CHAPTER

5

Fibroblast Growth Factor Receptor Inhibitors: Enhancing Therapeutic Strategies for Solid Tumors

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Abstract

Despite advances in the last decades, cancer continues to be one of the main causes of morbi-mortality worldwide. In fact, cancer remains the second leading cause of death globally. Although chemotherapy had been the mainstay therapeutic option for treating solid tumors, a new era began in the late 1990s with the appearance of targeted agents. Since then, an in-depth knowledge into the molecular biology of certain tumors has allowed the discovery of new predictive gene alterations. In this context, increasing data have shown that the fibroblast growth factor receptor (FGFR) pathway plays a key role in carcinogenesis, by directly interacting with some of the hallmarks of cancer. Thus, the FGFR pathway arises as a promising target for cancer treatment. In this chapter, we will depict the complexity of the FGFR pathway, reviewing the different molecular aberrations described and their clinical implications. We will position the FGFR inhibitors in the early drug development field, for understanding their mechanisms of action, their current development status, and which rational combinations they are undergoing. Only when we have a full comprehensive view of this signaling pathway will we be able to design future personalized options for enhancing the therapeutic strategies for solid tumors.

ABBREVIATIONS

ATP	Adenosine triphosphate
BC	Breast cancer
CRC	Colorectal cancer
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
ERK	Extracellular signal-regulated kinase
FGF	Fibroblast growth factor

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FGFR	Fibroblast growth factor receptor
GC	Gastric cancer
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumors
GOJ	Gastroesophageal junction cancer
GRB2	Growth factor receptor-bound protein 2
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
HPSG	Heparin sulfate proteoglycan
HPV	Human papillomavirus
Ig	Immunoglobulin
LVI	Lymphovascular invasion
MET	Mesenchymal–epithelial transcription factor
mTOR	Mammalian target of rapamycin
MTKI	Multityrosine kinase inhibitor
NSCLC	Non-small cell lung cancer
PDGFR	Platelet-derived growth factor receptor
PI3K	Phosphoinositide 3-kinase
PLC	Phospholipase C
SCLC	Small cell lung cancer
SOS	Son of Sevenless
STAT	Signal transducer and activator of transcription
TKI	Tyrosine kinase inhibitor
VEGF	Vascular endothelial growth factor
WT	Wild-type

5.1 INTRODUCTION

Until the late 1990s, chemotherapy remained the mainstay for cancer therapy, relying on suppression of the proliferative capabilities of tumor cells, without specific blockade of angiogenesis, immune mechanisms, or components of the intracellular signal transduction pathways. Imatinib mesylate, a small-molecule inhibitor of the tyrosine kinase activity of BCR-ABL and *c-kit*, radically changed the landscape, becoming the first targeted agent in demonstrating efficacy for treating molecularly aberrant patients [1]. In 2001 [2], the first reports of *c-kit*-positive metastatic gastrointestinal stromal tumors controlled with imatinib supported the hypothesis that inhibition of oncogene-addicted cells was therapeutically useful and served as a proof-of-principle that specific tyrosine kinase receptors could represent a critical target for certain solid tumors.

Over the last two decades, a deepening into the molecular biology of several tumor types has focused attention toward the multiple genomic abnormalities that can contribute to cancer. The parallel implementation of powerful high-throughput technologies that enable the detailed characterization of these aberrations has led to the discovery of potentially druggable alterations [3]. The identification of these cancer drivers has contributed to an understanding of the specific cellular and genetic contexts in which they act, emerging as potential predictive biomarkers of response for new targeted agents. Since then, significant progress has been made for incorporating different targeted agents as part of the armamentarium for treating cancer patients. For example, BRAF V600 mutant melanomas, which are currently treated with proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B (BRAF) inhibitors [4,5], or patients with non-small-cell

lung carcinomas (NSCLCs) with mutations in the gene encoding the epidermal growth factor receptor (EGFR), who benefit from receiving anti-EGFR drugs [6,7].

The fibroblast growth factor receptor (FGFR) signaling pathway has increasingly become a major key point in the oncology research field, emerging as a promising target for optimizing the therapeutic options for cancer patients. In this chapter, we will depict the complexity of the FGFR pathway, reviewing the different molecular aberrations described and their clinical implications. We will position the FGFR inhibitors in the current early drug development field, for understanding which hallmarks of cancer they can target, their current development status, and which rational combination strategies are currently under investigation.

5.2 THE FGFR/FGF PATHWAY

The FGFR/FGF axis is an intracellular signaling pathway that mediates several cellular processes, such as proliferation, differentiation, homeostasis, and metabolism. The FGFR/FGF is a complex family that in humans comprises four receptor tyrosine kinases, named FGFR1/2/3/4, and 22 structurally related FGF ligands [8].

A total of 22 genes encode the FGF superfamily. According to phylogenetic analysis, the different FGFs can be divided into different subfamilies: paracrine secreted FGFs (FGF1-10/16-18/20/22), receptor-independent intracrine FGFs (FGF11-14), and hormonal endocrine FGFs (FGF15/19/21/23) [9]. The majority of these FGFs are secreted peptides, although FGF1 and FGF2 are released through an endoplasmic reticulum–Golgi-independent exocytosis pathway or after cell damage in stress conditions [10]. Most of these FGFs are sequestered by matrix glycosaminoglycans within the extracellular space, namely heparin sulfate proteoglycans (HPSGs), or Klotho proteins in the case of hormonal FGFs [11]. The interaction between these HPSGs/Klotho proteins and FGFs serves to protect the ligands from extracellular degradation, generating a local reservoir of FGFs. The spatial pattern of expression of these matrix glycoproteins acts as a tight regulator mechanism of the available FGFs and their half-lives [12].

The four homologous FGFRs are highly conserved tyrosine kinase receptors sharing a common overall structure, comprising an extracellular domain, a single-pass transmembrane domain, and a carboxy-terminal cytoplasmic domain. In the extracellular portion, there are three different immunoglobulin (Ig)-like domains (I–III) that finely modulate the activity of the receptor: (a) the amino-terminal portion containing the acidic box, a serine-enriched portion between the IgI–IgII loops, plays a key role in receptor auto-inhibition; (b) HPSGs and Klotho proteins are docked in the IgII fold, for controlling the release and affinity of FGF ligands; (c) IgII–IgIII domains act as crucial ligand-binding sites for FGFR activation [13]. A fifth related receptor FGFR5 (known as FGFRL1) can bind FGF ligands but has no tyrosine kinase domain. Hence, FGFRL1 is thought to play a role as a ligand trap, also serving as a partner for dimerization with other tyrosine kinase receptors and as a negative feedback loop for limiting the phosphorylation of FGFR1-4 [14].

