Review

Clinical Cancer Research

Targeting FGFR Signaling in Cancer

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Abstract

The fibroblast growth factor signaling pathway (FGFR signaling) is an evolutionary conserved signaling cascade that regulates several basic biologic processes, including tissue development, angiogenesis, and tissue regeneration. Substantial evidence indicates that aberrant FGFR signaling is involved in the pathogenesis of cancer. Recent developments of deep sequencing technologies have allowed the discovery of frequent molecular alterations in components of FGFR signaling among several solid tumor types. Moreover, compelling preclinical models have demonstrated the oncogenic potential of these aberrations in driving tumor growth, promoting angiogenesis, and conferring resistance mechanisms to anticancer therapies. Recently, the field of FGFR targeting has exponentially progressed thanks to the development of novel agents inhibiting FGFs or FGFRs, which had manageable safety profiles in early-phase trials. Promising treatment efficacy has been observed in different types of malignancies, particularly in tumors harboring aberrant FGFR signaling, thus offering novel therapeutic opportunities in the era of precision medicine. The most exciting challenges now focus on selecting patients who are most likely to benefit from these agents, increasing the efficacy of therapies with the development of novel potent compounds and combination strategies, and overcoming toxicities associated with FGFR inhibitors. After examination of the basic and translational research studies that validated the oncogenic potential of aberrant FGFR signaling, this review focuses on recent data from clinical trials evaluating FGFR targeting therapies and discusses the challenges and perspectives for the development of these agents. *Clin Cancer Res; 21(12); 2684–94. ©2015 AACR.*

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Learning Objectives

Upon completion of this activity, the participant should have a better understanding of the biologic rationale for targeting the FGFR signaling pathway in cancer, and of the different approaches currently under clinical development.

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Introduction

Fibroblast growth factors (FGF) and their receptors (FGFR) regulate a wide range of physiologic cellular processes, such as embryonic development, differentiation, proliferation, survival, migration, and angiogenesis. FGFR signaling components are frequently altered in human cancer, and several preclinical models have provided compelling evidence for the oncogenic potential of aberrant FGFR signaling in carcinogenesis, thereby validating FGFR signaling as an attractive target for cancer treatment. Depending on the type of genomic aberration and the cellular context, the oncogenic potential of dysregulated FGFR signaling ranges from a driver event—responsible for oncogenesis and oncogene addiction—to an escape mechanism of secondary acquired resistance to other anticancer agents.

FGFR Signaling Pathway

FGFRs are transmembrane, receptor tyrosine kinases (RTK) consisting of three extracellular immunoglobulin-like domains

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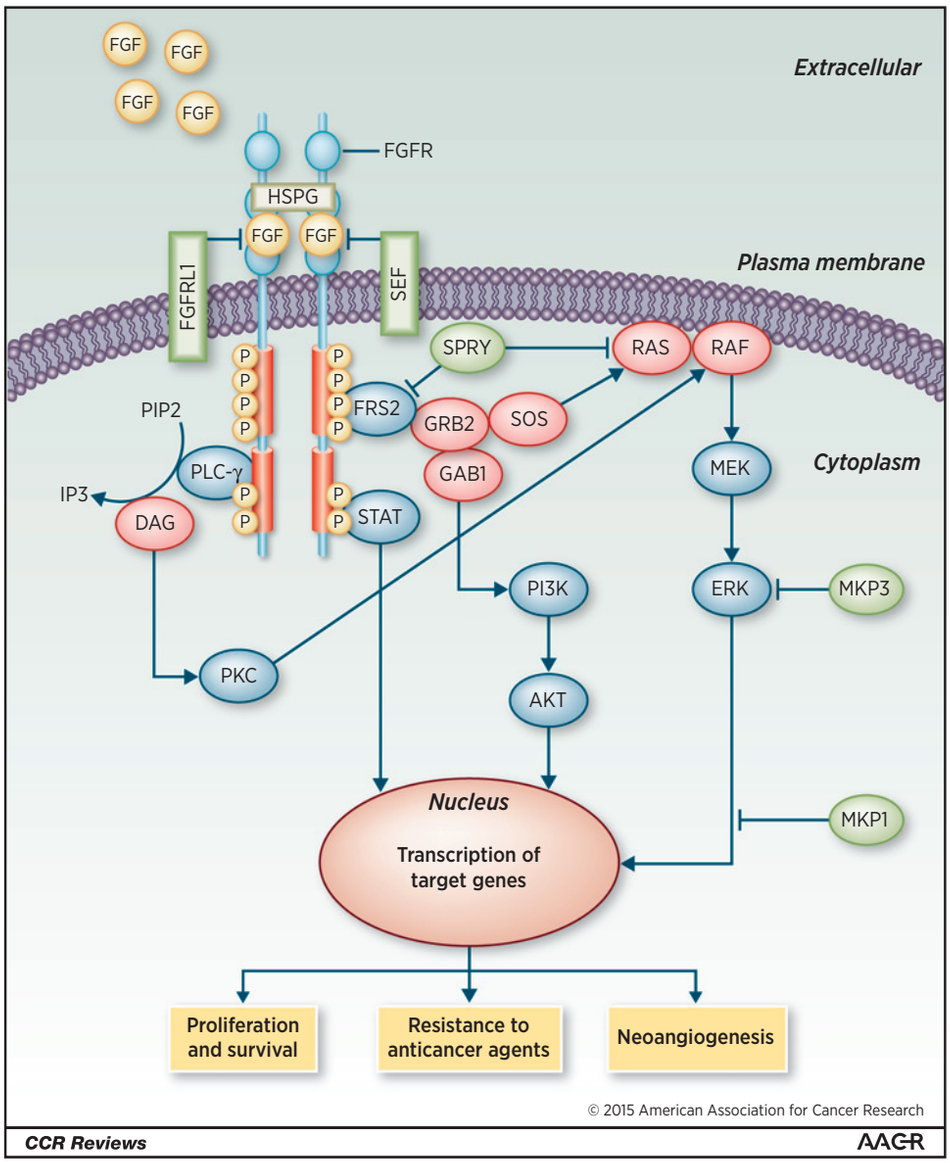

