patients had been screened, none qualified (clinicaltrials.gov; NCT01244438).

CHALLENGES AND PERSPECTIVES

As described in earlier sections, previous research has provided a strong rationale for the targeting of FGFRs as oncogenic drivers, a means to overcome resistance to treatment, or a means to target angiogenesis. Early development of FGFR inhibitors suggests that such drugs are bioactive against FGFR, present very specific toxicity profiles, and exhibit antitumor activity. Two drug families have emerged, that is, selective FGFR inhibitors and TKIs. Several challenges are being faced to further develop these compounds (Figure 2).

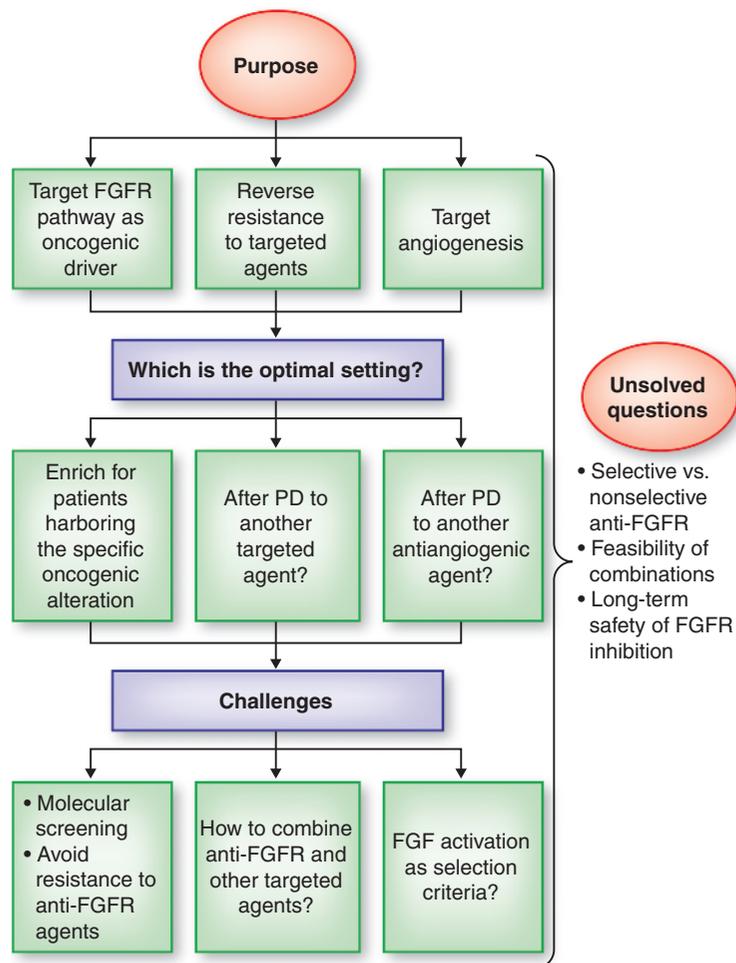


Figure 2. Challenges and open questions in anti-FGFR drug development.

Running Therapeutic Trials in Patients Presenting a Low-Frequency Genomic Alteration

As mentioned in the previous sections, FGF/FGFR genomic alterations are rare for each single cancer type. Preclinical studies suggest that patients presenting these genomic alterations are more likely to be sensitive to FGFR inhibitors. Therefore, early clinical trials should include patients presenting these genomic alterations to determine the efficacy of these agents in this rare subset of patients. This approach has been already pursued in the TKI258A2202 trial, which evaluated TKI258 in patients with breast cancer; indeed, in this trial, 50% of the patients who were enrolled showed *FGFR1* amplification. Many other ongoing phase I/II trials with anti-FGFR agents (e.g., TKI258, BGJ398, AZD4547, and E3810) are now including patients with specific FGF/FGFR alterations. In addition to the change in the population of early trials, validation randomized trials will likely need to include only patients with the genomic alteration under study.

This process of selecting patients emphasizes the need for development of optimal molecular diagnosis procedures for FGFR alterations. The challenge here is to be able to select the right patients for the FGFR compound while not denying another potentially effective compound to FGFR-negative patients. One possible strategy is to “screen” patients using multiplex approaches. This screening allows the detection

of several alterations and thus increases the likelihood of identifying at least one actionable genomic alteration in each patient. The “screened” alteration must be centrally confirmed in the context of a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. Several tests are being used for the diagnosis of genomic alterations in the FGF pathway, including FISH, chromogenic *in situ* hybridization (CISH), quantitative real-time PCR, and Sanger sequencing (91).