Under normal conditions, FGFs are engaged with HPSGs/Klotho proteins through electrostatic interactions. Following extracellular protease-mediated release, the binding of these FGFs to the receptors leads to the dimerization of the ternary complex HPSGs:FGFR:FGF. The dimerization triggers a conformational change that induces the autophosphorylation of

the tyrosine kinase domain, facilitating the attachment of docking proteins and activation of downstream pathways. The activated FGFR phosphorylates the FGFR substrate 2 (FRS2) on several sites, allowing the recruitment of other adaptor proteins, such as growth factor receptor-bound protein 2 (GRB2) and Son of Sevenless. Further downstream signaling occurs, ultimately leading to an upregulation of PI3K/AKT/mTOR (mammalian target of rapamycin) and RAS/RAF/ERK pathways, phospholipase C gamma (PLCγ), and signal transducer and activator of transcription STAT [15]. After activation, the complex is internalized and transported as an endocytosis vesicle to the lysosomes for its degradation and recycling [9]. Fig. 5.1 illustrates the complexity of this pathway.

5.2.1 FGFR/FGF Deregulation in Human Cancers and Clinical Implications

The FGFR/FGF axis plays a key role in normal cellular processes, such as embryogenesis, cell metabolism and proliferation, migration, and angiogenesis. Hence, it is not surprising that such a crucial pathway may be disrupted in human cancers, precipitating the carcinogenesis process and enabling malignant transformation. In fact, FGFR genes are among the most commonly altered kinase genes in solid tumors. To date, several FGFR/FGF molecular alterations have been described, as depicted in Fig. 5.2.

Cancers may present constitutive activation of the FGFR pathway as a result of gain-of-function missense mutations. Mutations are dichotomized molecular events, meaning that cells are mutated or not. Nevertheless, not all the mutations result in upregulation of the FGFR pathway. FGFR mutations located within the tyrosine kinase domain are rare (~1%), whereas the majority of the mutations considered oncogenic generate novel amino acid residues in the extracellular portion of the receptor [16]. It has been hypothesized that these mutations may activate FGFR independent of ligand binding, by facilitating receptor dimerization through newly formed disulfide or hydrogen bonds [17]. Second, FGFR gene translocations have progressively been described as druggable targets in multiple cancers. A number of different FGFR fusion partners have been identified. The activating mechanism for these partners consists in providing a dimerization domain that facilitates oligomerization of the fusion receptor, leading to constitutive activation of the kinase downstream [18]. Third, FGFR1-4 or FGF gene amplifications have been described [19]. Gene amplification arises from the presence of multiple copies of the particular gene, which in turn translates into an increase in the phenotypic characteristics attributed to that gene [20]. However, the level of FGFR amplification can significantly vary between tumors of different origin, and even more relevant, between tumors within the same histology. Interestingly, higher rates of FGFR amplification seem to correlate with the degree of oncogene addiction of a certain tumor [21].

Recently, other less well-described molecular aberrations have been postulated as potential mechanisms of FGFR upregulation. Certain FGFR isoforms resulting from alternative mRNA splicing processes can result in highly oncogenic proteins [22]. FGFR2-C3 isoforms detected among FGFR2-amplified gastric cancer patients [23] can lead to aberrant receptors that are constitutively FRS2-dependent activated, accompanied by C-terminal modifications that contribute to receptor accumulation [24]. On top of that, extracellular splicing mechanisms of the IgIII portion can modulate the FGFR tissue specificity for the FGFs, even increasing the affinity and number of ligands that can activate the same

