Advancing precision oncology: insights from C-terminal FGFR2/3 truncations and MYC-driven mTOR inhibitor resistance

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CHAPTER 2

FGFR REARRANGEMENTS: ONCOGENIC DRIVERS AND THERAPEUTIC TARGETS

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ABSTRACT

Genomic amplifications and hotspot mutations affecting fibroblast growth factor receptors (FGFRs) have long been recognized as oncogenic drivers across human cancers. However, recent studies have uncovered *FGFR* in-frame fusions and complex structural variants as an additional class of tumor driver alterations. Notably, the identification of *FGFR2* exon 18 truncations and the demonstration of their potent oncogenic competence have refined our understanding of *FGFR*-driven tumorigenesis and have impacted clinical trial design for FGFR-targeted agents. This review explores the biological and clinical implications of *FGFR* rearrangements. It covers their mechanisms in driving cancer, their potential as biomarkers to predict treatment response, and the emerging challenges and opportunities for FGFR-targeted therapy. Ultimately, a deeper understanding of *FGFR* rearrangements is critical for advancing precision oncology and improving patient benefit.

Highlights

- Fibroblast growth factor receptor *(FGFR)* rearrangements, including canonical in-frame fusions and noncanonical structural variants, function as oncogenic drivers in multiple cancers.
- Advances in next-generation sequencing technologies and the integration of multiomic diagnostics enable the detection of rare and complex noncanonical FGFR rearrangements that are expressed.
- Noncanonical FGFR rearrangements that involve noncoding or intergenic regions can generate functional oncogenic isoforms through pseudoexon formation or promoter/enhancer hijacking.
- Structural rearrangements that generate exon 18-truncated variants result in distinct functional consequences for FGFR2 versus FGFR3.
- *FGFR* rearrangements emerge as actionable biomarkers, guiding the use of FGFR-targeted therapy.

Hijacking growth: novel mechanisms underlying FGFR oncogenicity

Fibroblast growth factor (FGF) ligands and FGF receptors (FGFRs) were linked to cancer for the first time in the late 1980s and early 1990s, when genetic amplification and aberrant expression of FGFs and FGFRs were detected in various cancer tissues and cell lines [1–4]. Though these initial discoveries were made more than 3 decades ago, the full complexity of *FGFR* alterations in cancer has become apparent only through more recent large-scale oncogenomic studies, as well as the implementation of targeted tumor sequencing assays into routine clinical practice. A notable yet diverse class of previously underappreciated *FGFR* alterations is structural rearrangements that range from in-frame fusions to complex noncanonical events. Recent work has demonstrated that most of these rearrangements

can act as oncogenic drivers and consequently dictate therapeutic response to FGFR inhibitors. In particular, it has largely gone unnoticed that rearrangements in *FGFR2* and *FGFR3* typically truncate exon 18 (E18), which encodes the C-terminal tails of these receptor tyrosine kinases (RTKs) [5–7]. The E18-truncation event has turned out to be critical for FGFR2 and FGFR3 oncogenicity, but the full oncogenic competence of *FGFR3* rearrangements depends on distinct additional determinants [6,7]. These findings have redefined our understanding of FGFR-driven tumorigenesis and have impacted the design of clinical trials evaluating next-generation FGFR inhibitors.

Tumor sequencing studies, and in particular the ever-growing wealth of real-world oncogenomic data, will continue to identify novel *FGFR* rearrangements across cancer indications. However, their functional and clinical relevance will remain incompletely understood, highlighting the urgent need for systematic characterization to guide precision therapy more effectively. In this review, we explore the biology and clinical relevance of *FGFR* rearrangements in cancer. We examine how canonical and noncanonical rearrangements arise and contribute to tumorigenesis across various cancer types. We also discuss the oncogenic mechanisms that underlie these events and their utility as predictive biomarkers for FGFR-targeted therapies, focusing on approved small-molecule inhibitors, co-occurring alterations, and resistance mechanisms. Finally, we outline key challenges and future directions for the clinical translation of these insights into refined patient stratification and better treatment strategies.

