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Anti-Tumour Treatment

FGFR as potential target in the treatment of squamous non small cell lung cancer

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ABSTRACT

To date therapeutic options for squamous cell lung cancer patients remain scarce because no druggable targets have been identified so far. Aberrant signaling by FGFs (fibroblast growth factors) and FGFRs (fibroblast growth factors receptors) has been implicated in several human cancers and, particularly, in squamous non-small cell lung cancer (NSCLC).

FGFR gene amplifications, somatic missense mutations, chromosomal translocations are the most frequent mechanisms able to induce aberrant activation of this pathway. Data from literature have established that the presence of an aberrant FGFR signaling has to be considered a possible negative prognostic factor but predictive of potential sensitivity to FGFR inhibitors.

In the last years, clinical research efforts allowed to identify and evaluate promising FGFR inhibitors, such as monoclonal antibodies, ligand traps, non-selective or selective tyrosine kinase inhibitors. This review summarizes the current knowledge about FGFR alterations in NSCLC and the relative inhibitors in development, in particular in squamous NSCLC.

Introduction

Lung cancer is classified into two main histologic types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), accounting for 87% and 13% of all cases, respectively. The main histologic subtypes of NSCLC are adenocarcinoma (Ad-NSCLC, 50–60%), squamous cell carcinoma (Sq-NSCLC, 30–35%) and large-cell carcinoma (LCC, 5–10%) [1].

In the last years, potentially targetable oncogene products have been recognized in approximately 60% of Ad-NSCLC [2–5]; conversely, Sq-NSCLC remains an "orphan" tumor to date; in fact, targeted agents have not yet been developed and chemotherapy continues to be the standard of care in this histotype [6].

By using high-throughput molecular technologies, ever-growing information about distinct genomic alterations in Sq-NSCLC are becoming available [7,8]. Recently, the Cancer Genome Atlas Research Network reported an integrated analysis based on DNA copy number, exonic mutations, mRNA sequencing and expression and epigenetic alterations in 178 Sq-NSCLC samples [8]. A mean of 360 exonic mutations, 323 altered copy number segments and 165 genomic rearrangements per tumor was identified. SOX2 amplification, NFE2L2, KEAP1, discoidin domain receptor 2 (DDR2) mutations, phosphatidyl-inositol 3-kinase (PI3K) pathway changes and fibroblast growth factor receptor 1 (FGFR1) amplification, rare in Ad-NSCLC, confirmed the distinct molecular features of Sq-NSCLC. Potential druggable alterations were identified in 64% of cases.

Among them, DDR2 mutation was reported in 1–4% of Sq-NSCLC and its sensitivity to dasatinib inhibition was demonstrated both *in vitro* and *in vivo* [9,10]. Alterations in PI3K/AKT/mTOR pathway have shown to be mutually exclusive with EGFR ones (in contrast to that reported in Ad-NSCLC) and include PIK3CA mutations (3–10%) or amplification (25–40%), loss of PTEN (8–59%) or PTEN mutation (3–10%) and AKT1 or AKT2 overexpression (19% and 32%, respectively) [11]. Together with PI3K pathway, fibroblast growth factor receptor (FGFR) turns out as one of the most promising druggable target in Sq-NSCLC [12,13].

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FGF–FGFR: structure, signaling and functions

FGFs and FGFRs

In humans 22 members of FGFR ligands (FGFs) have been identified. The majority of FGFs contains a high sequence homology region, necessary for the ligand–receptor interaction. Furthermore, most of the FGFs contain a heparin sulfate proteoglycan (HSPG) region; the binding with HSPG protects the ligands from degradation and it is also involved in the complex formation between the FGFs and the FGFRs. [Fig. 1A] [14,15].

The FGFRs are 4 single-pass, transmembrane, tyrosine kinase (TK) receptors (FGFR1–4) consisting of an extracellular portion, a transmembrane region and an intracellular domain. The extracellular region is composed of three immunoglobulin-like domains (Ig-I, Ig-II and Ig-III). Ig-I is responsible for binding affinity; Ig-II constitutes the binding site for FGF and the latter is crucial for the ligand binding selectivity [Fig. 1B]. Due to alternative splicing in Ig-III domain of FGFR1–3, there are several isoforms with different FGF-binding specificity; among them, FGFR IIIb and IIIc are epithelial and mesenchymal isoforms, respectively [16]. The extracellular domain contains also the acidic box necessary for the interaction between HSPGs and FGFRs, the HSPG binding domain and another region responsible for the interaction with cellular adhesion molecules and extracellular matrix. The transmembrane domain acts as stabilizer of receptor conformation, essential for its ligand-dependent activation. The juxtamembrane region contains the binding sites for signaling effectors/modulators, such as PKC and FRS2α. Finally, the TK domains have the catalytic activity and recruit specific effectors able to activate different downstream signaling pathways [14,15]. In addition, there is a fifth FGFR (FGFRL1) without TK activity [17].

FGF/FGFR signaling and functions

Upon ligand–receptor binding, FGFR dimerizes and, in turn, it phosphorylates FRS2α, leading to GRB2 recruitment and, ultimately, to the activation of different pathways. The main downstream signaling pathways are RAS/MAPK and PI3K/AKT/mTOR cascades. The activation of these signaling pathways, together with PLCγ/Ca^{2+}, promotes cell survival, motility and invasiveness, cell proliferation, epithelial-to-mesenchymal transition (EMT), angiogenesis [Fig. 2]. After activation, the receptor complex is internalized by endocytosis, degraded by lysosomes or inactivated by polyubiquitination process [18].

FGFs and FGFRs are expressed in several normal cells and tissues of epithelial and mesenchymal origin. In embryonic life, they have a crucial role in angiogenesis, formation and development of different organs and specific FGFR2 and FGFR3 point mutations have been associated with congenital skeletal disorders [19–21]. In adults, FGF/FGFR signaling mediates tissue homeostasis and plays a fundamental role in inflammation processes, in neoangiogenesis and vessel maturation during wound healing and tissue repair [14,18,22,23].

FGFR alterations in NSCLC

In human cancers, FGF/FGFR signaling can be aberrantly activated as a result of ligand-dependent or ligand-independent mechanisms. FGFR gene amplifications, somatic missense mutations and chromosomal translocations, leading to receptor overexpression and/or constitutive FGFR or FGFR-TK activation; alternative splicing, leading to altered ligand–receptor specificity; paracrine/autocrine signaling, due to FGF upregulation, and FGFR germline single nucleotide polymorphisms (SNPs) are the most frequent mechanisms of activation [24]. Table 1 and Fig. 3 summarize the principal FGF/FGFR alterations in NSCLC cancers. In particular, in Sq-NSCLC, FGF/FGFR pathway has been recognized as one of the hallmark alterations with relevant clinical implications.

FGFR gene amplifications

The amplification of FGFR1 gene, located on chromosome 8p12, is a common potentially druggable alteration in NSCLC. Several studies have demonstrated that FGFR1 gene amplification incidence is significantly higher in Sq-NSCLC (22%) than in Ad-NSCLC (3%) [25–33]. Moreover, FGFR1 amplification tends to correlate with smoking status, with higher frequency in current smokers than in former and never-smokers [25,32]. No other specific clinico-demographic features correlate with FGFR1 amplification.

Recently, several groups have investigated the potential role of FGFR1 gene amplification as prognostic factor in resected NSCLC patients [29,31,32,34]. Kim and colleagues [32] showed that resected patients whose tumors harbored high FGFR1 gene amplification (34/262, 13%) had significant shorter disease-free survival (DFS) and overall survival (OS) than those without FGFR1 gene amplification (26.9 vs. 94.6 months, $p < 0.001$; 51.2 vs. 115.0 months, $p = 0.002$, respectively). A multivariate analysis confirmed FGFR1 gene amplification as an independent negative prognostic factor, as well as other studies [31,34,35], whereas a Canadian report did not [29]. A meta-analysis of 13 published studies in Sq-NSCLC showed a FGFR1 amplification rate of 19%, significantly correlated with smoking status and lymph node metastasis, not able to influence OS [25].