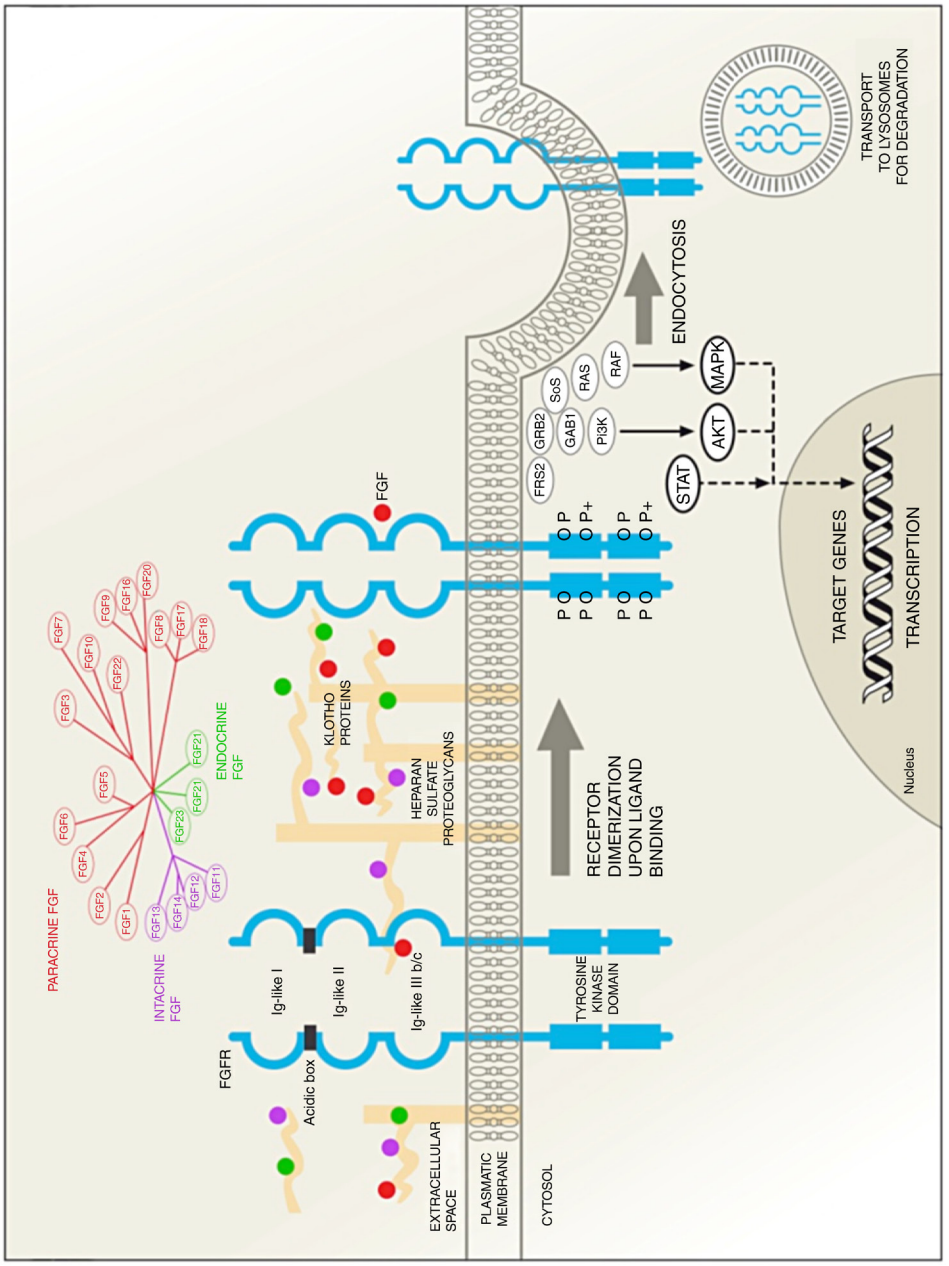

FIG. 5.1 **Illustration of the complexity of the FGFR/FGF pathway.**

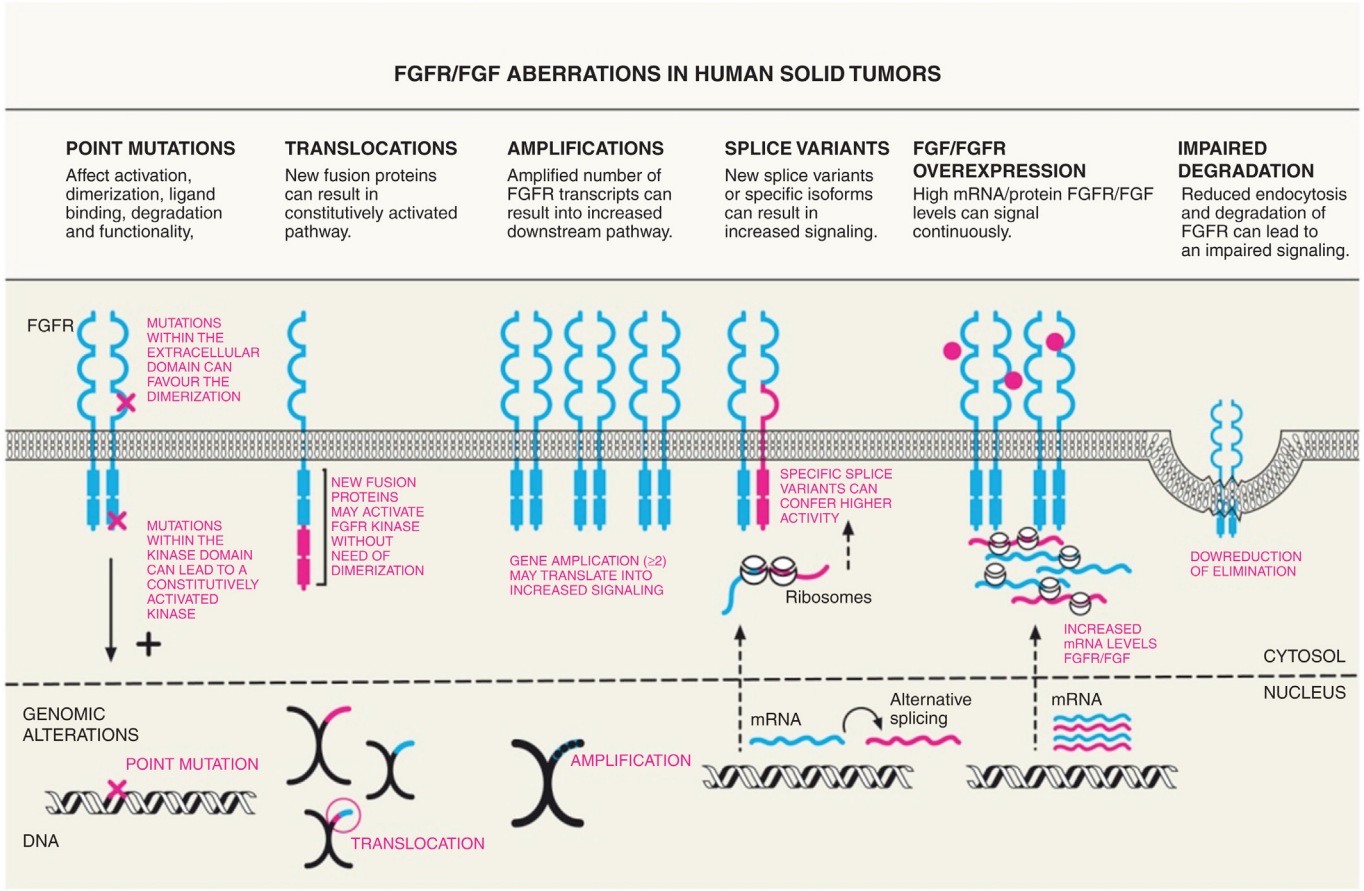

FIG. 5.2 **Heterogeneity of the FGFR/FGF molecular aberrations and associated mechanisms of upregulation of the signaling axis.** FGFR signaling contributes to the carcinogenesis process through several ligand-dependent and -independent mechanisms. In fact, several FGFR/FGF genomic alterations have been described across solid tumors, showing the huge heterogeneity of molecular aberrations that the axis may present: FGFR1-4 point mutations, gene translocations and amplifications, alternative FGFR splice variants that result in activating isoforms, increased mRNA levels that translate into increased protein levels of FGFR/FGF, and altered mechanisms of pre-activated receptor degradation. All these alterations share a common purpose, resulting in an upregulation of FGFR downstream effector signaling.

receptor [25]. Increased levels of mRNA expression of FGFR/FGF and/or protein levels might be produced in an autocrine fashion by cancer cells, establishing a vicious loop that promotes the pathogenic activation. Finally, mechanisms that alter the formation of endocytosis vesicles may lead to an impaired degradation of activated FGFRs, perpetuating the signaling of the pathway.

