Fibroblast Growth Factor Receptor (FGFR) as a Therapeutic Target in Lung and Head and Neck Cancer

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Abstract

Fibroblast growth factor receptor (FGFR) aberrations have been identified in various types of cancer. Squamous cell carcinomas of the lung and head and neck have been shown to harbor these genetic alterations in high frequencies. A number of agents that target the FGFR signaling pathway are currently in development in various tumor types. This review will summarize the potential roles of FGFR in lung and head and neck cancers, as well as discuss the current landscape of therapies in development that target the FGFR pathway by summarizing the clinical trials of FGFR inhibitors.

Key words: FGFR; lung cancer; head and neck cancer; therapeutic target; clinical trial

FGFR Pathway

The fibroblast growth factor/fibroblast growth factor receptor (FGF/FGFR) signaling pathway fundamentally regulates embryogenesis, adult tissue homeostasis, angiogenesis and wound repair.[1,2] It also plays important roles in cell functions, including proliferation, differentiation, apoptosis and migration.[3-5] Deregulated FGF/FGFR activations have been associated with a broad range of developmental disorders and cancer progression. Upon ligand binding, FGFRs activate a cascade of downstream signaling pathways, such as the mitogen activated protein kinase (MAPK), signal transducer and activator of transcription (STAT), the phosphoinositide-3-kinase (PI3K)/Akt pathways, and DAG-PKC, and IP3-Ca^{2+} releasing signaling branches via phospholipase Cγ (PLCγ) activation[6-9] (**Figure 1**). The alternatively spliced FGFR isoforms have been shown to result in oncogenic FGFR signaling, which promotes tumorigenesis. In this review, we will focus on the FGFR aberrations in lung and head and neck cancer, and compare them with other tumor types, such as bladder and gastric cancer. We will also discuss the current clinical trials of FGFR inhibitors that include lung and head and neck cancers.

FGFR Aberrations in Lung Cancer

FGFR1 has been shown to be amplified in 10%–20% of squamous non-small-cell lung cancers (SqNSCLC).[10-12] Preclinical studies have demonstrated that FGFR1 amplification confers FGFR signaling dependence.[10] Treatment of FGFR1-amplified SqNSCLC cell lines with selective FGFR inhibitor PD173074 resulted in cancer cell growth inhibition and apoptosis. In addition to squamous cell, small–cell lung cancer (SCLC) cell lines, as well as xenograft models derived from both cell lines and patient tumors treated with PD173074 have also shown tumor regression with PD173074 treatment through inhibition of both FGFR 1 and 2.[10,13] Activating FGFR2 mutations occurred in 5% of SqNSCLC[14], and 2.2% in non-small cell lung cancers (NSCLC).[15] *In vivo* NSCLC mice model with an FGFR2-mutated tumors were sensitive to a Pan-FGFR inhibitor.[16] In addition, increased FGFR3 cDNA expression was found in lung cancer tissues[17] from patients who progressed on prior chemotherapy treatments. Novel FGFR3 fusion genes were also identified in SqNSCLC[18]. More recently, it has been discovered that de-repression of FGFR2 and FGFR3 can cause rapid acquired resistance to EGFR tyrosine kinase inhibitors among NSCLC cell lines.[19] These recent findings have suggested a clear role of various FGFRs in lung cancer (henceforth referred to NSCLC unless otherwise specified) progression. Current research focus has been more towards FGFR1 amplification, the most common aberration.

FGFR Aberrations in Head and Neck Cancer

Advanced-stage head and neck squamous cell carcinoma (HNSCC) remains a challenging disease with poor outcomes. Overall survival has improved by about 10% over the past 20 years, despite advances in treatment modalities. The paucity of information on the dominant oncogenic drivers has been a major challenge to the effective application of targeted therapies in HNSCC. Recurrent FGFR1 amplification is seen in 10% to 17% of head and neck[20,21], and high FGFR2 and FGFR3 expression has been found in the majority of HNSCC cell lines.[22,23] Higher expression levels of FGFR1, 2, and 3 were also found to

be contributing to tumor initiation and early-stage progression in HNSCC.[20,24] It has been shown that a reduction of FGFR3 levels in HNSCC cell lines led to a 35% decrease in cell proliferation and higher radiation sensitivity.[23] The FGFR inhibitor PD173074 reduced cell proliferation and increased cell apoptosis in head and neck cancer *in vitro* and *in vivo*.[25] An aberrant FGFR signaling pathway has been implicated in acquired resistance to bevacizumab, an anti-vascular endothelial growth factor antibody.[26] Together, these results support that the aberrant FGFR pathway might be an important oncogenic pathway as well as a mechanism of acquired resistance to therapies in a subset of HNSCCs.