Canonical FGF/FGFR signaling

Structural features and signaling players

FGFRs belong to the RTK family and comprise four highly conserved transmembrane receptors (FGFR1-FGFR4), as well as the structurally related FGFR-like 1 (FGFRL1, also known as FGFR5). FGFR1-4 share a common architecture consisting of three extracellular immunoglobulin like domains (D1-D3) that mediate ligand binding, a single-pass transmembrane domain, and an intracellular region containing a split tyrosine kinase domain essential for signal transduction, followed by a short C-terminal tail that contributes to downstream signaling regulation (**Figure 1A**, Key figure) [8–10]. Alternative splicing of exons encoding the D3 domain of FGFR1-3 generates the *b* and *c* isoforms that confer distinct ligand-binding and tissue specificities [8,9]. FGFRL1 retains sequence similarity to the extracellular and transmembrane domains of FGFR1-4; however, it only possesses a short intracellular tail that lacks the split tyrosine kinase domain, precluding trans-autophosphorylation and engagement in canonical FGFR signaling pathways [11,12]. Given the lack of kinase activity of FGFRL1, the focus of this review is exclusively on the four canonical FGFRs (FGFR1-4).

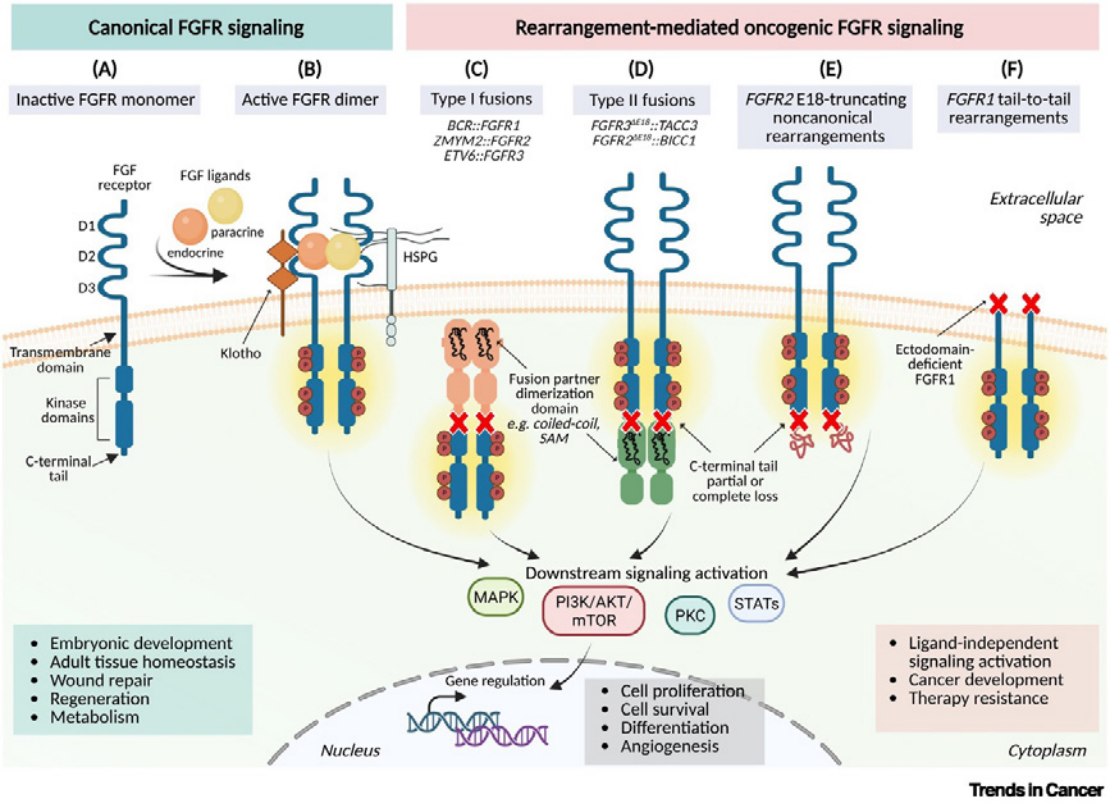


Figure 1. Overview of canonical versus rearrangement-mediated oncogenic FGFR signaling.