Interestingly, the FGFRs and their isoforms are distributed unevenly in a tissue-organ-related manner, translating into different roles at certain stages of the development. This tight correlation seems to be maintained throughout the oncogenic process, leading to a highly specific expression of each molecular FGFR/FGF aberration according to each tumor type. Table 5.1 depicts the most common FGFR/FGF alterations described in solid tumors, with the phenotypic characteristics and biological behaviors associated to them.

TABLE 5.1 Common FGFR/FGF Alterations in Solid Tumors and Their Clinical Implications

Tumor type	FGFR/FGF alteration	PREV (%)	Clinical implications	Reference
Squamous NSCLC	FGFR1 amplification	10–20	Poorer prognosis in NSCLC squamous, shorter survival Escape mechanism in NSCLC adenocarcinoma resistant to anti-EGFR chemotherapy resistance in SCLC	[26–34]
	11 amplification	12		
Adenocarcinoma NSCLC	FGFR1 amplification	6		
	11q amplification	4		
SCLC	FGFR1 amplification	6		
Squamous head and neck	FGFR1 amplification	10	Mutually exclusive with HPV infection Poorer overall survival in HPV-negative subtype	[35–36]
Squamous esophageal	FGFR1 amplification	9–12	Poorer prognosis	[37–39]
Gastric adenocarcinoma	FGFR2 amplification	7	Mutually exclusive with HER2/MET amplifications Worst survival with LVI+	[40–42]
Hepatocarcinoma	FGFR4 + βklotho + FGF19 overexpression	15–40	Poorer histological differentiation and higher αfeto-protein	[43–46]
Biliary tract carcinoma	FGFR2 translocation	8–13	Mutually exclusive with KRAS/BRAF mutations	[47,48]

(*Continued*)

TABLE 5.1 Common FGFR/FGF Alterations in Solid Tumors and Their Clinical Implications (*Cont.*)

Tumor type	FGFR/FGF alteration	PREV (%)	Clinical implications	Reference
Colon adenocarcinoma	FGFR4 amplification + FGF19 overexpression	4	Higher risk for more aggressive tumors Resistance to anti-EGFR if FGF19 upregulation	[49–51]
HR+ breast carcinoma	11q amplification	15	Development of distant metastasis earlier, shorter survival Poorer prognosis in luminal-type, endocrine resistance	[52–55]
	FGFR1 amplification	10		
TBNC	FGFR1 amplification	4		
	FGFR2 amplification	4		
Ovarian carcinoma	FGFR1 amplification	4	Resistance to platinum-based chemotherapies	[56,57]
Endometrial adenocarcinoma	FGFR2 mutation	12	Mutually exclusive with KRAS mutations Shorter disease-free survival interval	[58–61]
	FGFR1 amplification	4		
Squamous cervix	FGFR3 mutation	25		
Urothelial carcinoma (muscle-invasive)	FGFR3 mutation	15	Early recurrence detection in nonmuscle invasive pTa	[62,63]
	FGFR1 amplification	11		
	FGFR3-TACC3 translocation	6		
Prostate adenocarcinoma	FGFR1 amplification	8	Higher risk of resistance to castration in hormone-naïve patients	[64,65]
Glioblastoma	FGFR3-TACC3 translocation	3–7	Mutually exclusive with EGFR/PDGFR/MET amplifications	[66,67]
Melanoma	FGFR2 mutation	9	Unknown significance (passenger mutations?)	[68]
	FGFR1 mutation	4		
	FGFR4 mutation	4		
Rhabdomiosarcoma	FGFR4 mutation	8	Poorer response to chemotherapy in osteosarcomas	[69,70]
Osteosarcoma	FGFR1 amplification	18		

Abbreviations: PREV, prevalence; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; HR+ hormone receptor-positive; TBNC, triple breast negative cancer; EGFR, epidermal growth factor receptor; HPV, human papillomavirus; HER2, human epidermal growth factor receptor 2; MET, mesenchymal–epithelial transcription factor; LVI+, lymphovascular invasion-positive.

5.3 FGFR INHIBITORS: TARGETING SOME CRITICAL HALLMARKS OF CANCER

In the last quarter century, researchers have tried to shed some light into the layers of complexity that intrinsically involve cancer. The identification of the biological multistep process that guides the transformation of normal tissue cells into malignant cancers significantly contributed to a better understanding of the process of carcinogenesis in humans [71]. Among these physiological changes acquired by the tumoral cells, there are 10 capabilities known to be involved in the pathogenesis of some, and probably, all cancers. These 10 hallmarks described by Hanahan and Weinberg represent an organizing principle for understanding the neoplastic disease: (1) sustaining proliferative signaling; (2) evading growth suppressors; (3) avoiding immune destruction; (4) enabling replicative immortality; (5) tumor-promoting inflammation; (6) activating invasion and metastasis; (7) inducing angiogenesis; (8) genome instability and mutation; (9) resisting cell death; (10) deregulating cellular energetics [72]. The recognition of these tumoral traits has guided new modern approaches for developing novel anticancer drugs, aiming to overcome some of these hallmarks and/or their pathways involved [73].

The FGFR pathway is involved in normal organ-specific development and differentiation, stimulating cell proliferation and migration by downstream activation of PI3K/AKT/mTOR and RAS/RAF/ERK pathways [74]. Noteworthy, several malformation syndromes that involve skeletal disorders were already associated with mutations of the FGFR genes [75]. As the upregulation of the FGFR signaling is a common event in many cancer types, it has been postulated that this pathway plays a key role in sustaining proliferative signaling. In FGFR-aberrant tumors, the acquired oncogene alteration may induce cell growth and survival, by imitating the stimulatory signals that tightly regulate proliferation in normal conditions. In fact, small molecules blocking FGFR signaling in FGFR-dependent cell lines have translated into cell apoptosis and death [27]. Inhibition of the FGFR pathway decreased tumor growth in xenograft models, clearly reflecting the oncogenic addiction of tumoral cells to the acquired FGFR aberration [76].