More recently, it has been shown that tumorigenic potential of FGFR1 amplification depends on multiple factors. A recent study demonstrated a genomic heterogeneity of FGFR1-amplified Sq-NSCLC that could affect its sensitivity to FGFR inhibition. It has been shown that the 8p12 (including FGFR1) amplicon clustered together with the 11q13 (including CCND1, FGF4 and FGF19). This co-occurred event seems to be related to a higher sensitivity to FGFR inhibition. Furthermore, the co-expression of high levels of c-MYC, as well as FGFs, induced in FGFR1-amplified cells higher oncogenic transformation, cell-autonomous signaling and higher FGFR inhibitor sensitivity both *in vitro* and *in vivo* [30]. Hence, these data suggest an evidence to refine patients who will be likely benefit from FGFR inhibitor treatment.

FGFR gene mutations

Somatic FGFR mutations in lung tumors occur at the same positions to germline FGFR2 and FGFR3 mutations and may contribute to lung cancer development [36]. No correlation between FGFR mutations and histology subtype has been reported.

Recently, through a whole-genome sequencing platform, 210 human cancers were screened and more than one thousand somatic mutations were identified. In this cohort, 88 lung tumors were included and the highest prevalence (4.21 per Mb) of somatic mutations was seen among them. Overall, FGFR mutations were detected in 10% of lung tumor samples. FGFR2 mutations (3.4% in lung tumors) showed a high selection pressure with an excess of non-synonymous mutations, providing evidence for its role as oncogenic driver [37].

Another study evaluated FGFR2 and FGFR3 mutations in Sq-NSCLC. Overall, 12 (6.7%) mutations in the FGFR2 (6 cases) and FGFR3 (6 cases) genes were detected. The presence of specific mutations in the extracellular domains of FGFR2 (W290C and S320C) and FGFR3 (R248C and S249C) was responsible for cellular transformation, as did K660E and K660N mutations in the kinase domains of FGFR2, both *in vitro* and in xenograft models [38]. It is noteworthy that W290C, S320C and K660N mutations showed

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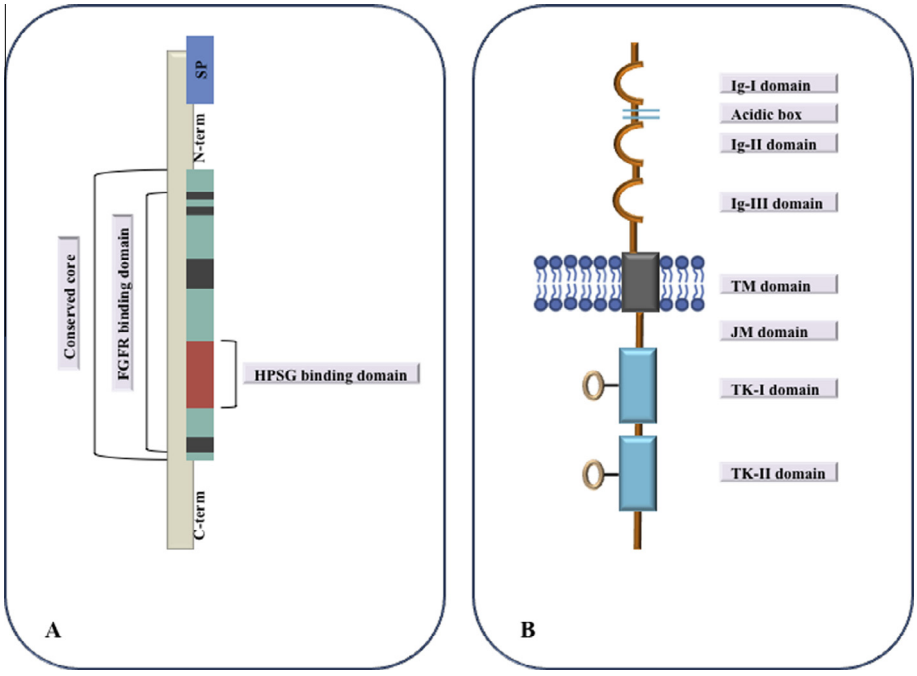

Fig. 1. Structure of the majority of FGFs (A) and FGF receptors (B). (A) FGF is composed of a signal peptide (SP), an amino-terminal coil, a conserved core (a high-sequence homology region), including both FGFR- and heparin (HPSG)-binding sites, and the carboxy-terminal coil. (B) FGF receptor includes three immunoglobulin (Ig) domains, an acidic box, a trans-membrane (TM) domain, a juxta-membrane (JM) region, and two tyrosine kinase (TK) domains.

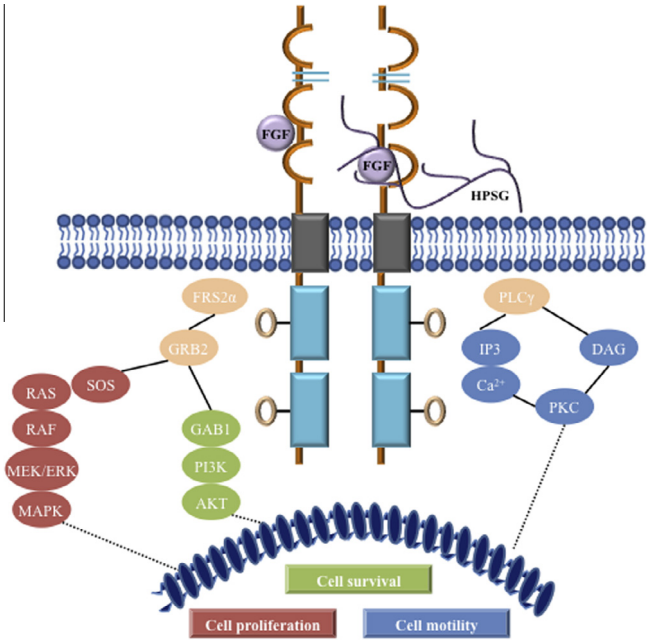

Fig. 2. The FGF/FGFR signaling cascade. The FGF/FGFR network regulates cell survival, proliferation and motility. The main downstream signaling pathways are RAS/MAPK and PI3K/AKT/mTOR cascades.

different oncogenic potential in xenograft models while other FGFR2 (E471Q and T787K) or FGFR3 (S435C and K717M) mutations were not oncogenic when tested in an anchorage-independent growth assay. However, *in vivo* oncogenic activity of many other variants has not been validated so far, and further studies are needed. In any case, the sensitivity to pan-FGFR and multi-kinase inhibitors provided preclinical evidence for their role as potential oncogenic driver and druggable targets [38]. Sporadic cases of non-synonymous FGFR4 mutations (P672T and E681K) in current smoker Ad-NSCLC patients have also been reported [36,39].

FGFR gene fusions

FGFR1/3 fusions occurred in about 1% of patients with NSCLC and 2–3.5% of patients with Sq-NSCLC [40,41].

By using an integrative whole-exome and transcriptome sequencing platform, Wu et al. [40], isolated from Sq-NSCLCs six rearrangements (1 BAG4-FGFR1, 1 FGFR2-KIAA1967 and 4 FGFR3-TACC3) biologically active and sensitive to FGFR inhibitors, such as PD173074 and pazopanib. It was noteworthy that FGFR3 gene fusion-positive tumors had enhanced susceptibility to FGFR inhibition over FGFR3-mutant cell lines [40].