During canonical FGFR signaling, an inactive FGFR monomer (**A**) is bound by an FGF ligand together with a cofactor, either an HSPG (paracrine) or Klotho (endocrine), thereby inducing receptor dimerization and subsequent transphosphorylation of tyrosine residues within the kinase domains (**B**). These phosphotyrosines act as docking sites for key intracellular effectors, leading to activation of downstream transduction pathways, including MAPK, PI3K/AKT/mTOR, PKC, and STATs. The resulting transcriptional programs drive cell proliferation, survival, differentiation, and angiogenesis, which in healthy conditions support embryonic development, adult tissue homeostasis, wound repair, regeneration, and metabolic processes. In contrast, rearrangement-mediated oncogenic FGFR signaling (**C-F**) occurs independently of ligand binding and promotes constitutive signaling, oncogenic transformation, and therapy resistance. Type I fusions (**C**) retain the intracellular kinase domain but lose the extracellular and transmembrane regions, which are replaced by a 5′ partner containing a dimerization domain, leading to altered subcellular localization. In type II fusions (**D**), the extracellular, transmembrane, and kinase domains are typically retained, whereas the C-terminal tail is truncated – commonly at intron 17 or exon 18 (E18) of the gene – and replaced by the fusion partner, which often contributes a dimerization domain. Canonical and noncanonical *FGFR2* E18-truncating rearrangements (**E**) disrupt the C-terminal tail of FGFR2, abolishing autoinhibitory motifs and thereby promoting unchecked kinase activity and downstream signaling. Noncanonical intragenic or "tail-to-tail" rearrangements within or near the *FGFR1* gene generate ectodomain-deficient (N-terminally truncated) FGFR1 (**F**). Created in https://BioRender.com. AKT: protein kinase B; FGF: fibroblast growth factor; FGFRs: fibroblast growth factor receptors; HSPG: heparan sulfate proteoglycan; MAPK: mitogen-activated protein kinase; mTOR: mammalian target of rapamycin; PI3K: phosphoinositide 3-kinase; PKC: protein kinase C; SAM: sterile alpha motif; STAT: signal transducer and activator of transcription.

FGFR activation is initiated by the binding of an FGF ligand to an inactive FGFR monomer, in conjunction with heparan sulfate proteoglycan (HSPG) or Klotho cofactors (**Figure 1A**). This induces a conformational change that promotes receptor dimerization and subsequent transphosphorylation of the tyrosine residues within the kinase domains (**Figure 1B**). First, the A-loop tyrosines are phosphorylated, followed by those in the carboxy (C)-terminal tail, kinase insert and juxtamembrane regions [8]. The phosphorylated tyrosine residues on activated FGFRs serve as docking sites for key intracellular signaling mediators. These are mainly the adaptor protein FGFR substrate 2α, which mediates the assembly of various signaling complexes, and the hydrolase phospholipase Cγ, which hydrolyzes phosphatidylinositol 4,5-bisphosphate, generating the second messenger molecules diacylglycerol and inositol trisphosphate. These coordinated events lead to the activation of multiple downstream transduction pathways, including rat sarcoma (RAS) – mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K) – protein kinase B (AKT) – mammalian target of rapamycin (mTOR), protein kinase C (PKC), and signal transducer and activator of transcription (STAT)-dependent signaling [8,10,13]. To date, 18 different secreted FGF ligands capable of activating FGFRs have been identified. The majority of FGFs are paracrine factors with broad but tissue-specific expression patterns (FGF1-10, FGF16-18, FGF20, and FGF22), whereas a subset of FGFs are secreted by endocrine organs and act systemically via circulation (FGF19, FGF21, and FGF23) [8,9]. The binding specificity between FGFs and their cognate receptors is determined by their sequence diversity and spatiotemporal expression patterns.

