STATE OF THE ART: CONCISE REVIEW

FGFR Signaling as a Target for Lung Cancer Therapy

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ABSTRACT

Lung cancer is the leading cause of cancer-related death in developed countries. Recently, molecular targeted therapies have shown promising results in the management of lung cancer. These therapies require a clear understanding of the relevant pathways that drive carcinogenesis and maintenance of the malignant phenotype. The fibroblast growth factor receptor (FGFR) signaling axis is one such pathway that plays a central role in normal cellular function. Alterations in this pathway have been found in many cancers. In this review article, we focus on the role of this pathway in lung cancer. We present the molecular structure of FGFR, the interaction of the receptor with its ligands (the fibroblast growth factors), its downstream signaling, and aberrations in the FGFR pathway. We also discuss clinical trials involving selective and multikinase FGFR inhibitors in lung cancer treatment.

Keywords: Lung cancer; FGFR pathway; FGFR inhibitors; FGFR abberations

Methods

A systematic analysis of the literature was conducted on March 15, 2015, by performing a MeSH (medical subject headings) search in PubMed using the terms *FGFR* and *FGF* combined with *NSCLC*, *squamous cell lung cancer*, and *therapeutics*. The search was limited to English-language articles published between January 1, 1990, and March 15, 2015. Abstracts from the annual meetings of the American Society of Clinical Oncology, European Society of Medical Oncology, and American Association for Cancer Research and the AACR-NCI-EORTC (American Association for Cancer Research–National Cancer Institute–European Organisation for Research and Treatment of Cancer) International Conference on Molecular Targets and Cancer Therapeutics published between January 1, 2000, and March 15, 2015, were also considered for inclusion. The references lists of the articles identified were also searched for other relevant articles.

Introduction

The fibroblast growth factor receptor (FGFR) pathway plays a key role in signal transduction in lung cancer. It controls cellular processes such as cell cycle progression, migration, metabolism, survival, proliferation, and differentiation.[1] It also activates multiple signal transduction pathways, including Rat Sarcoma (RAS) kinase and mitogen-activated protein kinase (MAPK), which in addition to performing other proliferative functions, are also involved in the formation of new blood vessels.[2] Thus, FGFR is central to angiogenesis, embryogenesis, inflammation, and malignant tumor cell proliferation.

Fibroblast growth factor receptors

The FGFRs constitute a family of four tyrosine kinase receptors, FGFR1 through FGFR4, which mediate cellular signaling after binding to their high-affinity ligands, the fibroblast growth factors (FGFs; Fig. 1). FGFR1 is encoded by a gene present on chromosome 8p, whereas FGFR2, FGFR3, and FGFR4 are encoded by genes present on chromosome 10q, chromosome 4p, and chromosome 5q, respectively.

The receptor consists of an extracellular ligand-binding domain, which is usually glycosylated, a

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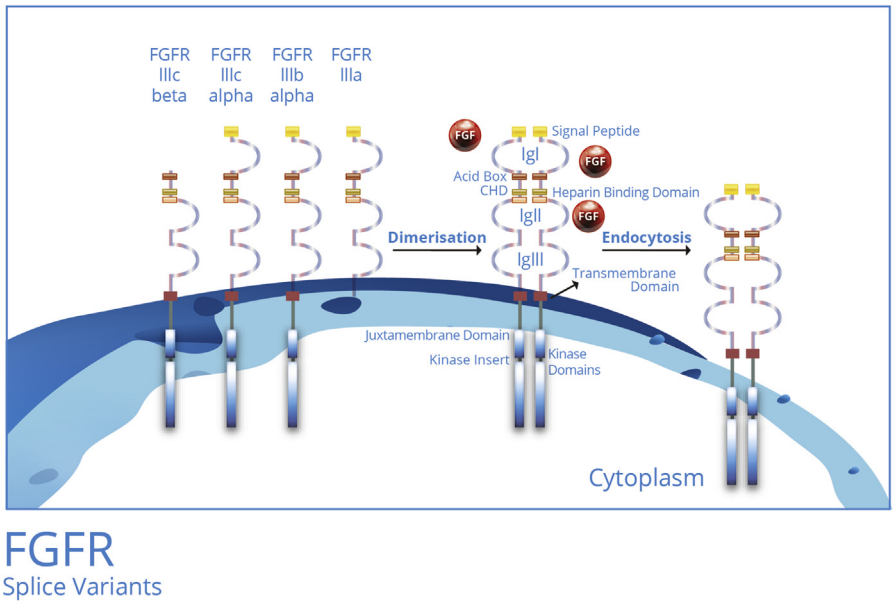

Figure 1. The various fibroblast growth factor receptor splice variants and receptor activation. Alternative splicing of the Ig3-like domain is responsible for the formation of isoforms with different ligand-binding specificity. Binding of fibroblast growth factor ligands and heparin sulfate proteoglycan to the fibroblast growth factor receptor activates the receptor, which results in dimerization of the receptor-ligand complex and in turn leads to transphosphorylation of the tyrosine kinase domains, endocytosis of the complex, and ultimately, activation of downstream signaling cascades.