In addition, autocrine and paracrine FGF/FGFR overexpression promotes carcinogenesis and progression. Therefore, developing anti-FGFR drugs only for the treatment of genomic aberrant tumors is short sighted and may miss other potentially therapeutic uses. Future research efforts must strive to define the subset of cancers driven by FGFR pathway component overexpression by means other than amplification and may benefit from an anti-FGFR approach. In the case of tumors driven by the overexpression of an FGF, research should define which of the FGFRs really mediates the effect of the upregulated ligand and then specifically target that FGFR.

Selecting the Right Drug Family: Nonselective TKI or Selective FGFR Inhibitors?

This dilemma of developing highly specific versus multi-target inhibitors is shared with other drug classes. Although the time is not right for direct comparisons between

nonselective and selective anti-FGFR TKIs, some considerations can be contemplated. As previously reported, multi-TKIs can cause adverse effects related to VEGF, in addition to potential FGF-related problems. In addition, these compounds present less bioactivity in terms of their actions against FGFR. On the basis of these considerations, the development of strongly bioactive, highly selective FGFR inhibitors is of greater need than multitarget inhibitors. Nevertheless, the most impressive antitumor activity to date has been observed with multitarget kinase inhibitors in patients presenting genomic alterations in the FGF pathway (78, 85). In addition, multitarget inhibitors are more advanced in the clinical development process, as dovitinib is part of a phase III registration trial for kidney cancer treatment and a phase II randomized trial for breast cancer treatment.

Overall, these considerations suggest that multitarget kinase inhibitors will be the first-in-class to gain approval. Highly bioactive FGFR inhibitors (e.g., BGJ398 and AZD4547) will come later and could prove to be interesting choices when combination therapies are needed. Indeed, they present FGFR-specific toxicity profiles that could favor their use in drug combinations. In contrast, the broad nonspecific toxicity profile of multitarget TKIs makes them difficult to include in drug combinations.

Managing Long-Term Toxicities of FGFR Inhibition

Given the multiple recognized physiologic functions of FGF/FGFR signaling and the suggested oncosuppressive role of FGF/FGFR activation in some contexts, the feasibility of a long-term FGF pathway inhibition is questionable. This issue will be investigated in ongoing studies; however, some efforts are currently under development. Anti-FGFR antibodies that target a single FGF or FGFR could offer an alternative and may display a more narrow range of toxicity as compared with pan-FGFR inhibitors. An additional suggestion aimed at avoiding continuous pan-FGFR inhibition could be the provision of therapeutic windows by continuing other treatments that target additional downstream kinases, such as MAPK.

Developing Third-Generation Angiogenesis Inhibitors

The identification of the most effective timing for adding FGF/FGFR inhibitors to VEGF inhibitors is an emerging area of interest. Current research has not elucidated whether targeting FGF signaling is more effective in the front-line setting or after the failure of a regimen of sunitinib or bevacizumab. Although inhibition of the VEGF and FGF pathways has been shown to be synergistic, preclinical and clinical evidence suggests that FGF levels increase at the time of anti-VEGF resistance, thereby suggesting that the addition of FGFR inhibitors at the time of the failure of anti-VEGF treatment, rather than upfront, makes the most clinical sense. From this perspective, it would be unlikely to expect great differences in terms of efficacy through a head-to-head, first-line drug comparison. Hence, the initial development of FGF inhibitors at the time of PD during VEGF exposure has the strongest basis. Optimally, eligible patients could be selected on the basis of FGF levels. In contrast, a

current, ongoing debate rages over whether treatment with an antiangiogenic drug may alter disease biology by making it more aggressive and finally hampering survival despite initial responses. Although the intrinsic mechanisms of this suggested “rebound” process are not completely clear, we can postulate that an upfront dual targeting of VEGF and FGF might help to prevent it. To better address these issues, researchers need to develop more representative preclinical models that have the increased capability to provide results that can be translated into the clinical setting. Furthermore, biomarker studies must be prioritized, and assays must be developed to better characterize the role of FGF-dependent angiogenesis during the different phases of diseases and its relationship with other angiogenic pathways. This practice will allow researchers to better define the clinical settings and study populations for further anti-FGF drug development.