Figure 1.
FGFR structure, network, and dysregulation in cancer. FGFRs are transmembrane RTKs consisting of three extracellular immunoglobulin-like domains and one intracellular split tyrosine kinase domain. A complex is formed among FGF, HSPG, and FGFR leading to receptor dimerization, and transphosphorylation of tyrosine kinase domains. Activation of downstream signaling occurs via FRS2, which functions as a key adaptor protein associated with GRB2, resulting in subsequent activation of MAPK and PI3K/AKT signaling pathways. 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-tri-phosphate (IP3) and diacylglycerol (DAG), thus activating protein kinase C (PKC), which converges with the MAPK pathway. Depending on the cellular context, several other pathways may be activated by FGFRs, including the p38 MAPK and Jun N-terminal kinase pathways, STAT signaling, and ribosomal protein S6 kinase 2 (RSK2). Multiple negative regulators may attenuate signaling at different levels, including FGFRL1, SEF, SPRY, and MAPK phosphatase 1 and 3 (MKP1 and MKP3). Aberrant FGFR signaling may result from (i) increased availability of FGFs (secreted by tumor or stromal cells) leading to ligand-dependent FGFR signaling (autocrine/paracrine loops), or (ii) ligand-independent FGFR signaling when a molecular alteration of an *FGFR* (mutation, translocation, or amplification) induces a constitutive activation of the kinase domain.

and one intracellular split tyrosine kinase domain (1, 2). In contrast with the multiple fibroblast growth factor (*FGF*) genes encoding 22 functionally distinct ligands, only four different *FGFRs* (*FGFR1–4*) are known. However, alternative splicing events of FGFR1–3 allow the generation of multiple isoforms, presenting a dramatically variable FGF-binding specificity (3). FGFs are secreted glycoproteins that are readily sequestered by the extracellular matrix and the cell surface by heparan sulfate proteoglycans (HPSG), which stabilize the FGF–FGFR interaction by protecting FGFs from protease-mediated degradation. The binding of an FGF to an FGFR leads to receptor dimerization and transphosphorylation of tyrosine kinase domains (Fig. 1;

refs. 4, 5). Activation of downstream signaling occurs via the intracellular receptor substrates FGFR substrate 2 (FRS2) and phospholipase Cγ (PLC-γ), leading to subsequent upregulation of RAS/mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/AKT signaling pathways. Other pathways can be activated, including STAT-dependent signaling (Fig. 1; refs. 1–5).

Dysregulation of FGFR Signaling in Human Malignancies

Aberrant FGFR signaling contributes to carcinogenesis in three main situations: (i) "driver mutations," where the acquisition of somatic molecular alterations directly stimulates cancer cell proliferation and survival; (ii) neoangiogenesis; and (iii) resistance to anticancer agents (1–5).

Molecular alterations of the FGFR signaling pathway as driver events: the oncogene addiction phenomenon

FGFR family fusion genes. Fusion genes are hybrid genes formed by the rearrangement of two previously independent genes. They can occur as a result of translocation, chromosomal inversion, duplication, or deletion. Several fusion proteins are known to play crucial roles in the initiation and progression of cancer, thereby representing ideal targets for rational drug design strategies. Examples of success include targeting BCR–ABL1 with imatinib (6) in chronic myeloid leukemia, PML–RARA with tretinoin in acute promyelocytic leukemia (7), or the EML4–ALK with crizotinib in lung adenocarcinoma (8).

Many recent efforts of molecular screening programs and precision medicine have allowed the identification of multiple fusion genes between *FGFR1*, *-2*, and *-3* and multiple partners (including *TACC1*, *TACC3*, *BAIAP2L1*, *BICC1*, and *AHCYL1*) in several malignancies such as glioblastoma, urothelial bladder carcinoma, non–small cell lung cancer (NSCLC), and cholangiocarcinoma (Table 1; refs. 9–15). Although a substantial effort remains to be achieved to delineate real drivers from passenger fusions, there is robust preclinical and clinical evidence supporting the oncogenic potential of these rare alterations. The underlying mechanisms, which vary according to the specific cellular context, include (i) ligand-independent activation of the FGFR kinase domain, resulting in constitutive activation of downstream MAPK signaling (9, 14, 15); (ii) mislocalization of the fusion protein to mitotic spindle poles resulting in increased chromosomal instability (9); and (iii) loss of genomic regulatory elements or fusion to a gene with a strong promoter resulting in overexpression of the fusion protein (10, 15).

Fusions involving *FGFR3* and *TACC3* (transforming acidic coiled-coil containing protein 3) are found in 3% to 7% of glioblastomas (9–11), 3% to 6% of urothelial bladder carcinomas (14–16), and other tumor types at lower frequencies (12–15). In mouse xenograft models, the induction of *FGFR3--TACC3* expression in human astrocytes resulted in the development of glioma-like tumors (9). *In vivo*, both *FGFR3–TACC3*–initiated bladder carcinoma (15) and glioblastoma (9) were extremely sensitive to specific FGFR inhibitors, suggesting oncogenic addiction to the fusion protein.

In intrahepatic cholangiocarcinoma, *FGFR2* fusions with either *AHCYL1* or *BICC1* have been described in 13.6% of cases and are mutually exclusive with *KRAS*/*BRAF* mutations (17). *In vivo* models demonstrated the transforming potential of these alterations, and high sensitivity to FGFR inhibitors (17).

These preclinical data provide a strong rationale for enrolling patients with tumors harboring *FGFR* fusions in clinical trials evaluating FGFR inhibitors, and preliminary data from early-phase trials are very encouraging (18).

FGFR-activating mutations. The screening of more than 1,000 exon mutations of protein kinase genes from 210 different malignancies (19) identified the FGFR signaling pathway as the most commonly mutated tyrosine kinase signaling pathway. Activating mutations in *FGFRs* may result in aberrant FGFR signaling through multiple mechanisms, including the following: (i) enhanced activation of the kinase domain; (ii) ligand-independent dimerization of the receptors; and (iii) altered affinity for FGF ligands.