transmembrane domain, and an active cytoplasmic tyrosine kinase domain. The extracellular region consists of a signal peptide at the N-terminus; three immunoglobulin-like domains, designated Ig1 through Ig3, with an acidic box consisting of 7 or 8 acidic residues present between Ig1 and Ig2; a cell adhesion molecule homology domain; and a positively charged heparin-binding domain at the beginning of Ig2.[3] Alternative splicing in Ig3 of FGFR1 through FGFR3 (see Fig. 1) results in isoforms with varying degrees of binding specificity; the FGFR3b and FGFR3c isoforms are mainly epithelial and mesenchymal, respectively.[4,5] The transmembrane domain is interposed between the extracellular and intracellular domains. The intracellular region consists of a juxtamembrane domain, which acts as a binding site for phosphotyrosine-binding domains of proteins such as FGFR substrate 2 (FRS2), and two kinase domains linked by a tyrosine kinase insert.[6] FRS2 functions as a lipid-anchored docking protein and targets signaling molecules to the plasma membrane in response to stimulation by FGF. This complex links receptor activation with the MAPK and other signaling pathways essential for cellular growth and differentiation.[7] The intracellular portion of FRS2 also contains additional regulatory sequences that are subjected to autophosphorylation and phosphorylation by heterologous protein kinases.[8]

Fibroblast growth factors

Each FGF receptor recognizes a unique subset of the FGF family of ligands. The FGFs bind FGFRs to regulate cell growth, migration, and differentiation during embryogenesis and homeostasis later in life.[9] They act both in mesenchymal and epithelial cells. There are 22 different FGFs, identified as FGF1 through FGF23 (note that there is no FGF15). The first family of FGFs consists of FGF1 and FGF2, which are either secreted or remain intracellular. The second and third families comprise FGF3 through FGF10 and FGF16 through FGF23, respectively, and they are always secreted. The final family consists of FGF11 through FGF14, which remain intracellular and do not bind FGFRs. This family is referred to as FHFs or FGF homologous factors. The secreted FGFs are further subdivided into 2 subfamilies: hormone-like and canonical forms. The hormone-like FGFs have low affinity for heparin-like molecules and rely on klotho proteins, which are transmembrane proteins that act as co-receptors for tissue-selective cofactors to help with FGFR interaction.[9] The ligand–receptor complex, in association with heparin or heparin sulfate proteoglycan, activates the receptor. FGFs have increased affinity toward certain FGFRs depending on the splicing pattern of these receptors. FGF1 is considered a universal FGF because it can activate all the FGFRs. FGF7, FGF10, and FGF22 strongly activate FGFR2b, whereas FGF8, FGF17, and FGF18 show higher relative activity on FGFR3c. FGF9, FGF16, and FGF20