Combining FGFR and Other Kinase Inhibitors

FGFR alterations in cancer can be associated with the activation of other oncogenic drivers. For example, *FGFR1* is frequently coamplified with *CCND1* on 11q mainly in luminal breast cancers. Evidence from breast cancer cell line assays shows a substantial functional interaction between the genes on 8p11-12q and their cooperation with major oncogenic pathways. These findings may represent the basis for the development of novel drug combinations, including an FGFR inhibitor and a CDK4 inhibitor (92). In addition, ER-positive breast cancers present a high frequency of *PIK3CA* mutations, and studies to evaluate whether these cases are more numerous in *FGFR1*-amplified breast cancer samples are ongoing. Such findings could provide a rationale to combine PI3K inhibitors and FGFR inhibitors in a treatment regimen. Such a combination may deserve evaluation even in the triple-negative breast cancer group and, more specifically, in the subtype showing mesenchymal features. Indeed, mesenchymal-like triple-negative cells may contain more FGF/FGFR pathway components and show sensitivity to PI3K inhibition (42, 51). One of the most evident mechanisms of endocrine resistance is the activation of the PI3K/AKT/mTOR pathway; thus, mTOR inhibitors (everolimus) will soon become a standard of care in ER-positive breast cancer. Further studies will evaluate to what extent FGFR1 could contribute to resistance to everolimus and whether evidence suggests the need to combine everolimus with FGFR inhibitors.

Additional data support the combination of FGFR and kinase inhibitors. Cancer cell line assay results suggest that cooperation exists between FGFR and receptors of the EGFR family in oncogenesis (20). Overexpression and activation of FGFR1 and HER2 have been observed in breast cancer, and the combined inhibition of both receptors led to a stronger antitumor activity compared with each treatment alone in a mouse model (93). In addition, we described different mechanisms by which FGFR signaling could contribute to resistance to available targeted treatments, such as anti-EGFRs (e.g., vemurafenib and imatinib), and future research must determine the optimal selection of the most appropriate combinations from the pool of new molecularly targeted agents.

Finally, targeted drugs may not be the only potential candidates for association with anti-FGFRs, as preclinical assays found increased levels of FGFR4 in chemotherapy-resistant breast cancer cell lines as a result of ectopic endogenous expression. Indeed, treatment with an anti-FGFR4 antibody restored sensitivity to chemotherapy-induced apoptosis (94).

Identifying Resistance to FGFR Inhibitors

Deeper insight into tumor biology from the performance of biomarker analysis is required not only to identify markers for sensitivity to FGFR inhibition but also to define possible markers of anti-FGFR resistance at earlier stages. As previously stated, cross-talk with other oncogenic or angiogenic pathways has been proposed; therefore, adaptation mechanisms that involve the activation of other downstream or parallel signals may occur, and those parallel signals may be targeted by different agents. Studies of tumor tissue evaluations before and after anti-FGFR treatments are preferred. In this context, the neoadjuvant setting can help in *in vivo* evaluating drug effects.

CONCLUSIONS

FGF/FGFR oncogenic driver alterations have been shown to define tumor segments across various cancer types. Moreover, the activation of the FGFR pathway may provide the means to resistance against the available targeted and antiangiogenic drugs. To date, data from phase I/II trials suggest that FGFR inhibitors actually present antitumor activity and should move to further steps in the clinical development process. The complex rationale for targeting the FGF/FGFR pathway in human cancer also recognizes current challenges in the drug development process. The following 3 major areas must be addressed: identifying ways to develop drugs in rare genomic segments; developing compounds that overcome resistance to conventional agents; and better targeting of the host (e.g., through angiogenesis). Implications for clinical trial design include the following: correct selection of study populations (e.g., through molecular screening programs or resistance under previous targeted treatments), development of feasible combination/sequential drug schedules, and completion of biomarker analysis for deeper insight into resistance mechanisms. Finally, a potent continuous blockage of the FGF pathway, which controls different fundamental physiologic processes, may represent an obstacle to drug development; therefore, management protocols for these emerging class toxicities are needed.

Disclosure of Potential Conflicts of Interest

F. Andre has received honoraria for serving on the speakers' bureau for Novartis and AstraZeneca and is a consultant/advisory board member for Novartis, AstraZeneca, and EOS. J.C. Soria has served as a consultant or advisory board member for EOS and AstraZeneca. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: F. Andre, M. Arnedos, J.C. Soria

Development of methodology: M. Arnedos

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.-C. Soria

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): F. Andre

Study supervision: F. Andre

Writing, review, and/or revision of the manuscript: M.V. Dieci, M. Arnedos, J.-C. Soria

Received August 1, 2012; revised November 27, 2012; accepted November 30, 2012; published OnlineFirst February 15, 2013.

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Cancer Discovery 2013;3:264-279. Published OnlineFirst February 15, 2013.

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