Urothelial bladder carcinoma has the most established association with altered FGFR signaling, with up to 80% of low-grade tumors harboring *FGFR* mutations and compelling *in vivo* and *in vitro* data (Table 1). Comprehensive molecular characterization of this cancer (16) revealed a cluster of tumors with papillary morphology characterized by a high rate of molecular alterations of *FGFR3* (mutations, copy number gain, fusions), which may have some degree of FGFR addiction (Table 1; refs. 20–28). The most common activating mutations affect either the extracellular (R248C, S249C) or the transmembrane (G370C, S371C, Y373C, G380R, A391E) domains of the protein. Kinase domain mutations (N540S, K650E, K650M, K650N, K650Q, and K650T) are rarer.

FGFR2 mutations have been found in 12% to 14% of endometrial cancer (29–31) and mainly consist of missense activating mutations of the extracellular domain (S252W, P253R). *In vitro* and *in vivo* models demonstrated the selective sensitivity of *FGFR2*-mutant endometrial cancer to FGFR inhibitors (29, 31–34).

Activating mutations of *FGFR4* (affecting the kinase domain) are found in 6% to 8% of patients with rhabdomyosarcoma (35, 36). In a comprehensive genomic analysis of 147 cases of rhabdomyosarcoma, FGFR signaling was the most significantly altered pathway in both fusion-positive and fusion-negative rhabdomyosarcomas. Cell lines and explants harboring *FGFR4*-activating mutations were both sensitive to FGFR inhibitors (36, 37).

FGFR overexpression. Overexpression of *FGFRs* may lead to ligand-independent FGFR signaling and is mainly caused by focal amplifications.

FGFR1 amplification has been found in approximately 7% to 20% of squamous non–small cell lung carcinoma (NSCLC; refs. 38, 39), 18% of osteosarcoma, and 6% of small-cell lung carcinoma (40), and is associated with sensitivity to FGFR inhibitors in preclinical *in vivo* models (refs. 38, 41, 42; Table 1). In breast cancer, amplification of *FGFR1*- and/or 11q12-14 (which contains *CCND1*, *FGF3*, *FGF4*, and *FGF19*) have been observed in 23% of hormone receptor-positive (HR^+), 27% of *HER2*-amplified, and 7% of triple-negative cases and is predictive for early relapses and poor outcome (43–47). Many *FGFR1*-amplified breast cancer cell lines are addicted to *FGFR1* amplification (45, 48, 49), and *FGFR1* amplification also drives resistance to endocrine therapy (48).

FGFR2 amplification (4% of triple-negative breast cancer, 4%–9% of gastric cancers) is associated with the maintenance of

Table 1. Common genetic alterations in FGFRs related to cancer and evidence for oncogenic potential of altered FGFRs

Molecular alteration	Tumor (prevalence, if known; refs.)	Consequences in preclinical models (tumor model; refs.)	Evidence of antitumor activity in clinical trials (refs.)
FGFR1 translocation	Glioblastoma (na; ref. 9) Breast cancer (na; ref. 15) Lung squamous cell carcinoma (na; ref. 15) 8p11 myeloproliferative syndrome (na; ref. 1)	Transforming potential, confer sensitivity to FGFR inhibitors (glioblastoma *in vivo* models; ref. 9)	na
FGFR1 mutation	Pilocytic astrocytoma (5%–8%; ref. 83) Gastric cancer (4%)	Transforming potential (pilocytic astrocytoma; ref. 83)	na
FGFR1 amplification	Small cell lung carcinoma (6%; ref. 40) Osteosarcoma (17%; refs. 3, 4) Breast cancer (10%–15%; refs. 43–47) Ovarian cancer (5%; refs. 3, 4) Squamous cell carcinomas: - Lung (7%–15%; refs. 38, 39) - Head and neck (10%–17%; ref. 3) - Esophageal (9%; ref. 3)	Transforming potential in several *in vivo* models, confer sensitivity to FGFR inhibitors (refs. 38, 42, 44, 48, 53) Drives resistance to endocrine therapy (HR^+ breast cancer), and to gefitinib (*EGFR*-mutant lung adenocarcinoma; refs. 38, 48, 63)	PRs mainly in patients with lung squamous cell carcinomas; little evidence supporting oncogene addiction in esophageal and breast cancers (refs. 41, 66, 71, 74)
FGFR2 translocation	Intrahepatic cholangiocarcinoma (14%; refs. 15, 17) Prostate cancer (na; ref. 15) Breast cancer (na; ref. 15)	Transforming potential, sensitivity to FGFR inhibitors (cholangiocarcinoma; refs. 15, 17)	PR in a patient with cholangiocarcinoma (ref. 74)
FGFR2 mutation	Endometrial cancer (12%–14%; refs. 30, 31) Squamous non–small cell lung carcinoma (5%; ref. 4)	Confer sensitivity to FGFR inhibitors (endometrial; refs. 29, 31–34)	na
FGFR2 amplification	Gastric cancer (5%–10%; refs. 51, 52) Breast cancer (4%; ref. 50)	Confer sensitivity to FGFR inhibitors; refs. 50–52)	na
FGFR3 translocation	Bladder carcinoma (3%–6%; refs. 14–16) Glioblastoma (3%; refs. 9–11) Myeloma (15%–20%; ref. 4) Lung adenocarcinoma (0, 5%; ref. 13) Squamous cell carcinomas: - Lung (3%; refs. 12, 13) - Head and neck (na; ref. 15)	Transforming potential, confer sensitivity to FGFR inhibitors (bladder carcinoma, glioblastoma; refs. 9–11, 14, 15)	PRs in patients with bladder cancer; clinical benefit with stabilization in patients with recurrent glioblastoma (refs. 11, 18)
FGFR3 mutation	Bladder carcinomas (60%–80% in non–muscle-invasive, 15–20% in muscle-invasive; refs. 16, 20–22, 24, 25) Cervical cancer (5%; ref. 4)	Transforming potential, confer sensitivity to FGFR inhibitors (refs. 21, 26–28)	PRs in patients with bladder cancer (ref. 74)
FGFR3 amplification	Bladder carcinoma (na; ref. 4) Salivary adenoid cystic cancer (na; ref. 4)	na	na
FGFR4 mutation	Rhabdomyosarcoma (6%–8%; refs. 35, 36)	Transforming potential, confer sensitivity to FGFR inhibitors (refs. 36, 37)	

Abbreviations: na, not available; PR, partial response.

tumor-initiating cells (50), poorer prognosis (51, 52), and high sensitivity to FGFR inhibitors (49, 50, 53).