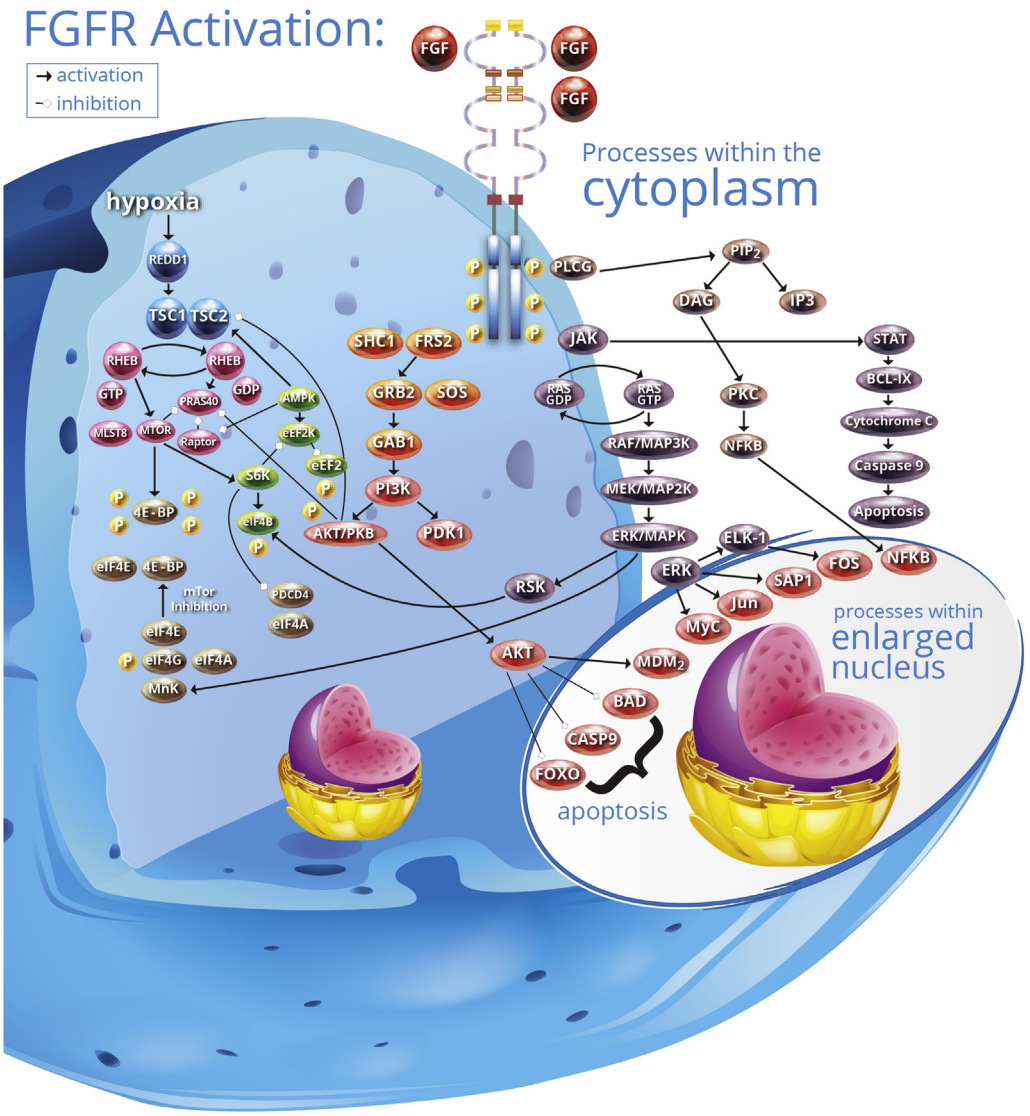

Figure 2. The downstream signaling pathway after activation of ligand-dependent fibroblast growth factor receptor. Activation of fibroblast growth factor receptor facilitates the attachment of docking proteins and activation of key downstream pathways: RAS-RAF-MAPK, phosphoinositide 3-kinase (PI3K)-AKT-mTOR (mammalian target of rapamycin), phospholipase c gamma, and signal transducer and activator of transcription (STAT). The mTOR complex (mTORC) consists of mTOR, raptor, proline-rich AKT substrate 40 kDa (PRAS40), and mammalian LST8 (mLST8), which is sensitive to and responsible for rapamycin-induced processes.[11] Activation of the P13K pathway by either growth factors or mutations leads to activation of AKT. AKT increases the downstream signaling of mTORC by phosphorylating TSC2 and PRAS40, thereby preventing the activity of negative regulators of mTORC.[14] This mTORC activation results in the phosphorylation of 4EBP1 (eukaryotic translation initiation factor 4E-binding protein), which prevents inactivation of Eif4E (eukaryotic initiation factor 4E), thereby leading to cellular proliferation and angiogenesis through increased mRNA translation of cyclin D, Bcl-2, and VEGF.[11] In addition, mTORC phosphorylates S6K1, thus leading to translation of mRNAs encoding for proteins and elongation factors. Hypoxia-mediated inhibition of mTORC1 requires expression of REDD1 (regulated in development and DNA damage responses 1) and is dependent on tuberous sclerosis complex function.[15]

preferentially activate the "c" splice forms of FGFR, and FGF19, FGF21, and FGF23 show consistent activity toward FGFR1c.[10]

FGFR signaling

FGFR signaling is achieved by changes in receptor conformation upon ligand binding, thus leading to receptor dimerization and subsequent activation by autophosphorylation of the tyrosine kinase intracellular domains (see Fig. 1). FGFs require heparin sulfate proteoglycans to activate FGFR.[12] The receptor dimer is stabilized by a secondary binding site involving interactions between FGF and Ig2 of the second receptor in the complex, as well as by receptor–receptor interactions. Heparin or heparin sulfate proteoglycans are also necessary for stable dimerization of the FGF–FGFR complexes.[13]

As shown in Figure 2, the activated FGFR phosphorylates FRS2 on several sites, thereby allowing the recruitment of the adaptor proteins, son of sevenless, and growth factor receptor–bound protein 2 (GRB2) to activate RAS and the downstream RAF and MAPK pathways.[7] The activated MAPK pathway is necessary for cell cycle progression. Further downstream signaling occurs by means of two main pathways through the intracellular receptor, FRS2 and phospholipase Cg, thus ultimately leading to up-regulation of the RAS-dependent MAPK and RAS-independent phosphoinositide 3-kinase–AKT signaling pathways.[17] After phospholipase Cg is activated, it hydrolyzes phosphatidylinositol-4,5-biphosphate (PIP2) to phosphatidylinositol-3,4,5-triphosphate and diacylglycerol,[18] thereby activating protein kinase C, which partly reinforces activation of the MAPK pathway by phosphorylating RAF. Several other pathways are also activated by FGFRs depending on the cellular context, including the p38 MAPK and Jun N-terminal kinase pathways, signal transducer and activator of transcription signaling,[19,20] and ribosomal protein S6 kinase 2.[21]

Molecular aberrations in the FGFR signaling pathway

Solid tumors

Although FGFRs are overexpressed in many cancers, the significance of protein expression per se is unclear. Molecular aberrations that are believed to be oncogenic and therefore targetable include somatic mutations, gene amplification, and chromosomal fusions.[22] Table 1 shows the genetic aberration in FGFR in various tumors.[16,23] Among human cancers, FGFRs are the most frequently mutated kinase genes.[17] Constitutive FGFR activation occurs in as many as 50% to 60% of non–muscle-invasive and 17% of high-grade bladder cancers. Endometrial cancer is associated with mutations in the kinase domain of FGFR2 in 12% of cases.[24] It has been reported that up to 10% of gastric cancers are associated with FGFR2 amplifications, which portend a poor prognosis.[25] FGFR1 gene amplification is present in 7.5% to 17% of all breast cancers and in 16% to 27% of luminal B–type breast cancer,[26,27] thus making this pathway an attractive target for breast cancer therapy.