Furthermore, it has been shown that compared with the FGFR fusion-negative group, patients with FGFR fusions were more likely to be smokers, significantly associated with larger tumor and with a tendency to be more poorly differentiated. No difference in terms of progression free survival (PFS) and OS was seen between FGFR1/3 fusion positive and negative tumor patients [42].

FGFR3-TACC3 fusion transcripts were also detected in 0.5% of Ad-NSCLC and predominantly in never/light smoker patients [41].

Table 1
Principal genomic FGFR alterations in NSCLC.

Tumor type	Gene	Alteration	Incidence (%)	Refs.
Sq-NSCLC	FGFR1	Amplification	11–22	[25–33]
	FGFR1	Mutation	2	[37]
	FGFR2	Mutation	3–5	[37,38]
	FGFR3	Mutation	2–3	[37,38]
	FGFR4	Mutation	2	[37]
	FGFR3-TACC3	Translocation	1–3.5	[40,42]
	BAG4-FGFR1	Translocation	0.3–0.6	[40,42]
	FGFR2-KIAA1967	Translocation	0.3	[40]
Ad-NSCLC	FGFR1	Amplification	2.2–3.4	[31,35]
	FGFR3-TACC3	Translocation	0.5	[41,42]

Sq-NSCLC, squamous non small cell lung cancer; Ad-NSCLC, adenocarcinoma non small cell lung cancer.

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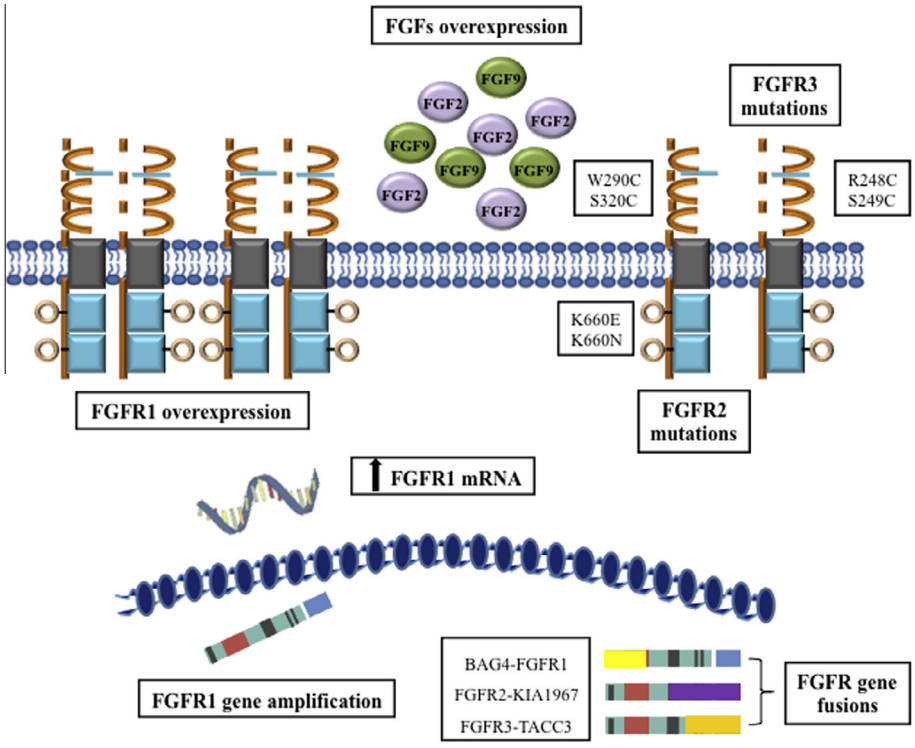

Fig. 3. FGF–FGFR alterations. Potential targetable FGF/FGFR biomarkers include overexpression of FGF family members, FGFR1 overexpression (by gene amplification or increased mRNA FGFR1 transcription), FGFR2 mutations in the extracellular and in the kinase domain (W290C, S320C and K660E/N respectively), FGFR3 mutation in the extracellular domain (R248C, S249C) and FGFR gene fusions (BAG4-FGFR1, FGFR2-KIA1967, FGFR3-TACC3).

Autocrine/paracrine signaling

Multiple FGFs, such as FGF2 (also called basic FGF, b-FGF) and FGF9, are upregulated in NSCLC cell lines and involved in EMT and cancer progression. Furthermore, the existence of an additive synergism between FGFs and other angiogenic pathways, such as VEGFR and PDGFR, has been shown [43]. The use of a FGF2-specific shRNA or a multiple anti-angiogenic TK inhibitor blocked cell proliferation and tumor growth by reduction of FGF2 expression [43]. Finally, high levels of FGF2 were predictive of resistance to EGFR-TK inhibitors [43], as also of resistance to VEGF and VEGFR-TK inhibitors in colorectal [44] and glioblastoma [45] models, respectively.

Different studies have evaluated b-FGF as prognostic factor in NSCLC [46–53]; some of them reported a significant correlation between tumor b-FGF expression and poor outcome [46,49]; conversely, others showed opposite results [47,50].

FGFR germline polymorphisms and new insights

Genetic variations, such as germline SNPs, have been associated with enhanced tumor risk. A correlation between specific variants in the FGFR2 gene and increased susceptibility to breast cancer has been confirmed [54]. Conversely, a specific polymorphism in the FGFR4 gene (Gly388Arg) has been associated with tumor progression rather than tumor risk in different cancer types [55,56], including also lung adenocarcinoma [57]. The analysis of the Gly388Arg polymorphism has revealed a significant association with an earlier age at cancer onset ($p = 0.002$), advanced stage ($p = 0.002$) and poor survival ($p = 0.007$) [57].

More recently, a large-scale RNAi-based mouse tumorigenesis screen identified twenty-four tumor suppressor genes (TSGs) that were significantly down-regulated in human Sq-NSCLCs. A part of these TSGs encoded repressors of FGFR signaling. The down-regulation of these suppressors led to activation of FGFR signaling, as a consequence of increased levels of phosphorylated FRS2-Y436, and rendered in most cases tumor cells sensitive to FGFR inhibitors. These data support the hypothesis that aberrant FGFR signaling pathway may drive tumorigenesis in human Sq-NSCLC even in the absence of FGFR amplification, translocation or activating mutation [58].

FGF/FGFR pathway as predictive factor

Several studies have identified FGFR1 amplification as the major predictive factor of response to FGFR inhibitors [26,27]. However, in a recent study on lung cancer cell lines with ponatinib, FGFR1 mRNA and protein expression, together with FGF2 and FGF9 mRNA, were better predictive biomarkers of sensitivity than FGFR1 gene copy number [59]. These data were evaluated also in resected lung tumors. Approximately 50% of Sq-NSCLC with high FGFR1 gene copy number expressed high FGFR1 mRNA levels. At once, increased FGFR1 gene copy number included a significant fraction of Sq-NSCLC not expressing FGFR1 mRNA or protein (18%), providing evidence for considering that FGFR1 amplification could be occurred in both sensitive and resistant cell lines [59].

Furthermore, hot topics on the role of FGF/FGFR pathway as predictor of resistance to other targeted agents are emerging. FGFR signaling seems to be involved in tumor growth by an autocrine mechanism and may be considered a specific pathway of insensitivity to EGFR-TK inhibitors. FGF2 and FGF9 mRNA levels were significantly higher in gefitinib-insensitive cells and the use of FGF2-specific shRNAs or FGFR TK inhibitors induced cell growth arrest [43,60,61]. Furthermore, also FGFR2 and FGFR3 were de-repressed after gefitinib exposure, leading to a rapid mechanism of acquired resistance to EGFR-TK inhibitor [62]. A treatment with gefitinib and AZD4547 allowed to prevent the outgrowth of drug resistant cell clones, supporting the use of a combinatorial therapy

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to prevent or delay acquired resistance in EGFR-addicted NSCLC [63]. Another study showed that the concomitant use of FGFR-TK inhibitors (SU5402 or PD166866) and EGFR-TK inhibitors (erlotinib or lapatinib) was responsible for a markedly reduced cell proliferation over FGFR-TK inhibitor alone. Conversely, the concomitant administration of FGFR inhibitors and chemotherapeutics was detrimental [64]. Unfortunately, when this approach was applied in clinical trials it failed because of toxicity (see phase I trial, NCT01515969, combining erlotinib and dovitinib in advanced NSCLC).