## Comparing the FGFR Landscape with Other Cancer Types—Bladder and Gastric Cancer

The FGFR pathway has been known to play a critical role in the tumorigenesis of bladder and gastric cancer.[27,28] While FGFR1 amplification is frequently reported in lung and head and neck cancers, FGFR2 amplification has been reported in gastric cancer. However, FGFR3 mutation not usually found in head and neck cancers or lung cancers is not an uncommon characteristic of bladder cancer. FGFR3 is frequently activated by mutation and not by amplification in bladder cancer, and represents a potential target for therapy. FGFR3 mutations have been described in approximately 75% of low-grade papillary bladder cancers, and FGFR3 overexpression was identified in 42% of muscle-invasive diseases.[27,29,30] FGFR1 amplification was also found in 3% of urinary bladder cancers.[31] The anti-FGFR3 monoclonal antibody inhibits *in vitro* cell growth and *in vivo* tumor burden for bladder cancer cells with FGFR3 point mutation mutation.[32]

In gastric cancer, multiple FGFR alterations (except FGFR3 mutation) were detected in patients' tumor specimens.[33] In particular, FGFR2 amplification was observed from 4-7% in different studies, and intratumoral heterogeneity was observed in 24% of FGFR2 amplified cases.[34,35] Furthermore, FGFR2 amplification may portend poor prognosis for patients with gastric cancer. Thus, FGFR2 has attracted significant attention as a potential therapeutic target for the development of novel personalized anticancer treatment. Several clinical trial studies have tried to functionally inhibit FGFR aberrancy in gastric cancer patients: small molecule pan FGFR inhibitors AZD4547 (NCT01457846, NCT01795768, and NCT00979134), TKI258 (NCT01719549, NCT01576380, and NCT01921673) and specific humanized monoclonal antibody FPA144 targeting FGFR2 (NCT02318329).

FGFR Inhibitor Clinical Trials in Lung and Head and Neck Cancers

Previous studies in other cancers have led to clinical trials using FGFR inhibitors for lung cancer and HNSCC (**Table 1**). Of

FIGURE 1. The signal transduction network downstream of FGFR along with FGFR alterations.
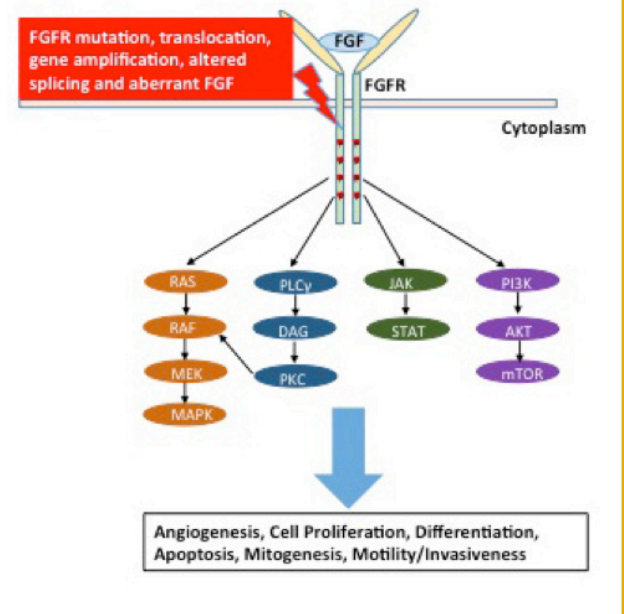
Following ligand binding and receptor dimerization, the kinase domains transphosphorylate each other, leading to the docking of adaptor proteins and the activation of four key downstream pathways: RAS–RAF–MAPK, PI3K–AKT, signal transducer and activator of transcription (STAT) and phospholipase Cγ (PLCγ).