Other abnormalities in the FGFR signaling axis have been described. Overproduction of autocrine FGF has been observed in various tumors, including lung, esophageal, colon, hepatocellular, and prostate cancers.[17,28] Paracrine FGF signaling has also been reported in small cell lung cancer (SCLC) and portends a poor prognosis. Furthermore, preclinical studies have demonstrated that paracrine production of FGFs leads to neoangiogenesis in cancer cells through FGFR1 and FGFR2.[29] Altered FGFR splicing results in an up-regulation of ligand-dependent signaling by increasing the range of FGFs that bind with and activate the receptors. Genome-wide association studies have shown that SNPs within intron 2 of the *FGFR2* gene increased the risk of early-onset breast cancer.[30] Mutations in proteins that regulate internalization of FGFR and thereby result in prolonged signaling have also been described,[31] as have mutations in the negative regulators, including SPRY2, which in turn leads to increased FGFR signaling.[17]

Non-small cell lung cancer

Mutations

Comprehensive analyses of genomic alteration in squamous cell lung cancer have shown that FGFR2 mutations are present in 3% of cases. The extracellular domain mutations W290C and S320C and the kinase domain mutations K660E and K660N are most often involved.[32] In a comprehensive analysis that sequenced 623 genes from 188 cases of primary lung adenocarcinoma, the FGFR family of receptors was among the highly dysregulated genes, with aberrations found in 19% of cases.[33]

Gene amplification

Gene amplification is a selective increase in the number of copies of a gene sequence without a proportional increase in other genes. *FGFR* gene amplification causes ligand-independent signaling. Weiss et al. found frequent *FGFR1* amplification in squamous cell lung cancer (155 of 232 lung cancer specimens) and confirmed the presence of *FGFR1* amplifications in an independent cohort of squamous cell lung cancer samples (22% of cases by fluorescence in situ hybridization [FISH]).[34] They demonstrated that the FGFR inhibitor PD173074 inhibited growth and induced apoptosis in lung cancer cells carrying amplified *FGFR1*. They further demonstrated that inhibition of *FGFR1* with a small molecule led to significant tumor shrinkage. A recent meta-analysis has demonstrated a prevalence of *FGFR1* amplification in lung squamous cell carcinoma of 19%.[35]

Chromosomal translocations

Some chromosomal rearrangements lead to proteins fusing to the kinase domain of FGFR. These fusion proteins do not undergo lysosomal degradation and are not susceptible to negative feedback inhibition leading to activation in the absence of a ligand and continued signaling.[36] Prominent among FGFR fusions that have been described are BAG4–FGFR1, FGFR2–KIAA1967, and FGFR3–TACC3.[22] Cells having FGFR fusions are characterized by increased sensitivity to FGFR inhibitors PD173074 and pazopanib.[22] Whole-genome sequencing of 148 Korean patients with lung squamous cell cancer

revealed that two had in-frame fusion of FGFR3 with TACC3. Analysis of the TCGA data set showed that four of the 178 samples had FGFR3–TACC3 fusions. FGFR3–TACC3 fusions are found in 2% of squamous cell lung cancer.[37]

Small cell lung cancer

Integrated genome analysis revealed focal amplification of *FGFR1* in 6% of SCLC cases.[38] In another study with PD173074, Pardo et al. used two human SCLC xenograft models, H-510 and H-69, and demonstrated decreased proliferation in a dose-dependent manner when the drug was administered orally for 28 days. Longer median survival was observed in the H-150 xenograft than in the control animals, with the effect of cisplatin being potentiated by concurrent use of PD173074. In addition, complete remission was observed in half the mice for longer than 6 months.[39] Voortman et al. reported high–copy number gains of the *FGFR1* gene in SCLC.[40] The frequency of 33.3%, suggests that this could be a possible therapeutic target. Yet another study of 13 SCLC cell lines and 68 SCLC tumor samples from patients reported that *FGFR1* mutations and focal amplifications were rare in SCLC (focal amplification of the *FGFR1* gene was present in only five tumor samples with high-level focal amplification in only one tumor sample).[41] A recent study reported a subset of patients with SCLC with an activated FGFR pathway that was evidenced by positive FGF2, FGF9, and FGFR1 protein or *FGFR1* gene copy number.[42] Further studies are warranted to test the benefit of FGFR inhibitors in this population of patients with SCLC. There are no approved targeted therapies in SCLC. This lack of approved therapies is due partly to the scarcity of tissue for molecular studies because of the difficulty in obtaining tissue samples on account of the aggressive nature of the disease process. Multiple phase 1 and phase 2 studies of the effect of FGFR inhibitors on patients with SCLC do exist, however (Tables 2 and 3).[43]

Clinical development of FGFR inhibitors in lung cancer

The first class of agents to be studied as FGFR inhibitors were multikinase antiangiogenic compounds that had initially been developed to target vascular endothelial growth factor receptor (VEGFR). With the emergence of FGFR as an important target for cancer therapy, however, these agents were repositioned as FGFR inhibitors and studied for their FGFR-inhibitory activity. These agents include brevanib, cediranib, dovitinib, lucitanib, and nintedanib. In the past few years, however, a number of potent and specific second-generation inhibitors of FGFR have been introduced into the clinic. These second-generation inhibitors are listed in Table 2.[43]