Aberrant autocrine/paracrine loops. In addition to *FGFR* molecular alterations, multiple autocrine and paracrine loops involving FGFRs and FGFs ligands have been described in several cancer models (including NSCLC, hepatocellular carcinoma, breast, prostate, and colorectal cancers). Aberrant loops result from increased release of FGFs by tumor or stromal cells, promoting proliferation, survival, and angiogenesis. Interestingly, several studies have associated these aberrant loops with antitumor activity of either tyrosine kinase inhibitors (TKI) or antibodies directed against FGFR ligands (54–56). However, available data emerge mainly from preclinical work on cell line models, and further clinical confirmation is required.

The FGFR signaling pathway promotes tumor angiogenesis

Angiogenesis plays a pivotal role during tumor growth and tissue invasion. FGFs—and especially FGF2—are among the earliest identified proangiogenic factors, and they have a direct effect on tumor angiogenesis at all steps of angiogenesis (5, 57, 58). Endothelial cells express FGFR1 more often than FGFR2, while the expression of FGFR3 or FGFR4 has not been reported (5). The activation of FGFR1 and/or FGFR2 signaling in

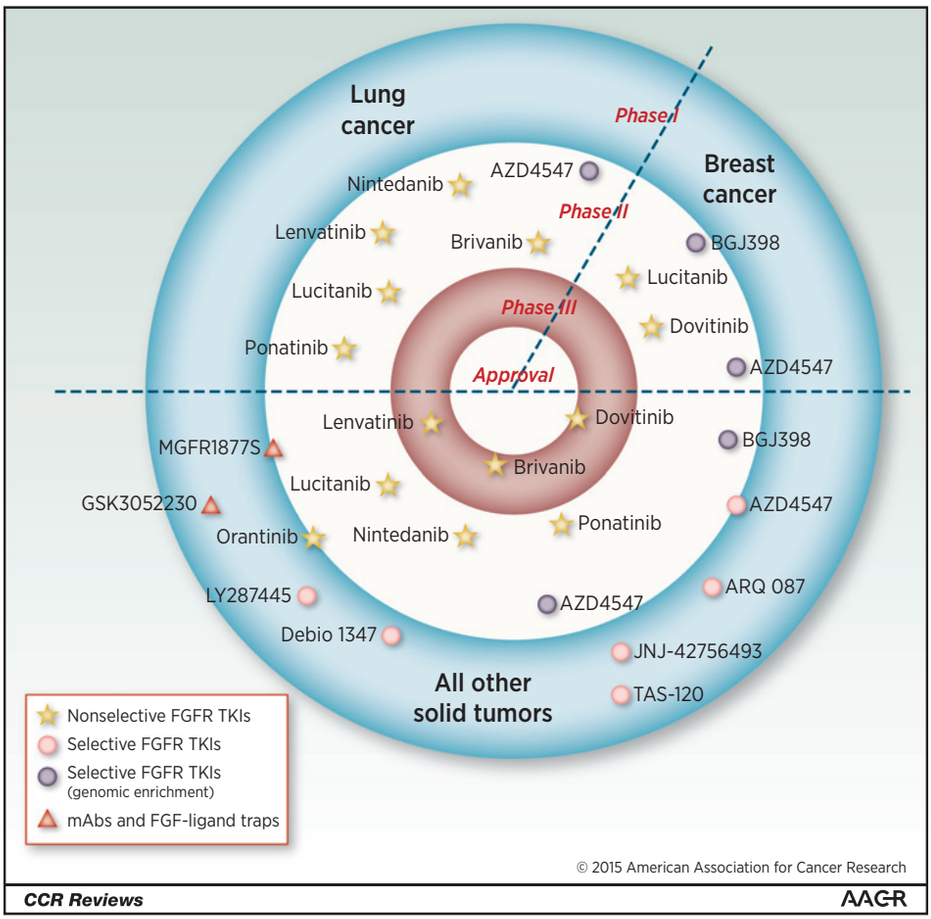

Figure 2.
Selected overview of clinical trials evaluating FGFR signaling–targeted therapies currently under development (monotherapy). Whereas several nonselective FGFR inhibitors have entered phase II/III trials, selective FGFR inhibitors are mostly in early-phase development programs. Phase II trials with genomic enrichment are ongoing with the selective FGFR inhibitors AZD4547 and BGJ398.

tumor cells may also play a critical role in the development and maintenance of the tumor vasculature, as suggested by preclinical models of triple-negative breast cancer and mouse glioma (59).

In addition to its direct proangiogenic effects, FGFR signaling indirectly activates the VEGFR signaling pathway and synergizes with VEGFR and platelet-derived growth factor receptor (PDGFR) pathways to promote tumor neoangiogenesis (5, 60). The complementary and overlapping functions of the FGFR and VEGF pathways in angiogenesis have suggested that FGFR signaling dysregulation may mediate resistance to anti-VEGF therapy. Interestingly, increased FGF2 levels have been reported in patients with various tumor types who exhibited disease progression while receiving VEGF-targeted therapies (61), and results from preclinical studies have suggested that targeting FGFR could be one effective strategy to restore sensitivity to antiangiogenic agents in patients progressing on anti-VEGF therapy (62).

The FGFR signaling pathway mediates resistance to anticancer therapy

Significant cross-talk between FGFR signaling and other oncogenic pathways may explain the role of FGFR signaling in the development of acquired resistance to anticancer therapies. For example, the activation of an FGF2–FGFR1 autocrine pathway has recently been proposed as a mechanism of acquired resistance to EGFR-specific TKIs in NSCLC–adenocarcinoma *EGFR*-mutant cell lines (63). Other studies have proposed FGFR3 activation as a mechanism of acquired resistance to cetuximab in *KRAS* wild-type squamous cell carcinoma (skin) and to vemurafenib in *BRAF* (V600E)-mutant melanoma cells (64, 65).

Also, *FGFR1* amplification may drive the proliferation of luminal B type breast cancer and promote resistance to hydroxytamoxifen, as the suppression of FGFR1 signaling by RNAi reverses this resistance (48). This possibility is currently being evaluated in clinical trials combining FGFR inhibitors (AZD4547) and endocrine therapy in estrogen receptor–positive (ER^+) breast cancer (NCT01202591).