the non-selective multikinase inhibitors, Dovitinib has a wide range of off-target effects including other receptors of the RTK (receptor tyrosine kinase) superfamily, in addition to FGFR3, vascular endothelial growth factor receptor (VEGFRs), FGFR1, platelet-derived growth factor receptor type 3 (PDGFR-3), FMS-like tyrosine kinase 3, stem cell factor receptor (c-KIT), and colony-stimulating factor receptor 1 is undergoing early phase clinical studies (NCT01831726, NCT01379534, NCT01732107, NCT01719549). In a phase III trial, another multikinase inhibitor, nintedanib, in combination with docetaxel compared to docetaxel plus placebo, showed a modest improvement in progression-free survival (PFS) 3–4 months versus 2–7 months; with a hazard ratio of 0–79 ($P = 0.0019$). The benefit was higher for the adenocarcinoma histology, where median overall survival was 6–12 months versus 3–10 months; HR 0–83 ($P = 0·0359$) favoring the combination group. Lucitanib is another novel dual inhibitor undergoing early-phase clinical trials. It targets FGFR in addition to VEGFRs and has been shown to have anti-angiogenic activity in addition to anti-tumor proliferation effects in preclinical studies (NCT01283945, NCT02109016).[36] Ponatinib, another multi-target kinase inhibitor, has also been used against FGFR-driven tumors, and has completed accrual (NCT01761747).

TABLE 1. Representative Genomically-Driven Clinical Trials of Various FGFR Inhibitors

Agent	Phase	Clinical trials. gov ID	Histology Inclusion Criteria	Status	Molecular Eligibility	Lung Cancer Enrollment	Head and Neck Cancer Enrollment
				**Nonselective FGFR inhibitors**			
Dovitinib	1	NCT01831726	Advanced and/or metastatic solid cancer or hematologic malignancies	Active, not recruiting	FGFR1-4 mutant tumors (mutations or translocations of FGFR, PDGFR, VEGF, cKIT, FLT3, CSFR1, Trk and RET)	Yes	Yes
	2	NCT01379534	Advanced and/or metastatic endometrial cancer	Completed	FGFR2-mutant or wild-type endometrial cancer	No	No
	2	NCT01732107	Early-stage urothelial carcinoma of the bladder defined as Ta, T1, or Tis stage	Active, not recruiting	FGFR3-mutant or overexpressed BCG refractory urothelial carcinoma	No	No
	2	NCT01719549	Metastatic or unresectable adenocarcinoma of stomach or gastroesophageal junction	Recruiting	FGFR2-amplified gastric cancer	No	No
Lucitanib	½	NCT01283945	Locally advanced or metastatic solid tumour, relapsed or refractory to standard therapy	Active, not recruiting	Expansion cohort in FGFR1-amplified tumors	Yes	Yes
	2	NCT02109016	Advanced/metastatic lung cancer	Recruiting	FGF, vascular endothelial growth factor receptor (VEGF), or platelet derived growth factor (PDGF) related genetic alterations.	Yes	No
Ponatinib	2/3	NCT01761747	Lung or head and neck squamous cell cancer with an alteration in FGFR kinase	Completed	Advanced squamous cell lung cancers with FGFR kinase alterations	Yes	Yes

(continued)

Other selective FGFR inhibitors such as BGJ398, BAY1163877, AZD4547, and JNJ-42756493 are being evaluated in several cancers harboring FGFR amplification and mutation. While several are being tested in lung cancers and various other solid tumors, a few are available for head and neck cancer in early-phase clinical trials as well. BGJ398 is a pan FGFR kinase inhibitor that has been tested in a phase I dose escalation study in patients with advanced solid malignancies harboring either FGFR1 or FGFR2 amplification or FGFR3 mutations (NCT01004224). AZD4547, a novel and selective inhibitor of the FGFR1, 2, and 3 tyrosine kinases[37], is investi-

gated in a phase I/II clinical trial, assessing the efficacy, safety, and tolerability of this inhibitor compared with or without paclitaxel in patients with recurrent non-small–cell lung cancer (NCT01824901). An ongoing JNJ-42756493 phase I study includes efforts to optimize dose and schedule and to analyze biomarkers. Expansion cohorts are currently enrolling patients with FGFR-aberrant tumors, including lung and breast cancer (NCT01703481). Several other selective FGFR targeted agent candidates are in various stages of clinical trials (NCT01212107, NCT01976741, NCT01752920).