Table 1. Genetic aberrations in FGFR in different tumors

Genetic abberation	Gene	Cancer type
Amplification	FGFR1	Squamous NSCLC (20%), breast cancer (10%), ovarian cancer (5%), bladder dancer (3%)
	FGFR2	Gastric cancer (10%), breast cancer (4%)
	FGFR3	Bladder cancer, salivary adenoid cystic cancer
	FGFR4	Colorectal cancer (5%)
Mutation	FGFR2	Endometrial cancer (12%), Squamous NSCLC (5%)
	FGFR3	Bladder cancer (non-muscle invasive) (50%-60%), bladder cancer (muscle invasive)(10%-15%), cervical cancer (5%), myeloma (5%), spermatocytic seminoma (7%), prostate cancer (3%), colrectal carcinoma and oral squamous cancer
	FGFR4	Rhabdomyosarcoma (7%-8%)
Translocation	FGFR3	Myeloma (15%-20%), bladder cancer (muscle invasive) (6%), glioblastoma (3%-7%)

FGFR, fibroblast growth factor receptor; SNP, single nucleotide polymorphism.
Data from Dieci et al.[16] and Dienstmann et al.[23]

Specific FGFR inhibitors

AZD4547 is a selective inhibitor of FGFR1, FGFR2, and FGFR3 tyrosine kinases that has shown potent antitumor activity against FGFR-deregulated tumors in preclinical models.[44] In a phase 1B open label multicenter study of AZD4547 in 15 patients with advanced solid tumors, eight had low amplification (FISH gene-to-centromere ratios between 2 and 2.8) and seven had high amplification (FISH ratios >2.8). The most common drug-related adverse events were central serous retinopathy and dyspnea. One partial response (in a patient with high *FGFR1* amplification), four patients with stable disease, and nine patients with progressive disease (seven cases of progression and two deaths) were reported. Therefore, AZD4547 did not meet its prespecified efficacy end point for overall response rate to warrant continuation. The increase in serum phosphate, however, indicated that AZD4547 at doses of 80 mg twice daily causes FGFR inhibition.[44] Gavine et al. studied the pharmacological profile of AZD4547 in a FGFR-driven human xenograft model; they reported potent dose-dependent antitumor activity correlating with continued plasma exposure.[45] AZD4547 has also been proven to effectively inhibit phosphorylation of FGFR2, thus resulting in a significant dose-dependent reduction in tumor growth in FGFR2-amplified xenograft (SNU-16)

Table 2. Active clinical trials of selective FGFR inhibitors in lung cancer

Drug	Mechanism	Trial identifier	Phase	Regimen	Target tissue	Status
AZD4547	FGFR1-3	NCT01824901	1, 2	Docetaxel with or without FGFR inhibitor AZD4547 in treating patients with recurrent NSCLC	NSCLC	Active, not recruiting
		NCT01795768	2	Proof-of-concept study of AZD4547 in patients with FGFR1- or FGFR2-amplified tumors	Gastric cancer, esophageal cancer, breast cancer, squamous cell carcinoma of the lung	Recruiting
		NCT00979134	1	Study designed to assess the safety and tolerability of AZD4547 at increasing doses in patients with advanced tumors	Cancer, advanced solid malignancies	Active, not recruiting
		NCT02154490	2, 3	Lung-MAP: S1400 biomarker-targeted second-line therapy in treating patients with recurrent stage IIIB-IV squamous cell lung cancer	NSCLC	Recruiting
		NCT02117167	2	Intergroup Trial UNICANCER UC 0105-1305/ IFCT 1301: efficacy of targeted drugs guided by genomic profiles in patients with metastatic NSCLC (SAFIR02_Lung)	NSCLC	Recruiting
BGJ398	FGFR1-3	NCT01928459	1	Phase 1b trial of BGJ398/BYL719 in solid tumors	Advanced solid tumors	Recruiting
		NCT02160041	2	BGJ398 for patients with tumors with FGFR genetic alterations (CBGJ398XUS04)	Solid tumor, hematologic malignancies	Recruiting
		NCT01697605	1	Phase I study of oral BGJ398 in Asian patients	Tumor with alterations of the FGF-R	Recruiting
		NCT01004224	1	Dose escalation study in adult patients with advanced solid malignancies	Tumors with FGFR1–3 amplification	Recruiting
LY2874455	FGFR1-4	NCT01212107	1	Study of LY2874455 in patients with advanced cancer	Advanced cancer	Active not recruiting
JNJ-42756493	FGFR1-4	NCT01962532	1	Study to evaluate the safety, pharmacokinetics, and pharmacodynamics of JNJ-42756493 in patients with advanced or refractory solid tumors or lymphoma	Advanced or refractory solid tumors or lymphoma	Active, recruiting
		NCT01703481	1	Study to evaluate the safety, pharmacokinetics, and pharmacodynamics of JNJ-42756493 in adult patients with advanced or refractory solid tumors or lymphoma	Advanced or refractory solid tumors or lymphoma	Active, recruiting
FP-1039 (Ligand Traps)	FGF1, FGF2, FGF4	NCT01868022	1	Study to evaluate GSK3052230 in combination with paclitaxel and carboplatin, or docetaxel or as single agent in subjects with solid malignancies and deregulated FGF pathway signaling	Cancer	Recruiting

FGFR, fibroblast growth factor receptor; NSCLC, non-small cell lung cancer; FGF, fibroblast growth factor.