Physiological functions and regulatory control

FGF/FGFR signaling plays critical roles throughout embryonic development by regulating early mesoderm patterning, organogenesis, differentiation, and cell proliferation and migration [9,10,14]. FGF/FGFR signaling is also vital during various adult physiological processes, such as tissue homeostasis, wound repair, and regeneration across multiple organ systems, including bone, muscle, and the vasculature, by sustaining cellular proliferation and survival and modulating metabolic processes [10]. Given its broad physiological relevance, FGF/FGFR signaling must be precisely regulated in space, time, and magnitude. To this end, cells have evolved an extensive repertoire of mechanisms that collectively ensure tight control of FGFR activity to prevent excessive signaling. These include receptor endocytosis, inhibitory adaptor proteins, dephosphorylation of key tyrosines by phosphatases, as well as serine/threonine phosphorylations that serve as inhibitory cues, typically installed by downstream signaling kinases as a negative-feedback loop [9,10,14,15]. The diversity and partial redundancy of the different negative control mechanisms underscore the critical need to tightly control and attenuate the FGF/FGFR pathway activity. Notably, its dysregulation is central to various pathologies, such as skeletal disorders, chronic kidney disease, and cancer [8,10].

Aberrant FGF/FGFR signaling in cancer

Over the past 2 decades, major progress has been made in understanding the roles of the FGF/FGFR signaling pathway in tumor initiation, progression, and angiogenesis [16]. Beyond its oncogenic functions, aberrant FGF/FGFR signaling also contributes to resistance against chemotherapy, radiotherapy, and targeted therapies such as CDK4/6 inhibitors, endocrine therapy, and human epidermal growth factor receptor 2 (HER2)-directed agents, underscoring its multifaceted role in tumor biology and treatment response [17–22].

Today, we know that aberrant FGF/FGFR signaling activation is primarily caused by genetic alterations in the *FGFR* genes and deregulation of the release of FGF ligands by cancer cells, as well as stromal fibroblasts and macrophages [16,23]. Up to 7.1% of all human cancers harbor alterations in the *FGFR* genes, which occur across a broad spectrum of tumor types (**Figure 2A**) [24–28]. *FGFR* amplifications are most frequent (~5%), followed by activating mutations (~2%) and gene rearrangements (~0.5%) [24,25,27,28]. Both the prevalence and