In terms of toxicity profiles, selective FGFR inhibitors have

(continued)

			Selective FGFR inhibitors				
AZD4547	1	NCT00979134	Solid malignant tumor without standard treatment options or resistance to standard therapies	Active, not recruiting	Expansion cohort in FGFR1- or FGFR2 amplified tumors	Yes	Not yet
	2	NCT01457846	Locally advanced or metastatic gastro adenocarcinoma	Completed	Gastric or lower-esophageal cancer, FGFR2-amplified or not, randomized to AZD4547 or paclitaxel	No	No
	½	NCT01202591	Breast cancer with ER+ receptor	Completed	Estrogen receptor + and FGFR1-amplified breast cancer, randomized to AZD4547 plus fulvestrant or fulvestrant alone	No	No
	2/3	NCT02154490	Non small cell lung cancers - stage 3B, 4 and recurrent; squamous cell lung cancer	Recruiting	Tumors positive for FGFR1, FGFR2, and FGFR3	Yes	No
	2	NCT01795768	Gastric, esophageal, breast and squamous lung cancers	Recruiting	FGFR1- or FGFR2-amplified	Yes	No
BGJ398	2	NCT02160041	Solid tumor (except with a primary diagnosis of urothelial cell carcinoma, cholangiocarcinoma, endometrial cancer, and glioblastoma multiforme) or hematologic malignancies	Recruiting	FGFR Genetic Alterations advanced cancer	Yes	Yes
	1	NCT01004224	Advanced solid tumors	Recruiting	FGFR1- or FGFR2-amplified, FGFR3-mutant advanced cancer	Yes	Yes
LY2874455	1	NCT01212107	Solid tumors, lymphoma, or chronic lymphocytic leukemia that is advanced and/or metastatic	Completed	Advanced cancer with FGFR aberrations during dose expansion	Yes	Yes
BAY1163877	1	NCT01976741	All solid malignancy, once MTD defined – lung and head and neck, and bladder cancer	Recruiting	Advanced cancer with FGFR aberrations during dose expansion	Yes	Yes
ARQ 087	1	NCT01752920	Advanced solid tumors	Recruiting	Expanded Cohort to include FGFR genetic alterations, including intrahepatic cholangiocarcinoma with FGFR2 gene fusion	Yes	Yes
JNJ-42756493	1	NCT01703481	Solid malignancy or lymphoma that is metastatic or unresectable	Recruiting	Expansion cohort in FGFR1-, FGFR2-, or FGFR4-amplified tumors	Yes	Yes

been able to overcome toxicity constraints of multi-target kinase inhibition, which often exhibit a wide range of toxicity. In the reported phase I results from the specific FGFR inhibitor JNJ-42756493 trial, the most common treatment-emergent adverse events included hyperphosphatemia (65%), asthenia (55%), dry mouth (45%), nail toxicity (35%), constipation (34%), decreased appetite (32%), and dysgeusia (31%).[38] Dose-dependent elevations in serum phosphate have been noted to be a predicted pharmacodynamics effect of selective FGFR inhibition, and guidelines to manage the toxicity have been published.[39]

Future Directions

Given the tolerability of selective FGFR inhibitors with manageable side effect profiles, they could be used in combination with other targeted therapies or immunotherapies for improving anti-cancer activity. Given the rationale of FGFR pathway aberration for acquired resistance to EGFR directed therapies, FGFR inhibitors may have a role to overcome this resistance if used in combination. Another potential strategy could be to combine with downstream inhibitors, such as either PI3K pathway or RAF/MEK inhibitors. With the approval of anti-programmed cell death protein 1 (anti PD-1) antibody in SqNSCLC, a cancer known to have aberrations in FGFR pathways and anticipated approval of the same antibody in head and neck cancer[40], future studies may be designed for the combination of FGFR inhibitors with immunotherapy.

Conclusion

The FGFR signaling pathway has been identified as a major contributing factor in the pathogenesis and progression of NSCLC and HNSCC. In addition, this pathway may function as a mechanism of resistance to anti-EGFR and anti-VEGF treatment. Targeting FGFRs is a promising therapeutic strategy in these cancers. Until now, phase I and II trials with FGFR inhibitors have shown an improvement for the survival of advanced cancer patients. The tolerability profile seems to be acceptable in these clinical trials. However, questions such as what class of agents are the most promising (nonselective vs selective FGFR inhibitors), and whether combination therapies are needed in order to obtain meaningful clinical benefit, are still being answered.

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