and patient-derived gastric cancer xenograft models.[46] A three-part phase 1 study of AZD4547 was conducted in patients with advanced solid tumors: part A was to determine the maximum tolerated dose and continuous tolerable dose (RD), part B to elucidate the pharmacokinetic and safety profile, and part C to access the safety and clinical activity of AZD4547 (80 mg twice daily with continuous dosing) in patients with amplification of *FGFR1* and *FGFR2*. When the interim data were reported, 43 patients had been treated in the dose escalation phase (part A) and the RD was determined to be 80 mg orally twice daily. Dose-limiting toxicities included elevated liver enzymes, stomatitis, renal failure, and hyperphosphatemia. In the dose expansion phase of the study (phase B) six patients were treated to confirm the tolerability of the RD. In part C1,

Table 3. Active clinical trials of multikinase inhibitors in lung cancer

Agent	Mechanism	Trial identifier	Phase	Regimen	Targeted tissue	Status
Brivanib	VEGFR, FGFR inhibitor	NCT00798252	1	Multiple-dose study of brivanib in combination with chemotherapy agents in subjects with advanced cancers	Advanced cancers	Active, not recruiting
Dovitinib	FGFR, PDGFR, VEGFR, FLT3, C-KIT	NCT01831726	2	Dovitinib for patients with tumor pathway activations inhibited by dovitinib (SIGNATURE)	NSCLC, RCC, solid tumors, hematologic malignancy	Active, recruiting
		NCT01676714	2	Study of dovitinib and biomarkers in advanced NSCLC or advanced CRC	Advanced NSCLC, CRC	Active, recruiting
		NCT01700270	1	Pharmacokinetic drug–drug interaction study of dovitinib (TKI258) in patients with advanced solid tumors (CTKI258A2120)	Advanced solid tumors, excluding breast cancer	Active, not recruiting
		NCT01596647	1	Pharmacokinetic drug–drug interaction study of dovitinib (TKI258) in patients with advanced solid tumors	Advanced solid tumors, excluding breast cancer	Ongoing, not recruiting
		NCT01421004	1	Bioequivalence of 2 formulations of TKI258 in patients with advanced solid tumors	Advanced solid tumors, excluding breast cancer	Active, not recruiting
		NCT01861197	2	Phase II study of dovitinib for FGFR1 amplified squamous NSCLC	NSCLC	Active, recruiting
Lenvatinib	FGFR, PDGFR, VEGFR	NCT00121719	1	Open-label phase I dose escalation study of E7080	Solid tumors	Active, not recruiting
		NCT01529112	2	Study comparing the combination of the best supportive care plus E7080 vs. best supportive care alone, in patients with advanced lung cancer or lung cancer that has spread, who have been previously treated, unsuccessfully, with at least 2 different treatments	NSCLC	Ongoing, not recruiting
		NCT01877083	2	Study of the safety and activity of lenvatinib (E7080) in subjects with KIF5B-RET–positive adenocarcinoma of the lung	KIF5B-RET–positive adenocarcinoma of the lung	Recruiting
Nintedanib	FGFR,PDGFR, VEGFR	NCT01948141	2	Nintedanib in treating patients with advanced NSCLC who have failed up to 2 previous chemotherapy regimens	NSCLC	Recruiting
		NCT02225405	1	Induction study of cisplatin, docetaxel, and nintedanib stage IB-IIIA NSCLC	Lung cancer	Not yet open
		NCT01346540	1	Phase I/II study of continuous oral treatment with BIBF 1120 added to standard gemcitabine/cisplatin therapy in first-line NSCLC patients with squamous cell histology	NSCLC	Active, not recruiting
		NCT01684111	1	Dose escalation trial of oral BIBF 1120 in combination with intravenous vinorelbine in elderly patients with advanced NSCLC, stage IV (VENUS-1)	NSCLC	Recruiting

(continued)

Table 3. Continued

Agent	Mechanism	Trial identifier	Phase	Regimen	Targeted tissue	Status
		NCT01683682	1	Dose escalation trial of oral BIBF 1120 in combination with intravenous carboplatin and vinorelbine in elderly patients with advanced NSCLC, stage IV (VENUS-2)	NSCLC	Recruiting
		NCT00876460	1	BIBF 1120 plus docetaxel (Japan) in patients with advanced NSCLC, phase I	NSCLC	Active, not recruiting
		NCT01349296	1	BIBF 1120 and RAD001 in solid tumors, phase I (BARIS)	Solid tumors	Recruiting
		NCT00805194	3	LUME-Lung 1: BIBF 1120 plus docetaxel as compared to placebo plus docetaxel in second-line NSCLC	NSCLC	Active, not recruiting
		NCT00806819	3	LUME-Lung 2: BIBF 1120 plus pemetrexed compared with placebo plus pemetrexed in second-line nonsquamous NSCLC	NSCLC	Active, not recruiting
		NCT00979576	1	BIBF 1120 in combination with pemetrexed in advanced NSCLC	NSCLC	Active, not recruiting
		NCT01441297	2	BIBF 1120 as second-line treatment for small cell lung cancer	Small cell lung cancer; small cell lung cancer, recurrent	Recruiting
PI-88	FGF 1, FGF 2, VEGF	NCT01828099	3	LDK378 vs. chemotherapy in previously untreated patients with ALK rearranged NSCLC	NSCLC	Recruiting
ENMD-2076	FGFR1, KDR, FGFR2, PDGFR, VEGFR, FLT3, c-KIT, Aurora K, FLT3	NCT00658671	1	Dose escalation study of ENMD-2076 administered orally to patients with advanced cancer	Tumors	Unknown
E-3810/ Lucitanib	FGFR1, VEGFR	NCT02109016	2	Study to assess the efficacy of the VEGFR-FGFR inhibitor, lucitanib, given to patients with FGFR1-driven lung cancer	Squamous NSCLC, NSCLC, stage IV lung cancer, metastatic lung cancer	Recruiting
		NCT01283945	1	Study of oral lucitanib (E-3810), a dual VEGFR-FGFR tyrosine kinase inhibitor, in patients with solid tumors	Solid tumors	Recruiting
FP-1039 (Ligand Traps)	FGF1, FGF2, FGF4	NCT01868022	1	Study to evaluate GSK3052230 in combination with paclitaxel and carboplatin, or docetaxel or as single agent in subjects with solid tumors and deregulated FGF pathway signaling	Cancer	Recruiting