Along with organogenesis, angiogenesis was one of the first areas in which the FGFR/FGF axis was demonstrated to be crucial [77]. FGFR1-2 are widely expressed on the surface of endothelial cells, and through FGF1-2 secreted by tumoral or microenvironmental stromal cells, can induce the generation of new blood vessels. Also, FGFR signaling is required for neovascularization after blood vessel injury [78]. Vascular endothelial growth factor (VEGF) and FGF2 may have a synergistic effect with complementary roles, and rising evidence has suggested that upregulation of the FGFR pathway is a resistance mechanism to anti-VEGF therapies [79]. Casanovas et al. [80] have demonstrated that cancer cells are able to develop resistance against anti-angiogenic blockade by the alternative secretion of FGFs, instead of VEGFs. These data have widened the horizon for developing new therapeutic options for overcoming resistance to anti-angiogenic drugs.

The finding of multiple FGFR/FGF aberrations in a wide range of solid tumors has led to a major interest in developing specific targeting agents against this signaling pathway, suggesting the therapeutic benefit of the FGFR blockade. The combined inhibition of two major hallmarks, proliferation and angiogenesis, may represent a convincing reason for developing FGFR inhibitors as anticancer drugs. Fig. 5.3 summarizes the hallmarks of cancer that could be targeted by FGFR inhibitors.

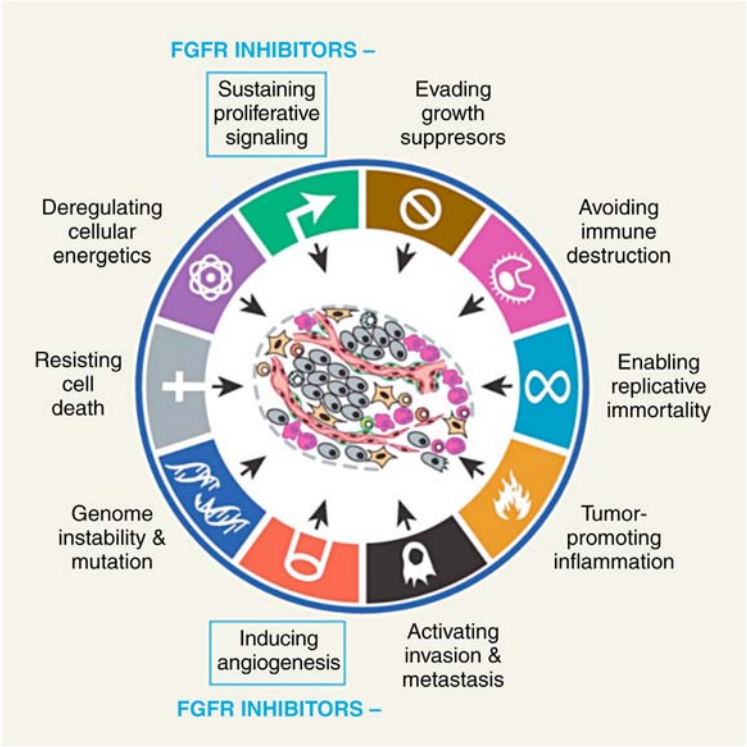

FIG. 5.3 **Hallmarks of cancer that can be targeted by FGFR inhibitors.** Ten different capabilities are known to be involved in the pathogenesis of cancers: (1) sustaining proliferative signaling; (2) evading growth suppressors; (3) avoiding immune destruction; (4) enabling replicative immortality; (5) tumor-promoting inflammation; (6) activating invasion and metastasis; (7) inducing angiogenesis; (8) genome instability and mutation; (9) resisting cell death; (10) deregulating cellular energetics. The FGFR/FGF signaling pathway plays a key role in controlling cellular proliferation and angiogenesis. By combining the dual strategy of blocking these two major hallmarks, FGFR inhibitors arise as a promising targeted option for FGFR-dependent tumors. Adapted from Hanahan and Weinberg [72] with permission from Elsevier.

5.4 FGFR INHIBITORS TO IMPROVE RESPONSE IN SOLID TUMORS

The inhibition of FGFR signaling has shown *in vitro* and *in vivo* activity in many tumor types depending on the FGFR addiction for proliferation and survival [34,81,82]. Therefore, a significant number of novel FGFR inhibitors have entered into the early drug development field in the last decade.

Current FGFR inhibitors can be mainly divided into two groups, according to their mechanism of action: (1) small oral molecules, classified as receptor tyrosine kinase inhibitors (TKIs). TKIs are adenosine triphosphate-competitive molecules that compete for the catalytic binding site of the intracellular kinase domain of FGFRs, diminishing autophosphorylation of the receptor and (2) antibodies. Different antibody strategies have been developed for

modulating FGFR activation: (a) anti-FGFR antibodies, which can bind the extracellular portion of the FGFR and reduce the affinity for the FGFs, leading to a reduced FGF:FGFR association and subsequent dimerization and (b) FGF ligand traps, which can sequester multiple extracellular ligands and reduce the activation of their corresponding FGFR partners [83].

The most commonly accepted classification of FGFR inhibitor family is made according to the grade of selectivity that these drugs exert against the different FGFRs and/or other tyrosine kinase receptors: (1) first-generation nonselective FGFR inhibitors include small molecules with a multitargeting kinase activity (MTKI), thereby despite an increased antitumor activity, these can result in increased undesired toxicities due to their off-FGFR target effects; (2) second-generation selective pan-FGFR inhibitors (FGFRinh), which comprise TKIs and FGF ligand traps with increased affinity for only FGFRs (IC_{50} < 10 nmol/L); and (3) third-generation ultra-selective FGFRinh, the newest and less developed strategy, which include isoform-specific antibodies aimed to target only one concrete FGFR. Fig. 5.4 illustrates these three generations of FGFR inhibitors and some of the current drugs under development in each one of the subgroups.