More recently, a potential role of FGFR3 as predictive marker for MET-targeted therapy has been reported. FGFR3 seems to be highly expressed in specific MET-amplified cells and its suppression enhanced the antiproliferative effects of a MET-monoclonal antibody, providing evidence for the presence of a specific crosstalk between FGFR and MET pathways [65].

Furthermore, a growing body of research have suggested that FGF/FGFR signaling pathway may also play a role in the resistance to anti-VEGF therapy after the evidence of high FGF2 levels in different cell models at the time of disease progression [22].

From preclinical evidences to clinical data

The deregulation of FGF/FGFR pathway can be considered as a mechanism of oncogene-addiction and, in some cases, oncogene-expedience. Therefore, different treatment strategies including the administration of a FGFR inhibitor alone or in combination with other target drugs or chemotherapy (concomitantly or sequentially) have to be investigated.

Several preclinical data have shown that selective FGFR-TK inhibitors [26,27], multi-TK inhibitors [38,40,41,43], FGFR1-specific shRNAs [27] or FGF2-specific shRNAs [43] were capable of blocking tumor growth in different FGFR-addicted NSCLC cell lines.

In the last years, clinical research efforts allowed to identify and evaluate promising FGFR inhibitors and some of them are under development in clinical trials.

To block FGF/FGFR pathway, different targeted molecules have been developed: (1) monoclonal antibodies (mAbs); (2) ligand traps; (3) non-selective TK inhibitors and (4) selective TK inhibitors. Ongoing clinical trials in lung cancer are reported in Table 2.

FGFR mAbs

The clinical development of several mAbs directed against specific FGFRs may be an attractive strategy for treating different FGFR-addicted solid tumors because of their high selectivity and low toxicity when compared with pan-FGFR inhibitors.

MFGR1877S is the most promising agent of this class. It specifically acts on isoforms IIIb/IIIc of FGFR3. A phase I dose escalation study showed that MFGR1877S was well tolerated in 26 patients with advanced solid malignancies. A maximum tolerated dose (MTD) was not reached. There was a dose limiting toxicity (DLT) of grade 4 thrombocytopenia and recommended phase 2 dose (RP2D) was set at 30 mg/kg. The most frequent adverse events (AEs) were nausea and fatigue. In terms of efficacy, 9 out of 26 patients (35%) experienced a disease stabilization [66]. No clinical trial of MFGR1877S is currently ongoing in lung cancer.

FGF-ligand traps

This class of compounds includes some specific proteins (FGF-traps) that are capable of blocking FGF-FGFR binding, by sequestering endogenous FGF ligands released by tumor cells or tumor stroma.

FP-1039/GSK3052230 is the first-in-class ligand trap, currently investigated in phase I/II clinical trials. It is a soluble decoy receptor containing the extracellular domains of human FGFR1c isoform linked to the Fc regions of human immunoglobulin G1.

In preclinical models, this compound demonstrated its activity by inhibiting tumor growth both *in vitro* and in xenograft models of several tumor types, including NSCLC [67].

A phase I dose escalation study reported preliminary data on safety. This study enrolled 33 patients with advanced solid tumors, including 3 with lung cancer. The main AEs were gastrointestinal disorders, fatigue, and peripheral edema. No DLTs were observed in the 15 patients dosed from 2.0 to 16.0 mg/kg and the maximum feasible dose (MFD) was set at 20 mg/kg weekly. Pharmacokinetics (PKs) supported weekly dosing and pharmacodynamics demonstrated a significant decrease of serum FGF2 levels during treatment period. Disease control rate (DCR) was 42% [68]. This compound is currently being evaluated in a three-arm, non-randomized, open-label phase Ib trial. The objective of this study is to evaluate safety and efficacy of FP1039 in combination with chemotherapy in FGFR1-amplified Sq-NSCLC and in malignant pleural mesothelioma [NCT01868022] [Table 2].

Non-selective FGFR-TK inhibitors

This class of compounds includes several ATP-competitive small molecules directed against FGFR TK domain, but also other structurally related tyrosine kinase domains, including VEGFR, RET, PDGFR, KIT, FLT3, BCR-ABL. These multitarget inhibitors have demonstrated to be active in the context of FGFR-addicted tumors but, because of the lack of kinase selectivity, their use is limited by a variety of side effects. Among them, the molecules at more advanced clinical development are dovitinib, nintedanib, cediranib, ponatinib, lucitanib and pazopanib. Other compounds, such as brivanib, lenvatinib, orantinib are under investigation in other tumor types and have demonstrated to be more active against VEGFR or other TKs than against FGFRs. The IC_{50} versus the different targets are shown in Table 3. The non-selective FGFR TK inhibitors have a specific toxicity profile primarily dependent on VEGF/VEGFR inhibition. Treatment with the VEGF inhibitors, such as bevacizumab, has shown a significant higher risk of cardiovascular complications and bleeding, particularly in Sq-NSCLC patients [69]. This risk led to approval bevacizumab in combination with chemotherapy as first-line treatment in NSCLC, except squamous histology. For these reasons, exclusion criteria in ongoing trials, particularly with non-selective FGFR TK inhibitors, do not allow to enroll patients with a history of clinically significant bleeding disorder or baseline hemoptysis, therapeutic anticoagulation and central tumors with cavitation.

Dovitinib (TKI258) is an inhibitor of VEGFR1–3, FGFR1/3, FLT3, KIT, RET and PDGFR-β. It has a potent anti-angiogenic activity through the inhibition of PDGFR, VEGFR and FGFR [70,71]. In a phase I dose escalation study enrolling 35 patients with advanced solid tumors a partial response (PR) and 2 long stable disease (SD) with a tolerable toxicity profile were observed. The most frequent AEs were diarrhea and fatigue; 14% of patients experienced toxicities related to VEGFR pathway inhibition, such as hypertension and left ventricular ejection fraction decrease [72]. Currently, this compound is being evaluated in different solid malignancies both in phase II and III trials [73,74]. A phase I trial enrolling advanced NSCLC patients for a combined therapy with dovitinib and erlotinib was suspended because of toxicity data at the interim analysis. Two phase II studies are currently evaluating dovitinib as monotherapy in NSCLC [NCT01676714] and in FGFR1-amplified Sq-NSCLC patients [NCT01861197] [Table 2].

Nintedanib (BIBF1120) is a multitarget small tyrosine kinase inhibitor directed against FGFR1–4, VEGFR1–3, PDGFRA-B and

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Table 2
Ongoing trials on FGFR inhibitors in NSCLC.