VEGFR, vascular endothelial growth factor; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; FLT3, Fms-related tyrosine kinase 3; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; CRC, colorectal cancer; FGF, fibroblast growth factor.

21 patients with *FGFR1*- or *FGFR2*-amplified tumors received AZD4547 (80 mg twice daily). Prolonged periods of disease stabilization (>24 weeks) were observed in four patients. Part C2 (squamous NSCLC) and part C3 (gastric cancer) are ongoing.[47]

BGJ398 is a potent inhibitor of FGFR1, FGFR2, and FGFR3 and has shown single-agent activity in patients with FGFR aberrations. Preliminary analysis of efficacy data in a phase 1 study of BGJ398 in 94 patients with advanced solid tumors with FGFR genetic alterations

showed tumor regression in four of five patients with urothelial cancer with *FGFR3*-activating mutations (with tumor reductions ranging from 27% to 48%) and a partial response in one patient with *FGFR1*-amplified squamous cell cancer. The maximum tolerated dose was 125 mg, with the most common adverse events being hyperphosphatemia (78%), stomatitis (37%), alopecia (32%), and decreased appetite (32%).[48] Three phase 1 studies and one phase 2 study of oral BGJ398 are currently recruiting patients with advanced solid tumors with alterations in FGFR.

JNJ-42756493 is a pan-FGFR inhibitor that has shown prolonged target inhibition in preclinical models with FGFR genetic aberrations. A multipart phase 1 study was conducted to evaluate the safety, efficacy, and antitumor activity of JNJ-42756493 in patients with advanced solid tumors with FGFR aberrations. The study comprised three parts. The first part consisted of dose escalation to determine the recommended phase 2 dose, the second part included the biopsy cohort to confirm the recommended phase 2 dose, and the third part involved the expansion cohort, which evaluated antitumor activity in selected patients. When the interim data were reported, a total of 28 patients had been treated at five dose levels (0.5, 2, 4, 6, and 9 mg daily continuously) in part 1 of the study. The pharmacokinetic studies were linear and revealed a half-life of 50 to 60 hours. Dose levels higher than 6 mg achieved predictable plasma concentrations that were found to be efficacious. The most common adverse events were hyperphosphatemia (57%), asthenia (46%), and dry mouth (32%).[49] Parera et al. showed that JNJ-42756493 is a single-digit nanomolar FGFR1, FGFR2, FGFR3, FGFR4 tyrosine kinase inhibitor in in vitro cell line–based xenografts and patient-derived xenografts with high distribution to the lung, liver, and kidney tissue.[50] The structure–activity relationship and chemical synthesis pathway of JNJ-42756493 were reported, which demonstrated the mechanism of fragment-based drug discovery to report FGFR1 through FGFR4 inhibitors with nanomolar affinity.[51] JNJ-42756493 has also been proven to inhibit the growth of glioma cells with FGFR3-TACC fusions both in vitro and in vivo.[52]

LY2874455 is a potent small molecule pan-FGFR inhibitor that exhibits a sixfold to ninefold higher selectivity in vitro and in vivo inhibition of FGF than does VEGF-mediated targeted signaling in mice.[53] In a phase 1 multicenter nonrandomized open label study of oral LY2874455 that consisted of dose escalation and expansion phases, 36 patients were treated with escalating doses of LY2874455. Patients received continuous dosing with 2 to 10 mg once daily or 8 to 24 mg twice daily. The most common adverse events related to the drug were gastrointestinal side effects (three patients). Pharmacokinetic studies revealed that the plasma area under the curve increased 1.1- to 2.3-fold with twice daily administration and the half-life was relatively short, with no evidence of drug accumulation from a single dose. The starting dose for the dose expansion cohort was selected as 16 mg orally twice daily.[54]

Monoclonal antibodies that bind to and inactivate specific FGF circulating ligands have been developed. These antibodies may potentially improve the side effect profile associated with inhibition of multiple FGFR isoforms.