Most first-generation MTKIs have been developed as anti-angiogenic therapies, tested in a wide variety of solid tumors irrespective of their FGFR status. That is the case of lenvatinib, subsequently developed in thyroid cancer (NCT01321554). Given the fact that the kinase domains of the FGFR, vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) are phylogenetically close, some of these MTKIs showed FGFR inhibition which could be used in FGFR-aberrant patients. Dovitinib demonstrated *in vivo* and *in vitro* activity in FGFR1-2-amplified breast models, supporting its further development in the clinic [21]. In a phase II trial testing dovitinib in breast cancer patients (NCT01528345), promising efficacy signs were detected: one unconfirmed partial response was reported in the subset of 15% women harboring FGFR1-amplified ER+ tumors. These data raised the question whether the activity was related to VEGFR/PDGFR inhibition, but the fact that no responses were seen among non-FGFR-amplified patients suggested the oncogenic role for FGFR in this subset of patients. Lucitanib, another MTKI that targets FGFR1-3/VEGFR1-4/PDGFRα-β, demonstrated an encouraging antitumor activity in a phase I/II trial (NCT01283945). With a disease control rate of 100%, 6 out of 12 breast cancer patients with FGFR1 amplification achieved long-term partial responses, with progression-free survival intervals of around 10 months [84]. Other MTKIs are currently under development, but the increased nonspecific toxicities commonly seen with these kinase inhibitors have limited the next steps. Hypertension, vomiting, diarrhea, fatigue, and proteinuria represent the most common adverse events seen with these MTKIs that may limit the possibility of an adequate dose-intensity FGFR blockade that translates into efficacy.

Within this context, second-generation selective FGFRinh have been developed, in order to increase the possibility of on-target FGFR inhibition while diminishing the toxicity derived from MTKIs. Most of these FGFRinh have focused on different tumor types but with a high likelihood of FGFR oncogene addiction. Interestingly, the retrospective analysis of the efficacy signs detected in the early clinical trials revealed a significant variability in antitumor activity between genomic alterations. AZD4547, a pan-FGFR1-2-3 inhibitor (NCT00979134), showed partial responses in two FGFR1-amplified squamous NSCLCs and in one FGFR2-amplified gastric cancer patient, on top of other tumor type patients who achieved prolonged stabilizations (one FGFR1-amplified breast cancer and two FGFR3-mutant bladder

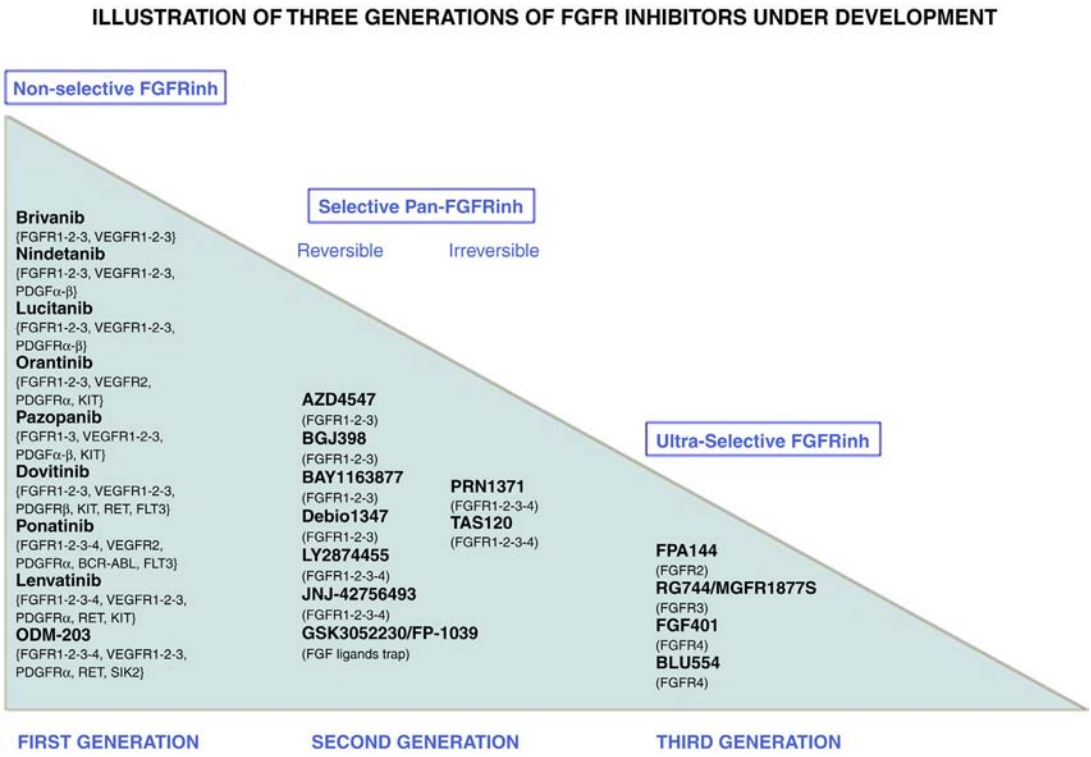

FIG. 5.4 **Clinical development of FGFR inhibitors.** Three major subgroups of FGFR inhibitors have progressively entered different phases of the early drug development field: (1) first generation of nonselective MTKIs include drugs such as brivanib, nindetanib, lucitanib, orantinib, pazopanib, dovitinib, ponatinib, lenvatinib, and ODM-203. Notice below each compound the spectrum of multitargeting kinase activity, with the majority of these inhibitors targeting also angiogenesis by blocking VEGFR and PDGFR; (2) second generation of highly selective pan-FGFR inhibitors (FGFRinh) comprise several molecules with increased affinity for only FGFRs, including both reversible—AZD4547, BGJ398, BAY1163877, Debio1347, LY2874455, JNJ-42756493, and GSK3052230—and irreversible—PRN1371 and TAS120—inhibitors; and (3) third-generation ultraselective FGFRinh, encompassing antibodies specifically developed for targeting a unique FGFR, aiming to treat cancer cells that rely on a particular receptor. That is the case of FPA144, RG744, FGF401, and BLU554. Abbreviation: MTKIs, multityrosine kinase inhibitors.

cancer patients) [85–88]. Another FGFR1-2-3inh, BGJ398, has been tested in a phase I trial enrolling FGFR1/2-amplified or FGFR3-mutant patients (NCT01004224). Partial responses were reported in 14 patients (six FGFR3-mutant bladder cancer and eight FGFR1-amplified squamous NSCLC patients), although minor tumor regressions were also seen among other histologies (FGFR1/2-amplified and FGFR3-mutant breast cancer, FGFR2-mutant and translocated cholangiocarcinoma) [89]. In an effort toward improving patient selection, novel prescreening strategies have been tested, such as assessing FGFR mRNA levels. With this strategy, the BAY1163877 phase I study (NCT01976741) identified new subsets of patients who benefitted from the FGFR blockade: one head and neck squamous carcinoma and one adenoid cystic carcinoma of the tongue [90]. However, most of these FGFRinh inhibit the

three receptors to varying degrees, due to similarities in the kinase domain of FGFR1-2-3 [91], but may lack activity against FGFR4 which has a different kinase structure [92]. JNJ-42756493, one of the first developed FGFRinh that also targets FGFR4, showed encouraging antitumor activity, particularly among FGFR-translocated patients (NCT01703481). Partial responses in three FGFR2/3-translocated urothelial carcinomas, one FGFR3-translocated glioblastoma, and one FGFR2-translocated endometrial carcinoma were reported within the escalation phase I [93].