Overall, compelling evidence demonstrates the oncogenic role of aberrant FGFR signaling in several human malignancies. FGFR-targeted agents may therefore be used to counteract tumor growth, to target angiogenesis, and to reverse or prevent acquired resistance to anticancer drugs. Data from clinical trials of FGFR-targeted therapies and challenges to be faced in the development of such treatments are discussed below.

Clinical Trials Evaluating FGFR-Targeted Agents

Recently, the field of FGFR targeting has exponentially progressed, thanks to the development of novel agents inhibiting FGFs or FGFRs, including (i) nonselective and selective TKIs; (ii) monoclonal antibodies; and (iii) FGF ligand traps (Fig. 2).

Small-molecule TKIs targeting FGFRs

TKIs are small molecules that directly inhibit receptor kinase activity by interfering with the binding of ATP or substrates of the tyrosine kinase domain. For historical reasons, the most clinically advanced compounds are nonselective TKIs (including ponatinib, brivanib, nintedanib, lenvatinib, dovitinib, and lucitanib) that have dominant activity against other RTKs (mainly VEGFRs and PDGFRs, but also FLT3, RET, KIT, and BCR–ABL), and also exert activity against FGFRs due to structural similarity of their kinase domains. Because of the simultaneous targeting of VEGFR, PDGFR, and FGFR signaling pathways, these compounds are being developed mainly as antiangiogenic agents. Although simultaneous inhibition of multiple RTKs may increase treatment efficacy by concomitant disturbance of redundant pathways, increased side effects also arise, and lack of bioactivity against FGFRs may limit their efficacy in tumors with aberrant FGFR signaling. This has justified the development of selective and highly potent FGFR TKIs (including JNJ-42756493, AZD4547, BGJ398, and TAS-120) with IC_{50} values below the nanomolar range for FGFRs (Fig. 2). Recent data from selected clinical trials evaluating FGFR TKIs are discussed below.

Nonselective FGFR TKIs. Lucitanib (E3810, Clovis Oncology) inhibits mainly VEGFR1-3, PDGFR-α/β, and FGFR1 (66, 67). In the phase I/II trial, 50% of patients with breast cancers harboring *FGFR1* and/or *FGF3/4/19* amplifications, or with tumors anticipated, who were expected to benefit from antiangiogenic agents, achieved partial response (PR, RECIST 1.1; ref. 66). This impressive efficacy was observed at all doses tested, with durable PRs in several tumor types (10/58 evaluable patients still in response after 1 year of treatment). The main dose-limiting toxicity (DLT) was glomerular thrombotic microangiopathy. Phase II trials are ongoing in HR^+ metastatic breast cancer (NCT02053636) and in *FGFR1*-amplified squamous-NSCLC (NCT02109016).

Dovitinib (TKI258, Novartis) exhibits biochemical IC_{50} values that are below 20 nmol/L for VEGFR1–3, PDGFR-β, FGFR1 and -3, FLT-3, KIT, RET, TrkA, and CSF-1 (49). After observation of antitumor activity in the phase I study patients with renal cell carcinoma (RCC; ref. 68), the phase II study demonstrated a progression-free survival (PFS) duration of 5.5 months and an overall survival (OS) duration of 11.8 months in patients with RCC (69). Sorafenib was selected as comparator in the phase III trial given the similar target profile between the two drugs. This study randomized 570 patients in the third-line setting (70). Although the study's results were negative, not showing an improvement in PFS with dovitinib over sorafenib, important data were generated. This trial established for the first time the activity of TKIs in the third-line setting in patients with RCC, and provided benchmark values for PFS (nearly 4 months) and OS (11 months). In a phase II trial, dovitinib showed antitumor activity in heavily pretreated breast cancer patients, but failed to reach its primary endpoint of improved overall response rate in the genomically selected arm (*FGFR1*-amplified tumors; ref. 49).

Ponatinib (AP24534, ARIAD Pharmaceuticals) is a multikinase inhibitor of BCR–ABL, LYN, FGFR1–2, VEGFR2, PDGFR-α, and KIT. In the phase II trial of ponatinib, 66% of patients with refractory chronic myeloid leukemia (CML) and Philadelphia-positive (Ph^+) acute lymphoblastic leukemia (ALL) showed a major cytogenetic response. Ponatinib was appoved by the FDA for patients with resistant or intolerant CML and Ph^+ ALL based on results of the PACE phase II trial (3, 4).

Other nonselective TKIs, such as nindetanib (BIBF1120, Boehringer-Ingelheim), brivanib (BMS582664, Bristol-Myers Squibb), lenvatinib (E7080, Eisai), and orantinib (TSU-68, Taiho Pharmaceutical) exert anti-FGFR activity but mainly target other kinases (refs. 1–4; Fig. 2).

Selective FGFR TKIs. JNJ-42756493 (Johnson & Johnson) is a potent oral pan-FGFR inhibitor with IC_{50} values in the low nanomolar range for FGFR1, -2, -3, and -4. Preliminary results from the ongoing phase I trial are available. Clinical benefit was documented in patients with tumors harboring *FGFR3–TACC3* fusions (long-lasting PR in 1 bladder urothelial carcinoma and stabilization in 2 recurrent glioblastoma; refs. 11, 18), and 1 near complete response was observed in a patient with a urothelial cancer of the renal pelvis harboring FGFR2 truncation. Four patients with *FGFR1* amplification achieved stable disease [SD; lung cancer ($n = 2$), chondrosarcoma ($n = 1$), and breast cancer ($n = 1$)]. The most common ($\geq$20% of patients) adverse events (AE) were hyperphosphatemia (60%), asthenia (46%), dry mouth (30%), constipation (27%), abdominal pain, stomatitis, and vomiting (22% each). Toxicity was grade ≤ 2 in all cases. Ten (27%) patients had grade ≥ 3 toxicities, and 1 grade 3 DLT (AST/ALT elevation) was documented at the 12-mg dose (18). Expansion stage of the study is ongoing.