Drug	Target (s)	Tumor type (s)	Inclusion criteria	Phase	Arm (s)	Objectives	Status
FGF traps							
FP-1039/GSK3052230	FGF	Metastatic recurrent Sq-NSCLC with FGFR1 amplification and recurrent/unresectable MPM [NCT01868022]	Sq-NSCLC • FGFR1-ampl • 1st line (Arm A) • 2nd line (Arm B) MPM • FGF2 expression • 1st line (Arm C) • ECOG PS 0–1 (Arm A) • ECOG PS 0–2 (Arms B, C)	Ib	A. FP1039 5 mg/kg i.v. weekly + paclitaxel 200 mg/mq and CBDCA AUC 6 d1 q21 B. FP1039 5 mg/kg i.v. weekly + docetaxel 75 mg/mq d1 q21 C. FP1039 5 mg/kg i.v. weekly + pemetrexed 500 mg/mq and CDDP 75 mg/mq d1 q21	AEs, DLTs, MTD, ORR; PFS, PK	Currently recruiting
Non-selective FGFR inhibitors							
Dovitinib/TKI258	VEGFR1–3, FGFR1/3, FLT3, KIT, RET, PDGFRB	Advanced NSCLC or colorectal cancer (CRC) previously treated with anti-VEGF therapy [NCT01676714]	• Immediate prior treatment regimen with a anti-VEGF agent (bevacizumab, sunitinib, sorafenib) • No potentially curative treatment options	II	Dovitinib 500 mg once daily for 5 continuous day weekly	ORR; DCR, PFS, toxicities	Currently recruiting
		Previously treated FGFR1-amplified Sq-NSCLC patients [NCT01861197]	• Sq-NSCLC • 1–2 prior therapies • FGFR-ampl (FISH > 5 gene copies)	II	Dovitinib 500 mg daily for 5 days on/2 day off	ORR	Currently recruiting
Nintedanib/BIBF1120	VEGFR1–3 PDGFRα-β FGFR1–3	Phase I dose escalation trial in elderly patients with stage IV NSCLC [NCT01684111]	• Age > 70 years • ECOG PS < 2 • No previous therapies	I	Nintedanib 150 mg BID (starting dose level) + Vinorelbine25 mg/mq i.v. dd1,8 q21	MTD; AEs, PK, ORR	Currently recruiting
		Phase I safety run-in trial in Japanese patients with advanced/metastatic Ad-NSCLC [NCT02300298]	• Ad-NSCLC • Japanese population • Prior 1st line platinum-based • ECOG PS ⩽ 1	I	Nintedanib 200 mg BID q28 + docetaxel 75 mg/mq iv q21	DLTs cycle 1; AEs, PK	Currently recruiting
		First-line treatment in Sq-NSCLC [NCT01346540]	• Stage IIIB/IV or recurrent Sq-NSCLC • ECOG PS ⩽ 1 • No PRO after 2 cycles of GEM/CDDP • No previous therapy with other antivascular drugs	I/II	Phase I (open label): nintedanib + gemcitabine and cisplatin Phase II: ⩾SD after 2 courses of gemcitabine + cisplatin: A. Nintedanib + gemcitabine and cisplatin B. Placebo + gemcitabine and cisplatin	MTD (Phase I), PFS (Phase II); ORR, OS, AEs	Ongoing, not recruiting
		Recurrent FGFR1-amplified and wild-type Sq-NSCLC after failure of 1 or 2 chemotherapy regimens [NCT01948141]	• Sq-NSCLC • Prior 2 chemoterapies • ECOG PS ⩽ 1 • FGFR1 ampl/non ampl	II	Nintedanib 200 mg BID q28	6-month PFS in FRGF1-amplified tumor group; 6-month PFS in FGFR1-wild type and FGFR1-amplified groups; PFS, OS, ORR by FGFR1 group; FGFR polymorphism, toxicity and efficacy	Currently recruiting
Ponatinib/AP24534	Pan-FGFR PDGFRA/B VEGFR1/3 RET	Locally-advanced or metastatic lung cancer preselected using different candidate predictive biomarkers [NCT01935336]	• Any histology (except carcinoid) • NSCLC (IIIA-IV) • SCLC (LD-ED) • EGFR wild type • No ALK fusions • FGFR1 [SISH+/ISH+, SISH+/ISH−, SISH−/ISH+, SISH−/ISH−] • RET FISH positive • ECOG PS ⩽ 2	II	Ponatinib 45 mg orally once or twice daily q28	Biomarkers, ORR; AEs	Currently recruiting
		Open-label study in advanced NSCLC with RET translocations [NCT01813734]	• RET translocation • No restriction on number of prior therapies	II	Ponatinib 45 mg orally once a day q28	ORR; DCR, PFS, 1-year OS rate, AEs, safety and tolerability	Currently recruiting

Table 2 (*continued*)

Drug	Target (s)	Tumor type (s)	Inclusion criteria	Phase	Arm (s)	Objectives	Status
Lucitanib/E3810	FGFR1/2 VEGFR1–3	FGFR1-amplified Sq-NSCLC [NCT02109016]	• Sq-NSCLC • FGFR1 amplification • At least one prior therapy • ECOG PS $\leqslant$ 1	II	Lucitanib 15 mg once daily q28	ORR; CBR, PFS, DOR, OS, AEs, PK, PD	Currently recruiting
Pazopanib/GW786034	FGFR1/3 VEGFR PDGFRc-KIT	First-line treatment for advanced NSCLC patients not eligible for front-line therapy with a platinum doublet [NCT01179269]	• No previous therapy • ECOG PS $\leqslant$ 2 • Unfit for doublet-chemotherapy regimen	II	Pazopanib daily and weekly paclitaxel i.v.	ORR	Currently recruiting
Selective FGFR TK inhibitors							
AZD4547	FGFR1–3	Recurrent Sq-NSCLC [NCT01824901]	• Sq-NSCLC • 2nd line treatment • ECOG PS $\leqslant$ 1 • FGFR1-ampl (Phase II)	I/II	Phase I: docetaxel d1 + AZD4547 d2–15 q21 Phase II: A. Docetaxel d1 q21 × 6 → PRO → AZD4547 d1–14 q21 B. Docetaxel d1 q21 × 6 + AZD4547 d1–14 q21 → AZD4547 d1–14 q21	RP2D (Ph I), PFS (Ph II); PK, safety/toxicity, clinical activity, ORR, OS	Ongoing, not recruiting
		FGFR1-amplified mBC, advanced Sq-NSCLC and FGFR2-amplified gastric cancer progressed following previous chemotherapy [NCT01795768]	Sq-NSCLC • FGFR1-ampl • 1–2 previous therapies Breast • FGFR1-ampl • Her2 negative • At least 1 prior hormone therapy • 1–3 previous chemotherapy Gastro-oesophageal • FGFR2-ampl • 1–2 previous chemotherapy • ECOG PS $\leqslant$ 1	II	AZD4547 80 mg orally twice daily 2 weeks on/1 week off q21	Antitumor activity; ORR, safety, DCR, PFS	Currently recruiting
		Metastatic NSCLC according to genomic profiles, including FGFR [NCT02117167]	• Squamous • Non-squamous • No previous chemotherapy • Suitable for 1st line platinum-based • ECOG PS $\leqslant$ 1 • No PRO after current line • EGFR wild type • No ALK fusions • Targeted therapy according to specific genomic profile (FGFR, mTOR, AKT, HER2/EGFR, MEK, VEGF/EGFR)	II	Induction platinum-based chemotherapy for 4 cycles with SD or PR → Maintenance: A. AZD4547 (FGFR) 80 mg BID; AZD2014 (mTOR) 50 mg BID; AZD5363 (AKT) 480 mg BID 4 days on/3 days off; AZD8931 (HER2, EGFR) 40 mg BID; Selumetinib (MEK) 75 mg BID; Vandetanib (VEGF, EGFR) 300 mg B. Pemetrexed 500 mg/mq eV d1 q21 (NSq-NSCLC); Erlotinib 150 mg (Sq-NSCLC)	PFS; OS, ORR, toxicities	Currently recruiting
		Recurrent IIIB/IV Sq-NSCLC [NCT02154490]	• Sq-NSCLC • 2nd line treatment • ECOG PS $\leqslant$ 2 • EGFR wild type • No ALK fusions • No drug-biomarkers (Arm A) • PIK3CA positive (Arm B) • CDK4/6, CCND1, CCND2 and CCND3 positive (Arm C) • FGFR1–3 positive (Arm D) • HGF-cMET positive (Arm E)	II/III	A. MEDI4736 (anti-B7H1) eV d1 q14 vs docetaxel d1 q21 B. GDC-0032 once daily q21 vs docetaxel d1 q21 C. Palbociclib once daily d1–21 q28 vs Docetaxel d1 q21 D. AZD4547 BID d1–21 vs docetaxel d1 q21 E. Rilotumumab eV d1 + erlotinib once daily q21 vs erlotinib once daily q21	PFS (Ph II), OS (Ph III); ORR, toxicities	Currently recruiting