Furthermore, published data have suggested a crucial role for ligand overexpression as an upregulating mechanism of the FGFR pathway [94]. While further studies may clarify whether it is crucial to target FGFs, new FGF ligand traps have emerged as an interesting therapeutic option. By sequestering several extracellular ligands that may signal through a unique FGFR, FP-1039 (NCT00687505) has shown stabilizations in 41% of patients irrespective of their FGFR status, with a significant 20% decrease in tumor size in prostate cancer [95]. Lately, highly potent irreversible FGFRinh have demonstrated *in vivo* and *in vitro* activity against gatekeeper mutations, known to confer resistance to FGFRinh [96]. The fact that new emerging FGFR2 mutations have been progressively detected in tumors treated with reversible FGFRinh has envisaged a new scenario for developing these irreversible FGFRinh [97]. TAS120 (NCT02052778) and PRN1371 (NCT02608125) are currently under development in phase I trials, focused on selected FGFR-aberrant patients and allowing the enrollment of patients previously treated with reversible FGFRinh [98,99].

Finally, it has been noticed that the different FGFR aberrations present a certain preference for organ-specific cancers, such as FGFR4 overexpression in hepatocarcinomas. This finding may be explained by the fact that FGF19/FGFR4 expression plays a key role in the homeostasis of the healthy liver, promoting glycogenesis and suppressing gluconeogenesis/bile acid synthesis [100]. FGFR4 is known to be necessary for FGF19-mediated hepatocarcinoma tumorigenesis *in vivo* [44], and specific treatment with FGFR4-directed strategies may inhibit the proliferation of liver tumors while avoiding unnecessary adverse events derived from other FGFR inhibition. These observations established the basis for developing a third-generation of ultraselective FGFRinh, aimed at specific tumor types that rely on a particular FGFR aberration. Several isoform-specific antibodies are under development in phase I trials. FPA144 is a humanized IgG1 antibody directed against the 2b isoform of the FGFR2 (NCT02318329) and MFGR1877S/RG744 is a human monoclonal antibody targeting FGFR3 (NCT01363024). A couple of specific FGFR4 inhibitors, FGF401 (NCT02325739) and BLU554 (NCT02508467), are currently being tested in phase I trials selectively enrolling hepatocarcinoma patients with high FGFR4/βklotho overexpression. Future development of these selective inhibitors seems a promising strategy for implementing more personalized therapeutic options for FGFR-aberrant tumors.

5.4.1 Combination Strategies of FGFR Inhibitors With Other Anticancer Agents

Despite encouraging efficacy results observed with early studies testing FGFR inhibitors in monotherapy, limited antitumor activity has been reported with these targeted agents so far. Nevertheless, based on the evidence that the combination of these FGFR inhibitors with other anticancer strategies may increase the possibilities of response rate maintaining an adequate safety profile, several combination strategies have been proposed.

FGFR inhibitors have demonstrated promising efficacy signals when combined with different chemotherapy regimens—irinotecan, paclitaxel, and etoposide—by enhancing the apoptosis rates induced by chemotherapeutic agents in drug-resistant cell lines [101]. The combined therapy of 5-fluorouracil with Ki23057 (FGFR2 inhibitor) produced synergistic antitumor effects in FGFR2-aberrant gastric cancer cell lines [102]. However, ponatinib has not shown synergistic effects in combination with gemcitabine plus cisplatin when tested *in vivo* in an FGFR2-CCDC6 fusion intrahepatic cholangiocarcinoma [18]. These contradictory results highlight the need for further research into the synergistic mechanisms that can potentiate certain combination strategies, while avoiding some combinations that may result into severely increased toxicities and detrimental effects. In fact, several combinations with FGFR inhibitors and systemic chemotherapies have been early terminated due to unacceptable toxicity (e.g., phase I trials testing dovitinib plus paclitaxel or platinum/gemcitabine).

Significant cross-talk between FGFR and other oncogenic signaling pathways has been described, as well as the capacity that tumoral cells have for initiating compensatory escape mechanisms through other tyrosine kinase receptors when one pathway is inhibited [14]. The addition of FGFR inhibitors with other targeted agents, such as EGFR, MET, MEK, or PIK3CA inhibitors, may be a feasible option to consider. The BOLERO-2 study testing everolimus and exemestane in breast cancer patients revealed the co-existence of activating mutations in PIK-3CA and FGFR1 amplifications [103]. These observations provided the rationale for initiating a phase I combination trial with BGJ398 and BYL719 (PIK3/AKT/mTOR inhibitor) for validating the hypothesis of double blockade in patients harboring co-alterations within the FGFR/PIK3CA pathways (NCT01928459). On top of that, some of the FGFR aberrations have been described as endocrine therapy resistance mechanisms. That is the case of FGFR1 amplification in ER+ breast cancer patients, where increasing data suggest that FGFR inhibitors may be able to overcome and reverse hormone therapy resistance [104]. Several studies have been initiated for assessing the role that the addition of FGFR inhibitors may represent with combined endocrine therapy, such as a phase Ib trial combining lucitanib with fulvestrant in ER+/FGFR1-amplified luminal breast cancer patients (ISRCTN23201971). Table 5.2 depicts some of the clinical trials that have assessed potential combinations of FGFR inhibitors, both MTKIs and FGFRinh, with chemotherapy, endocrine therapy, targeted agents, or immunotherapies.