AZD4547 (AstraZeneca) is a highly potent and selective FGFR1–3 inhibitor. During the phase I trial, minimal activity was observed in 5 of 20 patients with tumors harboring FGFR signaling aberrations. Efficacy was higher in patients with a high level of *FGFR* amplification (ratio FGFR:Centromeric probe ≥ 3.0; refs. 71–73). Two randomized phase II trials will evaluate the safety and efficacy of AZD4547 in patients with *FGFR1*-amplified gastric/esophagogastric cancers (NCT01457846) and in *FGFR1*-amplified ER^+ breast cancer (NCT01202591).

BGJ398 (Novartis) is a selective inhibitor of FGFR1–3 (41, 74). Preliminary results (in 94 patients) of the ongoing phase I trial documented clinical benefit in 8 patients with tumors harboring FGFR signaling alterations (4 patients with *FGFR1*-amplified squamous-NSCLC achieved PRs, and 4 of 5 patients with *FGFR3*-mutant bladder carcinoma had tumor reductions), 4 of which lasted for more than 16 weeks. In addition, tumor reductions were observed in patients with cholangiocarcinoma with *FGFR2* fusion and *FGFR1*-amplified breast cancer (41, 74). AEs were generally mild (grade $\leq$ 2) and included dose-dependent hyperphosphatemia, diarrhea, fatigue, and nausea.

LY287445, and Debio 1347 are other selective FGFR TKIs that are currently being evaluated in phase I trials (3, 4). TAS-120 is a second-generation highly potent irreversible inhibitor selective of all FGFRs (75) currently being evaluated in a phase I trial.

Monoclonal antibodies and FGF ligand traps

Monoclonal antibodies (mAb) targeting FGFs or FGFRs can block FGFR signaling by interfering with ligand binding or receptor dimerization. mAbs target specifically particular FGF or FGFR isoforms due to the high specificity of antigen–mAb interactions, which might limit the AEs associated with the inhibition of FGFR signaling.

MFGR1877S (Genentech) is a human anti-FGFR3 mAb that showed antitumor activity in preclinical models of bladder cancer with *FGFR3* overexpression. Two phase I studies of MFGR1877S in patients with advanced solid tumors or myeloma have been completed. A preliminary report on the solid tumor study

documented long-lasting stabilization in 4 of 10 patients with bladder cancer. The DLT was thrombocytopenia in 1 patient, and a recommended phase II dose was determined (76). Further clinical development of MFGR1877S or other mAbs targeting FGFR signaling is unknown at this time.

FGF ligand traps sequester FGF ligands, blocking their ability to bind to and activate FGFRs. FP-1039 (GSK3052230, GlaxoSmithKline) is a soluble fusion protein consisting of the extracellular domain of FGFR1c fused to the Fc region of IgG1 that prevents binding of FGF1, FGF2, and FGF4 (77). A phase II trial in patients with endometrial cancers harboring specific *FGFR2* mutations was withdrawn because of unfeasibility (after screening of 70 patients, none qualified; NCT01244438). A phase I trial is currently evaluating FP-1039 in association with chemotherapy in patients with lung cancer (NCT01868022).

Development of FGFR-Targeted Therapies: Current State of the Art and Challenges

Lessons learned from the clinical development of FGFR inhibitors

Preliminary data from early-phase trials evaluating FGFR inhibitors have provided substantial information. First, proof-of-concept of an effective inhibition of FGFR signaling by TKIs in patients with cancer has been achieved, and increased serum FGF23, phosphate, and vitamin D levels have been identified as potential pharmacodynamic markers associated with on-target effect (18, 71, 74). Second, the safety and feasibility of FGFR targeting have been demonstrated, with several phase I/II trials reporting manageable toxicities.

Third, evidence of oncogene addiction has been reported with highly specific inhibitors in patients with lung cancer and bladder carcinoma presenting *FGFR* alterations (18, 71, 74). Clinical benefit and tumor reduction were also reported in patients with glioblastoma and cholangiocarcinoma harboring *FGFR* translocations, and ongoing trials may help to validate the relevance of these targets. Nevertheless, only a small subset of patients presented objective response and the key challenge will be to identify biomarkers of primary resistance to better select patients who should be included in further phase III trials. One possible biomarker could be the level of amplification (71, 74). In breast cancer, there is little evidence supporting oncogene addiction in patients treated with AZD4547 and BGJ398, suggesting that targeting the *FGFR1* amplification itself is not enough to generate antitumor effects. Interestingly, when multikinase TKIs (targeting FGFRs, VEGFRs, and PDGFRs) were evaluated (lucitanib, and to a lesser extend dovitinib; refs. 49, 66), phase I/II trials reported convincing evidence of antitumor activity. This suggests a synergism between FGFR and VEGFR/PDGFR targeting (58–60). The mechanisms of this synergism are yet to be defined. In gastric cancers, there is no evidence that targeting *FGFR2* amplification will lead to antitumor effects.

Overall, the results obtained with FGFR inhibitors differ substantially from one tumor to another and from one drug family to another. This suggests that inhibitors in development may not have equivalent efficiency, and that *FGFR* alterations could have different biologic meanings according to tumor types. In a subset of lung cancer, bladder carcinoma, glioblastoma, and cholangiocarcinoma this alteration could be involved in cancer progression. In breast cancers, the *FGFR1* amplification could be involved in resistance to endocrine therapy and could confer some sensitivity to multikinase inhibitors. In gastric cancers, the evidence that *FGFR2* amplifications are drivers is lacking.

The main challenges will now be (i) the recognition of patients most likely to benefit from FGFR inhibitor; (ii) the choice of the most clinically relevant compound for registration, taking into account the selectivity of the agents, their potency at durably inhibiting specific FGFR alterations, and their toxicity profiles; and (iii) the design and implementation of rational combination strategies (Fig. 3). Results from ongoing phase I/II trials evaluating highly potent inhibitors will certainly clarify some of these unresolved questions. At this stage it is unclear whether some FGFR TKIs will reach the level of efficacy of imatinib in KIT-mutant gastrointestinal stromal tumors or the efficacy of EGFR–TKIs in EGFR-addicted NSCLC. Additional clinical data in appropriately selected patients and long-term findings will help in determining the best strategy to efficiently target FGFR signaling.