FP-1039 (GSK230) is one such soluble FGF receptor 1 Fc fusion protein that traps FGF ligands by means of high-affinity binding, thereby preventing FGF-dependent angiogenesis and tumor growth. FP-1039 selectively blocks mitogenic FGFs (FGF1 through FGF10, FGF16 through FGF18, FGF20, and FGF22) without binding the hormonal FGFs (FGF19, FGF21, and FGF23), which require a membrane anchored co-receptor klotho for high-affinity binding and signaling. This limits the side effect profile preventing development of hyperphosphatemia due to inhibition of FGF23. FP-1039 has been shown to inhibit tumor growth in preclinical models with FGFR1 gene amplification.[55,56] A multiarm nonrandomized open label phase 1B study is currently recruiting patients to evaluate the safety and preliminary efficacy of FP-1039 in combination with paclitaxel and carboplatin in previously untreated *FGFR1*-amplified metastatic squamous NSCLC (arm A), in combination with docetaxel in *FGFR1*-amplified metastatic squamous NSCLC that progressed after one line of chemotherapy (arm B), or in combination with pemetrexed and cisplatin in patients with untreated and unresectable metastatic pleural mesothelioma (arm C). The study plan calls for administering FP-1039 as a 30-minute intravenous infusion once a week in a 21-day cycle. The starting dose will be 5 mg/kg and will be escalated until the maximum tolerated dose or maximum feasible dose in combination with chemotherapy is achieved.[57]

Mechanism-based toxicity of FGFR inhibition

Hyperphosphatemia has emerged as a mechanism-based toxicity that defines specific potent FGFR inhibitors. FGF23 is a circulating factor secreted by osteocytes that inhibits phosphate reabsorption in the proximal tubular epithelial cells of the kidney; elevated levels cause renal phosphate wasting.[58] Klotho functions as a cofactor for FGF23 and is important in FGF signaling.[9] Potent inhibitors such as AZD4547 and BGJ398 inhibit FGF23/klotho signaling, whereas FGF “trap” agents such as FP-1039 bind circulating FGF23. The inhibition of FGF23 through these mechanisms results in a decrease in renal phosphate excretion and hyperphosphatemia. Thus, similar to the incidence of hypertension with potent

VEGFR inhibitors, hyperphosphatemia has been used as a pharmacodynamic marker of FGFR pathway inhibition.[48]

Resistance to FGFR inhibitors

Comprehensive profiling of two different *FGFR1*-amplified lung cancer subtype xenografts, NCI-H1581 (large cell lung cancer [LCLC]) and DMS114 (SCLC), that are intrinsically resistant to FGFR inhibitors revealed that the two LCLC and SCLC models have different mechanisms of resistance. MET pathway activation was found in the LCLC model, and activation of the insulin-like growth factor-1 receptor was found to be responsible for FGFR inhibitor resistance in the SCLC model. Targeted therapies aimed at blocking both these pathways was observed to prevent the intrinsic resistance in these FGFR-driven tumors.[59]

Multikinase FGFR inhibitors

Multikinase FGFR inhibitors are not selective and target the tyrosine kinase domains present in a wide array of receptors, including VEGFR, platelet-derived growth factor receptor, and FGFR. They are predominantly VEGFR inhibitors with relatively weak FGFR inhibitory activity.[60] A number of these inhibitors, including brivanib, dovitinib, lenvatinib, and nintedanib, have been studied in lung and other tumors (predominantly as antiangiogenic compounds), and they are now being evaluated for their anti-FGFR properties. One agent in this class, lucitanib, is a relatively potent inhibitor of FGFR, VEGFR, and platelet-derived growth factor receptor, and it has shown striking activity in an early clinical trial. This open label, dose escalation, phase I/IIa study evaluated the safety and efficacy of lucitanib as monotherapy in 76 patients with advanced solid tumors. The maximum tolerated dose was 30 mg/day, with the most common adverse events being hypertension (91%), asthenia (42%), and proteinuria (57%) related to inhibition of the VEGFR pathway. The clinical RECIST (response evaluation criteria in solid tumors) response was 26%, and the progression-free survival time was 25 weeks. Fifty percent of patients with FGF-aberrant breast cancer achieved a RECIST partial response with a median progression-free survival time of 40.4 weeks.[61]

Conclusions

The FGFR pathway is crucial to normal cellular functioning. Dysregulation in this pathway has been identified in NSCLC, particularly squamous cell lung cancer. A number of FGFR inhibitors are being evaluated in NSCLC. Unfortunately, as described earlier, clinical activity to date has been modest at best. In the current era, agents inhibiting protein targets of genetic derangements that drive lung cancer growth, such as EGFR tyrosine kinase inhibitors and ALK and ROS inhibitors, yield response rates in excess of 40%. Thus, the low-level responses seen with the aforementioned FGFR inhibitors have been considered disappointing. Several potential reasons underlying this low activity exist. First, the frequency of activating mutations in the *FGFR* gene in NSCLC is extremely low. Second, most studies have selected tumors with amplification of the *FGFR* gene, but the definition of gene amplification in clinical trials has not been uniform.

Gene amplification is the production of multiple copies of a particular gene, which then amplify the phenotype attributed to the gene. Gene copy number can also be increased in cases of polysomy, which is distinguished by an increase in copy number of all genes on the polysomic chromosome and is therefore not a selective phenomenon. Unlike mutations that are dichotomized molecular events—cells are mutated or not—the level of gene amplification can vary. It is quite likely that the cell's degree of "addiction" to a gene may be proportional to the number of excess copies. In support of this idea, a recent report by Gadgeel et al.[62] demonstrated that a 3.5-fold amplification of *FGFR* was of clinical significance. Interestingly, in their series the rates of *FGFR1* amplification using the cutoff level of 3.5 were 5.1% in squamous cell and 4.1% in adenocarcinoma. Thus, future studies may have to either use a higher cutoff for defining *FGFR* amplification, or stratify patients into "low," "moderate," and "high" amplification groups to better discern the efficacy of these compounds.

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