Despite the strong rationale behind some of these combinations, only nindetanib, a potent first-generation MTKI with triple FGFR/VEGFR/PDGFR antiangiogenic and antitumor activity [105], has been approved in the Europe for a subset of NSCLC. The LUME-Lung 1 trial (NCT00805194) was a phase III trial enrolling both squamous and adenocarcinoma NSCLCs, irrespective of their FGFR status, and patients were randomized to receive nindetanib/placebo plus docetaxel. The experimental combination met the primary endpoint of the study, showing improved progression free survival (median PFS 3.4 months vs 2.7 months; hazard ratio = 0.79 with 95% confidence interval 0.68–0.92, $P = 0.0019$) in all patients. However, nindetanib plus docetaxel only extended overall survival (median OS 12.6 months vs 10.3 months; hazard ratio = 0.83 with 95% confidence interval 0.70–0.99, $P = 0.0359$) in the prespecified adenocarcinoma histology population. In light of these results, nindetanib has been approved in combination with docetaxel for treating metastatic or locally advanced NSCLC with adenocarcinoma histology after receiving one line of platinum-based chemotherapy [106,107]. Unfortunately, no biomarker analysis was performed in this study, and no available

TABLE 5.2 Clinical Trials Testing Some Combinations of FGFR Inhibitors and Other Anticancer Therapies

FGFR inhibitor	Trial identifier	Ph	Status	Combination regimen	Tumor type
1. First-generation multityrosine kinase inhibitors					
Brivanib	NCT00798252	1	Completed	Brivanib + capecitabine or doxorubicin or docetaxel or paclitaxel or ixabelipone	All solid tumors
	NCT00300027	1	Terminated	Brivanib + folfox	GI
	NCT01046864	1	Completed	Brivanib + folfiri or LV + 5FU	GI
	NCT00640471	3	Completed	Brivanib + cetuximab	RAS WT mCRC
Nindetanib	NCT02856425	1	Recruiting	Nindetanib + pembrolizumab	All solid tumors
	NCT02619162	1	Recruiting	Nindetanib + letrozol	ER+ BC
	NCT02393755	1/2	Recruiting	Nindetanib + capecitabine	mCRC
	NCT01684111	1	Completed	Nindetanib + vinorelbina	NSCLC
	NCT01015118	3	Completed	Nindetanib + carboplatin/paclitaxel	Ovarian
	NCT00805194	3	Ongoing	Nindetanib + docetaxel	NSCLC
	NCT00806819	3	Completed	Nindetanib + pemetrexed	NSCLC
Pazopanib	NCT01542047	1	Terminated	Pazopanib + carboplatin	All solid tumors
	NCT02279576	1	Terminated	Pazopanib + paclitaxel	Penile
	NCT01600573	1/2	Recruiting	Pazopanib + topotecan	Ovarian
	NCT01130805	2	Completed	Pazopanib + CAPOX	GOJ/GC
	NCT02331498	1/2	Recruiting	Pazopanib + temozolamida	Glioblastoma
Dovitinib	NCT01548924	1	Terminated	Dovitinib + paclitaxel	All solid tumors
	NCT01496534	1	Terminated	Dovitinib + gemcitabine/cisplatin or carboplatin	All solid tumors
	NCT01921673	1/2	Completed	Dovitinib + docetaxel	GOJ/GC
	NCT01484041	1/2	Terminated	Dovitinib + aromatase inhibitors	BC
Lenvatinib	NCT02640508	1	Recruiting	Lenvatinib + eribulin	All solid tumors
	NCT00832819	1	Completed	Lenvatinib + carboplatin/paclitaxel	NSCLC
	NCT02788708	1	Recruiting	Lenvatinib + paclitaxel	Ovarian
	NCT02501096	1/2	Recruiting	Lenvatinib + pembrolizumab	All solid tumors

(*Continued*)

TABLE 5.2 Clinical Trials Testing Some Combinations of FGFR Inhibitors and Other Anticancer Therapies (*Cont.*)

FGFR inhibitor	Trial identifier	Ph	Status	Combination regimen	Tumor type
2. Second-generation selective pan-FGFR inhibitors					
AZD4547	NCT01202591	1/2	Completed	AZD4547 + fulvestrant	ER+ BC
	NCT01791985	1/2	Recruiting	AZD4547 + letrozol or anastrozol	ER+ BC
	NCT01824901	1/2	Completed	AZD4547 + docetaxel	NSCLC
GSK3052230	NCT01868022	1	Ongoing	GSK3052230 + carboplatin/paclitaxel or docetaxel or cisplatin/pemetrexed	Nsclc mesothelioma

Abbreviations: FGFR, fibroblast growth factor receptor; Ph, phase; GI, gastrointestinal cancers; WT, wild-type; mCRC, metastatic colorectal cancer; ER+, estrogen receptor-positive; BC, breast cancer; NSCLC, non-small cell lung cancer; GOJ, gastroesophageal junction cancer; GC, gastric cancer.

data regarding FGFR aberrations among enrolled patients is available. This prevents conclusions to be drawn on the potential predictive biomarkers of response to nindetanib and to FGFR inhibitors, in general.

5.5 CONCLUSIONS

Upregulation of FGFR/FGF signaling is a common event in carcinogenesis, and considering the multiple FGFR aberrations detected among cancer patients, FGFR inhibition arises as a promising therapeutic strategy. Despite the preclinical evidence that blocking this pathway leads to a degree of tumor control, the initial results of FGFR inhibitors tested in FGFR-altered patients have not been so successful. This highlights the need for further research into the insights of this signaling pathway and the identification of reliable predictive biomarkers. Only by preselecting the subset population who may achieve greater benefit from FGFR blockade will we be able to avoid unnecessary adverse events to patients with low chances of success and ensure that we are not missing potential candidates that could still benefit from these drugs. In this line, a better delineation of the molecular prescreening strategies in parallel with the performance of these early clinical trials testing new FGFR inhibitors and/or their combinations is crucial [108]. The identification of reliable response biomarkers that define the most suitable patient population that may benefit from receiving FGFRinh will clearly increase the possibilities of success of new therapeutic strategies for FGFR-aberrant patients [109].

In addition, characterization of the mechanism of action of FGFR inhibitors seems mandatory for considering future combination strategies. Taking into consideration the adaptive behavior of the FGFR axis as a resistance mechanism to other anticancer agents, the implementation timing of the FGFR blockade and possibilities of combinations or sequential strategies warrant further consideration. Whether any other hallmarks of cancer apart from proliferation and angiogenesis are modulated by these FGFR inhibitors remains unclear. In the era of emerging immunotherapeutic strategies, epigenetics, and microenvironment modulation, studies are needed to ascertain the role of the FGFR pathway in cancer and the implications

of its blockade. Even with these challenges, the preclinical and early clinical data position the FGFR inhibitors as a new promising targeted agent family for enhancing the therapeutic strategies against solid tumors.

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