Identifying patients with tumors addicted to FGFR signaling and conducting clinical trials in patients presenting with low-frequency molecular alterations

FGFR signaling–related molecular alterations are found at relatively low frequencies in most tumors (Table 1), and molecular screening is therefore a crucial challenge for the development of FGFR inhibitors as patient selection is key in this context (Fig. 3). We can applaud that most phase I/II trials have endeavored to enroll patients harboring specific FGFR alterations, as this has allowed the identification of several hurdles for patient selection, which will hopefully expedite the development of these agents in later-phase trials. There is urgent need for validating clinically useful companion diagnostics, allowing detection of patients most likely to benefit (or not) from FGFR-targeted therapies, and/or enabling monitoring and optimization of response to treatment (78). The main challenges have included (i) determining optimal diagnostic procedures for FGFR molecular alterations, and standardizing the definition of *FGFRs* amplification; (ii) detecting rare-frequency fusion genes involving various partners; (iii) discriminating between passenger and driver alterations; and (iv) integrating the available information within a specific cellular and tumor heterogeneity context. In the context of low-frequency molecular aberrations, we will prioritize multiplex genetic testing that allows parallel screening of components of FGFR signaling, and other frequently altered pathways. This practice will certainly make it possible to increase the potential for detecting any targetable alterations in known cancer driver genes.

Identifying mechanisms of primary and acquired resistance to FGFR-targeted therapies and implementing combination strategies

Failure of FGFR TKIs may result from non–TKI-sensitizing genetic alterations, lack of efficacy of TKIs, altered drug influx/efflux, and emergence of subclonal resistant populations. Some preclinical studies have uncovered potential mechanisms of intrinsic or acquired resistance to FGFR inhibitors, including the following: (i) mutations in the tyrosine kinase domain (*FGFR2* N550K) that decrease the affinity of dovitinib to its binding domain (29); (ii) mutations of the ATP binding cleft ("gatekeeper residue"; *FGFR3* V555M; refs. 29, 79); and (iii) activation of the ERBB family members resulting in a switch from dependency from FGFR signaling to ERBB signaling, which can be overcome

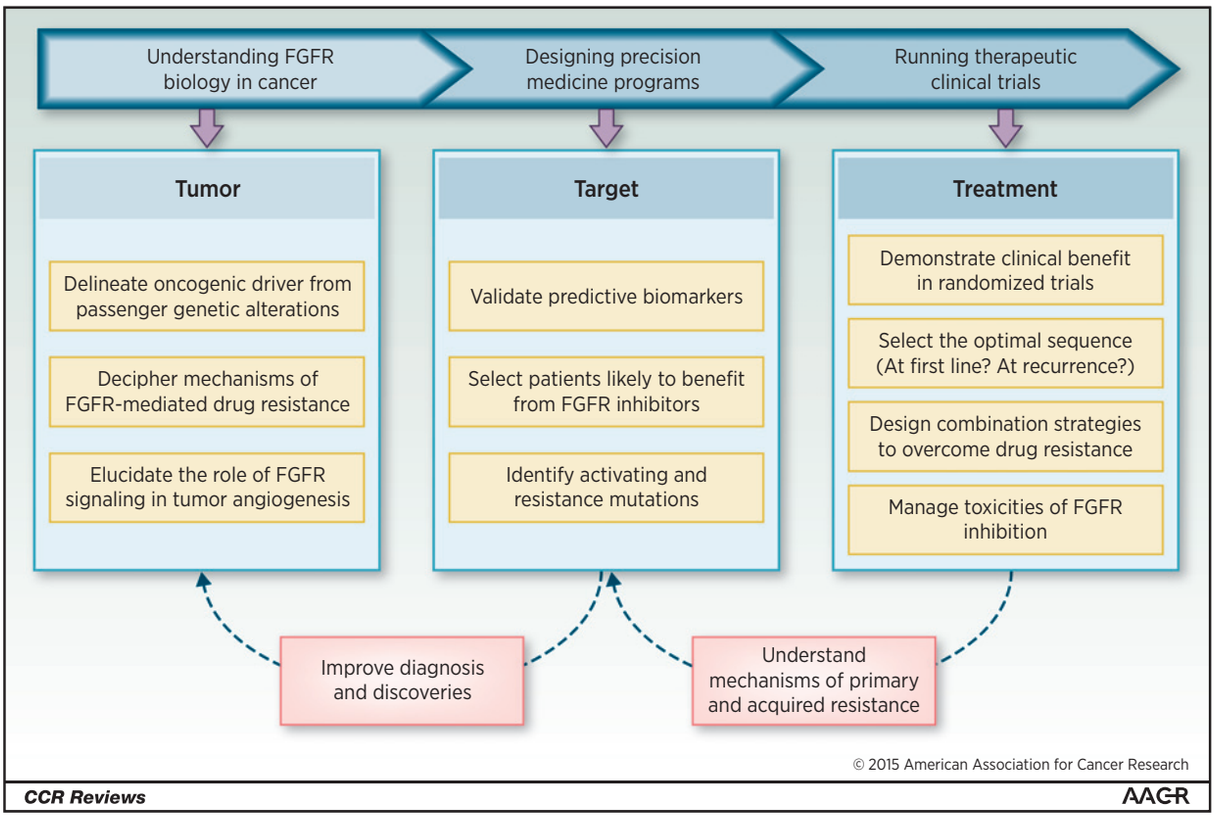

Figure 3.
FGFR research in cancer: from bench to bedside. Overview of challenges and prospects for the development of FGFR-targeted therapies.

with a combination of FGFR and EGFR inhibitors (28, 80). The variability of resistance mechanisms added to a context of tumor heterogeneity justifies consideration of biopsy in secondary resistant tumors to individualize subsequent treatment, as well as discovery of novel resistance mechanisms.

Combination strategies have been proposed to prevent or delay the emergence of resistance. For example, the combination of ponatinib and ridaforolimus in an endometrial xenograft model with an *FGFR2*-activating mutation resulted in superior efficacy and tumor regression (4). Also, *in vivo* models of breast cancer demonstrated that concomitant administration of dovitinib with either a PI3K/mTOR inhibitor or a pan-ERBB2 inhibitor resulted in strong inhibition of tumor growth and blocked metastatic spread (81). Finally, two recent preclinical studies showed that FGFR inhibition was synergistic with MET inhibition in xenograft models, and that FGFR inhibition could restore sensitivity to MET inhibition in tumor cells that acquired resistance to MET inhibitors (4).