(*continued on next page*)

Table 2 (*continued*)

Drug	Target (s)	Tumor type (s)	Inclusion criteria	Phase	Arm (s)	Objectives	Status
BGJ398	Pan-FGFR	Advanced solid tumors with FGFR1/2 amplifications or FGFR3 mutations [NCT01004224]	• FGFR1–3 gene alterations • FGFR1-ampl (Sq-NSCLC) • FGFR3 mutation/fusion (bladder cancer)	I	BGJ398 orally	MTD, RP2D, schedule; safety, tolerability, PK, PD, preliminary activity	Currently recruiting
		Advanced solid tumors with FGFR alteration in Asian patients [NCT01697605]	• FGFR gene alteration • Asian ethnicity • ECOG PS $\leqslant$ 2	I	BGJ398 orally once daily or twice daily	DLT; AEs, ORR, PFS	Currently recruiting
		Advanced solid tumors (ASTs) expressing PIK3CA mutations with or without FGFR alterations [NCT01928459]	• PIK3CA mutations (dose escalation + expansion) • FGFR gene alteration (expansion cohort) • No CRC (expansion cohort) • ECOG PS $\leqslant$ 2	Ib	BGJ398 orally once daily d1–21 q28 + BYL719 orally once daily die 1–28 Dose escalation part: A. ASTs PIK3CA mut Expansion part: B. mBC (PIK3CA mut + FGFR pos) C. ASTs (PIK3CA mut) D. ASTs (PIK3CA mut + FGFR pos)	DLT; safety and tolerability, ORR, PFS, PK	Currently recruiting
		Advanced solid tumors, including NSCLC, and haematological malignancies with FGFR genetic alterations [NCT02160041]	• FGFR gene alteration • ECOG PS $\leqslant$ 1	II	BGJ398 125 mg once daily d1–21 q28	CBR; ORR, PFS, OS, DOR, safety and tolerability	Currently recruiting
BAY1163877	Pan-FGFR	Advanced solid tumors (dose escalation), including Ad-NSCLC and Sq-NSCLC according to FGFR profile [NCT01976741]	• Ad-NSCLC • Sq-NSCLC • High FGFR expression • FGFR mutation	I	BAY1163877 BID	MTD, PK, PD, safety, tolerability; tumor response	Currently recruiting
JNJ-42756493	Pan-FGFR	Advanced solid tumors, including NSCLC, or lymphoma [NCT01703481]	• Pre- and post-treatment biopsies • Sq-NSCLC • ECOG PS $\leqslant$ 1	I	JNJ-42756493 once daily q21 Part 1: ASTs or lymphoma Part 2: ASTs Part 3: •NSCLC (cohort A) •SCLC (cohort B) •mBC (cohort C) •ASTs (cohort D)	MTD; PK, PD, ORR, AEs, DOR, PFS	Currently recruiting
GSK3052230	FGFR1	Advanced solid tumors and deregulated FGF pathway signaling [NCT01868022]	Sq-NSCLC • FGFR1-ampl • 1st line (Arm A) • 2nd line (Arm B) MPM • FGF2 expression • 1st line (Arm C) • ECOG PS $\leqslant$ 1 (Arm A) • ECOG PS $\leqslant$ 2 (Arms B, C)	Ib	A. GSK3052230 eV d1,8,15 + paclitaxel d1 + CBDCA d1 q21 B. GSK3052230 eV d1,8,15 + docetaxel d1 q21 C. GSK3052230 eV d1,8,15 + pemetrexed d1 + cisplatin d1 q21	AEs, safety and tolerability, DLT, MTD, ORR; PFS, PK	Currently recruiting

FGFR, fibroblast growth factor receptor; i.v., intravenous; Ad-NSCLC, adenocarcinoma-non small cell lung cancer; Sq-NSCLC, squamous non small cell lung cancer; MPM, malignant pleural mesothelioma; ECOG PS, Eastern Cooperative Oncology Group (ECOG) performance status (PS); CBDCA, carboplatin; CDDP, cisplatin; AEs, adverse events; DLTs, dose limiting toxicities; MTD, maximum tolerated dose; ORR, overall response rate; PFS, progression free survival, PK, pharmacokinetic; AST, advanced solid tumors; H/N, head/neck cancer; BID, bis in die; PD, pharmacodynamics; AEs, adverse events; DOR, duration of response; PIK3CA mut, PIK3CA mutation; CRC, colorectal cancer; mBC, metastatic breast cancer; DLT, dose limiting toxicity; RP2D, recommended phase 2 dose; PRO, progression disease; FGF, fibroblast growth factor; VEGFR, vascular endothelial growth factor receptor; BSA, body surface area; CBR, clinical benefit rate; QoL, quality of life; LD, limited disease; ED, extensive disease; SISH, silver in situ hybridization; ISH, in situ hybridization; FISH, fluorescent in situ hybridization.

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Table 3
Targets and IC_{50} values (nM).

	FGFR1	FGFR2	FGFR3	FGFR4	VEGFR1	VEGFR2	VEGFR3	PDGFR-α	PDGFR-β
Non-selective FGFR-TK inhibitors									
Dovitinib/TKI258									
Ref. [70]*	8	–	9	–	10	13	8	200	27
Ref. [71]*	16	50	53	341					
Nintedanib/BIBF1120									
Ref. [75]*	69	37	108	610	34	21	13	59	65
Ref. [71]*	47	63	122	451					
Cediranib/AZD2171									
Ref. [81]*	26	–	–	–	5.0	1.0	3.0	36	5
Ref. [71]*	5	33	36	697					
Ponatinib/AP24534									
Ref. [86]*	2.2	1.6	18.2	7.7	3.7	1.5	2.3	1.1	7.7
Ref. [71]*	2	2	18	8					
Lucitanib/E3810									
Ref. [88]*	17	82	237	>1000	7	25	10	175	525
Ref. [89]**	7	–	–	–	12	4	–	13	8
Pazopanib/GW786034									
Ref. [91]*	140	–	130	800	10	30	47	71	84
Selective FGFR-TK inhibitors									
LY2874455									
Ref. [94]*	2.8	2.6	6.4	6.0	–	7	–	–	–
AZD4547									
Ref. [95]*	0.2	2.5	1.8	165	–	24	–	–	–
BGJ398									
Ref. [100]*	0.9	1.4	1	60	–	–	–	–	–

* Biochemical kinase inhibition assay.
** Elisa assay.

FLT-3 [71,75]. Phase I studies evaluated this agent as single agent [76], in combination with pemetrexed in pretreated NSCLC patients [77] and with carboplatin and paclitaxel as first-line treatment of NSCLC [78], showing gastrointestinal disorders as the most frequent AEs and a response rate of 5–27%.

A phase I/II study evaluating nintedanib with cisplatin-gemcitabine as first-line treatment in advanced Sq-NSCLC patients is ongoing [NCT01346540] [Table 2]. A phase II trial confirmed its promising anti-tumor activity as monotherapy in 73 previously treated advanced NSCLC patients, with 1 PR and 35 SD and median PFS and OS of 6.9 and 21.9 weeks, respectively. The toxicity profile was similar to that seen in phase I trials [79].

Considering its activity and tolerable toxicity profile, nintedanib has been evaluated in two phase III trials (LUME-Lung 1 and 2) performed in advanced NSCLC patients after failure of first-line standard treatment. LUME-Lung 1 was designed to assess the efficacy and safety of docetaxel plus nintedanib as second-line treatment with PFS as primary end-point both in adenocarcinoma and in intent-to-treat (ITT) population. Patients were assigned to receive docetaxel plus nintedanib ($n = 655$) or plus placebo ($n = 659$). Nintedanib significantly improved PFS in ITT (3.4 vs. 2.7 months; $p = 0.0019$), adenocarcinoma ($p = 0.0193$) and in squamous ($p = 0.02$) populations. A significant improvement in OS was seen in adenocarcinoma group (12.6 vs. 10.3 months; $p = 0.0359$), but not in squamous one (8.6 vs. 8.7 months; $p = 0.8907$). The most common AEs in the experimental arm were diarrhea (42.3% vs. 21.8%), increased alanine aminotransferase (ALT) (28.5% vs. 8.4%) and aspartate aminotransferase (AST) (22.5% vs. 6.6%) [80].

LUME-Lung 2 trial enrolled only pretreated patients with non-squamous histology and was stopped after an interim futility analysis. Considering the LUME-Lung 1 results, EMA approved nintedanib in combination with docetaxel for the treatment of locally advanced, metastatic or locally recurrent NSCLC of only adenocarcinoma histology after first-line chemotherapy.

Other trials evaluating nintedanib in NSCLC are reported in Table 2.

Cediranib (AZD2171) is a multitarget tyrosine kinase inhibitor primarily directed against VEGFR2, but it has also demonstrated some inhibitory activity against FGFR1 and FGFR2 [71,81].

In a phase I trial 20 advanced NSCLC patients were treated with cediranib in combination with paclitaxel and carboplatin and the reported ORR was 45% [82].

Two randomized phase II/III studies assessed the safety and efficacy of cediranib in association with carboplatin and paclitaxel [83] or gemcitabine [84] as first-line treatment in advanced NSCLC patients. Both studies provided a starting cediranib dose of 45 mg orally once daily; however, this dose was not tolerated and it was set at 30 mg.

The first study [83] enrolled 296 patients and showed a significant higher response rate (38% vs. 16%; $p > 0.0001$) regardless of histology in oral cediranib arm over placebo, but no significant advantage in survival was seen.

In the phase II portion of the N0528 trial [84], 91 patients were randomized, but only 20% of all population had tumors with squamous cell histology. The study did not meet its primary end-point (ORR: 19% versus 20%, $p = 1.0$); furthermore, patients in the cediranib arm experienced significantly higher rates of non-hematological toxicities of grade $\geqslant 3$ (71% versus 45%, $p = 0.01$). Interestingly, an exploratory pharmacogenetic study focused on SNPs of target genes, such as VEGFR1–3, FGFR1–3, showed that genetic variants of FGFR2 (rs17542768, $p = 0.019$; rs2071616, $p = 0.010$) were significantly associated with lower toxicity, whereas other variants of FGFR1 (rs7012413, $p = 0.007$) and FGFR2 (rs2912791, $p = 0.0002$) were associated with survival.

Another phase II trial evaluated cediranib in combination with pemetrexed in previously treated NSCLC patients, regardless of histology. The combination was tolerable and promising, but it appeared ineffective in recurrent squamous cell patients [85]. A

randomized phase III trial of cediranib plus carboplatin and paclitaxel in patients with recurrent or metastatic NSCLC patients has been completed. Its primary endpoint was OS and results are awaited [NCT00795340].

Ponatinib (AP24534) is an oral multi-TK inhibitor that primarily inhibits BCR-ABL. It has been demonstrated that it is highly active in most solid tumor cell lines harboring different FGFR alterations, including NSCLCs, both *in vitro* and *in vivo*. Furthermore, its inhibitory capacity was more potent than that of other anti-FGFR compounds [71,86]. These data have suggested the investigation of ponatinib in clinical trials for patients with FGFR-addicted solid tumors. A phase II study of ponatinib in advanced lung and head and neck cancers with FGFR kinase alterations has suspended recruitment due to increase risk of blood clot [NCT01761747]. Another phase II trial evaluating the safety and effectiveness of ponatinib in lung cancer patients preselected for specific predictive biomarkers is currently ongoing [NCT01935336] [Table 2].

Lucitanib (E3810) is a potent oral dual TK inhibitor directed against VEGFR1–3 and FGFR1–2. Lucitanib showed its antitumor activity as single agent in FGFR1-amplified lung cancers both *in vitro* and in xenograft models [87–89]. Recently, the results of an open-label phase I/IIa study have been published. Seventy-six patients with advanced and potentially sensitive solid tumors (tumors harboring FGF-aberrant pathway or sensitive to angiogenic inhibition) were enrolled. In overall population, 7 patients (9%) had NSCLC. In the dose expansion phase, based on the emerged safety data, lucitanib dose was set at 15 mg daily. The most frequent AEs were hypertension, proteinuria, thrombotic microangiopathy, asthenia, hypothyroidism, anorexia, diarrhea, nausea, weight decrease, thrombocytopenia. Treatment-related AEs of grade 4 were reported in two patients and consisted of a case of increased lipase and a case of depressed level of consciousness. Sixty-four out of 76 patients were evaluable for response and 58 had misurable disease; among these, 4 patients with NSCLC (3 with FGFR1+ and 1 with 11q+) obtained a SD as the best response. In the overall population the DCR reached 80% with several durable responses and long-lasting SD [90]. To date, a phase II trial is currently ongoing for evaluating the efficacy of lucitanib in FGFR1-amplified Sq-NSCLC [NCT02109016] [Table 2].

Pazopanib (GW786034) is a multi-TK inhibitor including FGFR family [91]. A phase II study comparing first-line combination pazopanib–pemetrexed with the standard cisplatin–pemetrexed in NSCLC was terminated early due to unacceptable levels of toxicity [92]. Results from a phase II study of pazopanib in 15 patients with stage IV non-squamous NSCLC progressed to first line therapy containing bevacizumab, demonstrated limited activity to justify additional accrual [93]. A phase II trial is currently ongoing evaluating the efficacy of first-line treatment of pazopanib in combination with paclitaxel for advanced NSCLC patients not eligible for front-line therapy with a platinum doublet [NCT01179269] [Table 2].

Selective FGFR-TK inhibitors

This class of compounds includes several selective small molecules specifically directed against one or more FGFR tyrosine kinase domains. The IC_{50} versus the different targets are shown in Table 3.

LY2874455, an ATP-competitive pan-FGFR inhibitor, has demonstrated its potent and selective antitumor activity both in cell lines and in tumor xenografts. Its inhibitory activity was particularly evident in cancer cell lines with elevated FGF or FGFR levels, whereas its activity against VEGFR2 was significantly lower. In xenograft models derived from diverse cancer cell lines (including NSCLCs), its administration promoted tumor growth arrest, through inhibition of FRS2 phosphorylation [94]. This compound has been evaluated in a phase I trial [NCT01212107] and its results are awaited.

AZD4547, a novel and selective FGFR1–3 inhibitor [95], was investigated both in FGFR1-amplified NSCLC cell lines and patient-derived tumor xenograft models. Its potent antitumor activity was shown in FGFR1-addicted NSCLCs and correlated with FGFR1 gene copies (FISH score 6) and protein (IHC 3+) expression. Inhibition of p-ERK and p-S6 correlated with its efficacy, suggesting a possible role as pharmacodynamic biomarkers [96]. Recently, the results of a dose escalation phase I trial of AZD4547 have been presented. The most common AEs were alopecia, fatigue, different gastrointestinal disturbances, nail disorders, dry skin, hyperphosphatemia and retinal pigment epithelial detachment. Encouraging evidence of antitumor activity was seen in some patients; clinical benefit was observed in 5 out of 20 patients with FGFR alterations (two of whom with Sq-NSCLC) [97]. The responder patient with Sq-NSCLC (prolonged SD) had high FGFR1 amplification together with amplification of 11q13 (containing FGF3/4/19 genes) and CCND1 [98]. Recently, the results of phase I expansion of AZD4547 in patients with previously treated metastatic FGFR1-amplified Sq-NSCLC have been updated. Among 15 patients, fourteen were evaluable for tumor response with 1 PR and 4 SD. The PR was observed in a patient with high FGFR1 amplification (FISH ratio > 2.8). AZD4547 was well tolerated but did not meet its efficacy endpoint (ORR) for continuation. Moreover, the increase in serum phosphatase levels could be a circulating biomarker of pharmacologic target inhibition [99].