Taking into account the currently available preclinical/clinical data, the most promising synergistic combination with minimally overlapping toxicities will associate FGFR inhibitors with (i) EGFR inhibitors (or inhibitors targeting other RTKs or downstream MAPK and PI3K/AKT signaling), (ii) endocrine therapy (ongoing trial NCT01202591 evaluating AZD4547 in combination with endocrine therapy in ER^+ breast cancer), (iii) anti-VEGF (this is achieved by multikinase inhibitors), or (iv) immunotherapeutics (82).

Managing toxicities of FGFR inhibition

Given the multiple physiologic functions of FGFR signaling, the feasibility of long-term FGFR signaling inhibition is questionable. Although nonselective FGFR inhibitors have toxicity profiles close to those for VEGFR TKIs, selective FGFR TKIs display their own class-specific toxicity related to a potent and specific FGFR signaling inhibition (Fig. 4). The main specific drug-related AEs observed to date are all mild and manageable, and include hyperphosphatemia, nail and mucosal disorder, fatigue, and reversible retinal pigmented epithelial detachment. In cases of long-term inhibition of FGFR signaling, these class-specific AEs may induce a clinically relevant deterioration in quality of life, and should therefore be prevented and optimally managed to avoid dose reductions.

Conclusions

Activation of the FGFR signaling pathway represents one of the founding events in carcinogenesis. Recent efforts in cancer research have enabled us to identify multiple oncogenic molecular alterations involving the FGFR signaling pathway across several malignancies. Given the established roles of aberrant FGFR signaling in oncogenesis, FGFR-targeted agents may be used to stunt tumor growth, to target angiogenesis, and to reverse acquired resistance to anticancer agents. Preliminary results from early development trials of FGFR inhibitors are very promising, with manageable toxicities and significant antitumor activity

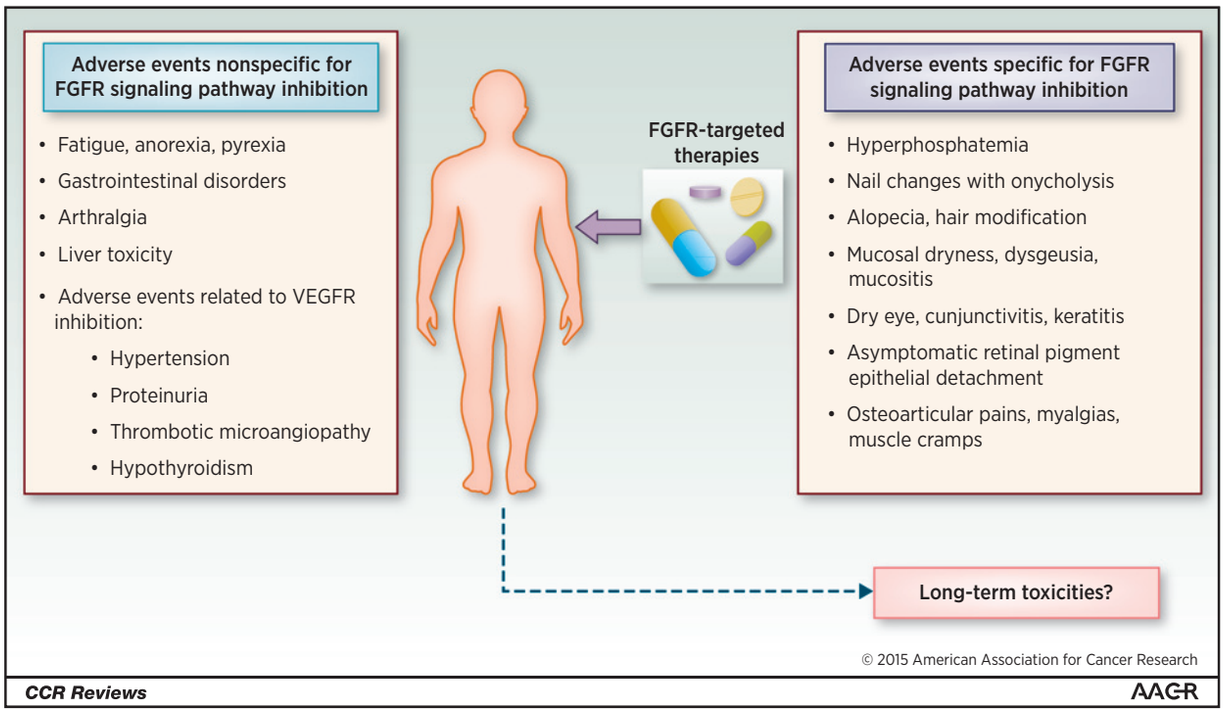

Figure 4.
Common AEs associated with selective and nonselective FGFR TKIs. AEs nonspecific for FGFR blockade are listed in the left box. These include common toxicities associated with TKIs and toxicities that are related to VEGFR inhibition (e.g., when a multikinase inhibitor exerts potent activity against VEGFRs). AEs specific for FGFR blockade are listed in the right box. Those are observed with TKIs that achieve potent inhibition of FGFR signaling (mainly selective TKIs). Hyperphosphatemia is the main AE associated with highly potent and selective FGFR TKIs. It can be managed through a phosphate-lowering diet and therapy (phosphate binders to decrease phosphate intestinal absorption) and interrupted schedules. Hyperphosphatemia requires regular monitoring of serum phosphate levels that should be maintained at <7 mg/dL to avoid soft tissue calcifications. Nail, hair, skin, and mucosal disorders are frequently observed with selective FGFR TKIs and require specific monitoring and treatment.

observed in molecularly selected populations, including patients with lung cancer, breast cancer, bladder carcinoma, glioblastoma, and cholangiocarcinoma, providing evidence of oncogene addiction. Efforts are needed to recognize patients most likely to benefit from FGFR inhibitors, to validate clinically useful companion diagnostics, to implement combination strategies, to overcome chronic toxicities, and to determine the most clinically relevant compound for registration. Considering the low frequencies of specific FGFR molecular alterations in each cancer type, well-designed phase II trials with strong efficacy results could lead to approval for clinical use.

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