AZD4547 is currently being evaluated in phase II/III trials across a range of solid tumors, including patients with FGFR1-amplified Sq-NSCLC [Table 2].

BGJ398 is a novel and selective FGFR1–3 inhibitor that demonstrated its dose-dependent activity in different xenograft tumor models [100]. Preliminary results on the first 26 patients enrolled in a phase I trial have been reported [NCT01004224]. The patients had advanced solid tumors harboring FGFR1/2 amplifications or FGFR3 mutations and among them 3 had FGFR1-amplified Sq-NSCLC. DLT was related to grade 3 elevation in AST/ALT levels and grade 2 corneal events at the dose of 100 mg. However, AEs were generally of mild/moderate grade and included fatigue (37%), diarrhea (37%), nausea (32%) and hyperphosphatemia (30%). A patient with FGFR1-amplified Sq-NSCLC obtained a confirmed PR, providing early evidence that inhibition of the FGFR pathway was effective in patients with FGFR-addicted tumors [101]. This trial is currently recruiting together with others, particularly in genetically pre-selected solid tumors [Table 2].

BAY1163877 and JNJ42756493 are selective FGFR family inhibitors with nanomolar affinity [102,103] currently under evaluation in phase I trials [NCT01976741–NCT01703481, Table 2]. JNJ-42756493, an orally bioavailable pan-FGFR inhibitor, has been evaluated in a phase I study [NCT01962532] in different solid tumors (including squamous NSCLC) with FGFR gene amplification, mutations or translocations. A total of 41 patients have been enrolled. The investigational drug was safe and well tolerated; 9 mg daily was the first RP2D, but safety evaluation at higher doses is ongoing. Hyperphosphatemia was the most common but manageable on-target AE (58.5% of any grade in ITT population). Two FGFR-positive NSCLC patients had a clinical benefit (1 PR and 1 SD) at a dose of 12 mg daily. Pharmacodynamic serum (e.g., increased phosphate, FGF23 and calcium levels and decreased PTH levels) and tissue biomarkers (e.g., decreased phospho-ERK levels after drug exposure), capable to predict tumor response are being studied [104].

Irreversible FGRF inhibitors: FIIN-1 is the first covalent FGRF irreversible inhibitor targeting a cysteine residue conserved in all four FGFR kinases. *In vitro* the inhibitor inhibited numerous FGFR-dependent cancer cell lines with a potency in the nM range [105].

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Very recently, a second generation of irreversible FGFR inhibitors (FIIN-2 and FIIN-3) with improved affinity for wild type and gatekeeper mutants has been developed and characterized [106]. These new inhibitors can overcome clinical resistance to first-generation FGFR inhibitors.

Conclusions: open issues and future perspectives

FGF/FGFR signaling pathway has been recognized as one of the hallmark alterations with relevant clinical implications, particularly in Sq-NSCLC. Data from literature have established that the presence of an aberrant FGFR pathway has to be considered as possible prognostic factor of poor outcome and predictive of potential sensitivity to FGFR inhibitors.

Among the several DNA alterations involved in aberrant FGFR pathway, FGFR1 amplification, identified particularly in Sq-NSCLC, is the most frequent. Several techniques are being used to detect specific genomic aberrations involving FGFR pathway, such as in situ hybridization assays (FISH and CISH), quantitative real-time PCR and RNA sequencing. Among them, FISH represents the standard assay to screen tumor samples, but various studies have considered different cut-off values. Therefore, no standardized criteria have been defined to consider test as positive to date. Moreover, traditional FISH analysis is not able to detect some variants of FGFR gene fusions. By using this test, at least 20% of patients potentially suitable for FGFR inhibition, such as those with FGF/FGFR tumor upregulation or FGFR mutations, may be missed. Therefore, this issue remains a relevant question because of implication in screening patients amenable for FGFR-targeted therapy and in drug clinical development.

Standardization of different molecular diagnostic procedures, together with the use of high throughput sequencing technologies, will allow us to better select patients suitable for FGFR targeted therapy and, at the same time, to increase the number of significant and potentially predictive alterations in the FGFR pathway.

Initially, FGFR inhibitors were tested primarily as anti-angiogenics and in molecularly unselected patients. In these populations, the results of different clinical trials have shown a potential benefit from adding non-selective FGFR inhibitors to standard chemotherapy, due to their synergistic antiangiogenic activity. Both preclinical and clinical data have demonstrated a biologic rationale to use an FGFR inhibitor in this setting, although we are not able to establish when we have to consider this combination treatment.

Furthermore, it seems that a possible explanation of disease progression during a VEGFR inhibitor-based therapy would be related to high levels of FGFs; at this time, the use of an FGFR inhibitor may be able to overcome resistance. Nowadays, we are not able to recognize the best treatment strategy (up-front versus after anti-VEGF treatment failure) because of the lack of comparison trials. Probably, there are no significant differences in terms of efficacy between the two strategies, although a patients' selection according to serum FGF levels might allow optimizing the treatment strategy.

Both nonselective and selective FGFR inhibitors demonstrated their activity in FGFR-addicted NSCLC. Efficacy data with multitarget inhibitors are more robust, but selective FGFR inhibitors might be more potent. The time for obtaining these data is not mature, because direct comparison trials lack, and poses the fascinating question of whether the patients' selection can be influenced and enriched by these different molecules.

Furthermore, there is a potential role of FGFR inhibitors in combination with other targeted agents. It is possible that a combined treatment might be a feasible strategy to delay or overcome acquired resistance to EGFR inhibitor. Unfortunately, when applied in clinical trial, it failed because of toxicity. At this regard, several data have been reported on different toxicity profiles between selective and nonselective anti-FGFR drugs. The prevalent side effects of non-selective FGFR inhibitors are related to VEGF inhibition (e.g., hypertension, proteinuria, hypotiroidism and cardiovascular events); in addition, other common (off-target) adverse events are gastrointestinal disorders and skin reaction. This broad toxicity profile has limited the use of these compounds in combination with other anticancer drugs, particularly with anti-EGFR agents. Conversely, selective FGFR inhibitors showed a limited toxicity profile with hyperphosphatemia as the principal on-target toxicity and no events related to VEGF inhibition. In addition, new FGF inhibitors (FGF-ligand traps) have a better tolerability, also avoiding the onset of hyperphosphatemia, due to their little or no affinity for the hormonal FGFs (19, 21 and 23). Therefore, selective FGFR inhibitors lend themselves to combination with other drugs, according to their favorable toxicity profile, or alone after progression to another targeted agent.

The development of new covalent, irreversible FGFR inhibitors may overcome resistance to first-generation inhibitor even if at this time, no clinical data are available about mechanisms of resistance to anti-FGFR inhibitors.

Finally, in absence of clinical data on different activity and long-term safety of FGFR inhibition, in our opinion the toxicity profile, host and tumor selection (FGFR status and predictive biomarkers) should drive the drug development and the design of clinical trials.

In conclusion, it is plausible to hope that in the next years the research efforts in preclinical and clinical fields allow to establish an optimal treatment strategy also in FGFR-addicted NSCLC population.

Conflict of interest

All authors of this paper have not conflict of interest to disclose.

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