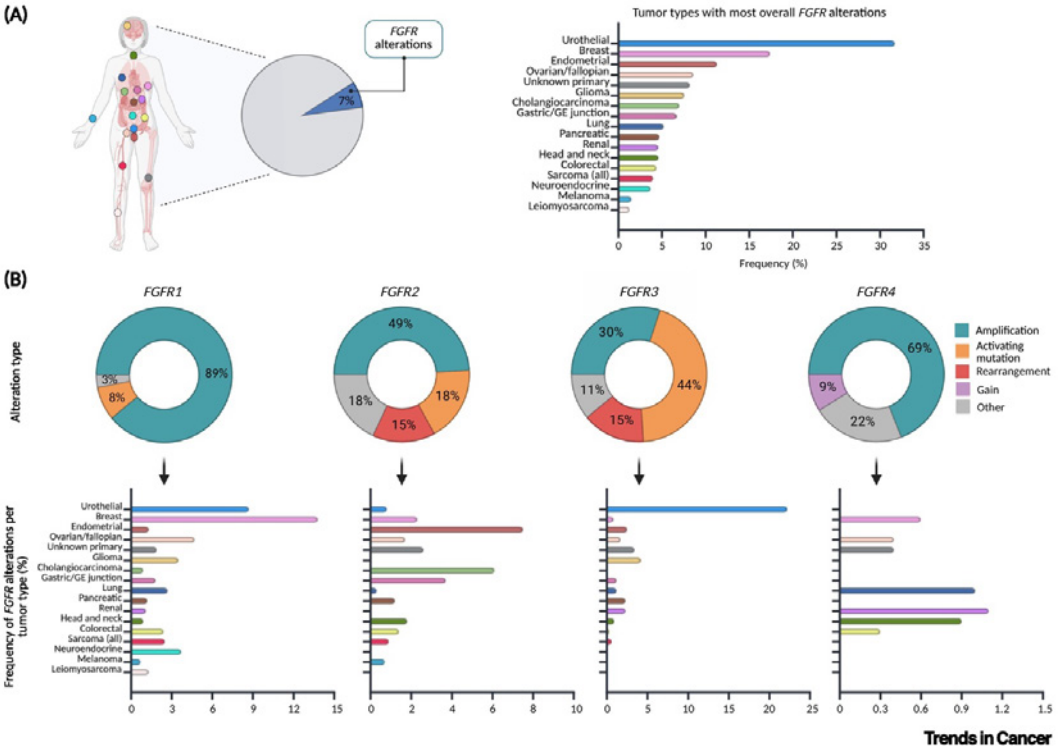


Figure 2. Landscape of *FGFR* genomic alterations across human cancers.

(**A**) Overall prevalence and tumor type distribution of *FGFR* genomic alterations. (**B**) Comparative alteration spectra across *FGFR1-FGFR4*, showing that each receptor exhibits its own characteristic mix of genomic events (amplification, activating mutation, rearrangement, gain, or other) and tumor type distributions. Data derived from [24]. Created in https://BioRender.com. GE: gastroesophageal.

the types of *FGFR* alterations vary significantly across tumor types (**Figure 2B**). For instance, oncogenic *FGFR* alterations are frequent in urothelial (~32%), breast (~18%), endometrial (~13%), and squamous lung cancers (~13%), whereas they are rare in soft tissue sarcomas, melanomas, and neuroendocrine tumors [24]. *FGFR3* hotspot mutations are the most common alteration type in urothelial carcinomas. Conversely, *FGFR1* amplifications and *FGFR2* mutations are prevalent in breast and squamous cell carcinomas and in endometrial cancer, respectively.

The functional impact of each *FGFR* alteration depends on both the specific genetic change and the tissue type affected, ultimately shaping tumor behavior and influencing patient response to FGFR-targeted therapies [16]. The growing catalog of *FGFR* rearrangements revealed by recent oncogenomic studies reflects the complexity of FGFR-driven oncogenesis. Yet, their biological and clinical significance remains only partially understood, warranting comprehensive functional characterization to inform precision oncology.

FGFR gene rearrangements in cancer

Genomic rearrangements are large-scale structural alterations of the genome that disrupt the normal linear organization of the DNA. They include large insertions, duplications, deletions, inversions, and chromosomal translocations, which can span kilobases to megabases and affect gene function by duplicating or removing coding sequences, creating fusion genes, or altering regulatory elements. In addition to these chromosomal events, extrachromosomal DNA represents a distinct mode of genome reorganization in which circular DNA fragments carrying oncogenes or enhancers are excised from chromosomes, amplified independently, and can subsequently reintegrate into the genome to drive oncogene expression [29]. Rearrangements can occur within the same chromosome (intrachromosomal) or between different chromosomes (interchromosomal). At the molecular level, gene rearrangements typically arise from DNA double-strand breaks followed by faulty repair or replication processes, with the resulting structural variations largely shaped by the interplay between error-prone DNA repair pathways [i.e., **nonhomologous end joining** (see Glossary) and **microhomology-mediated end joining**], replication-associated errors, and the broader genomic context [30]. Catastrophic events such as **chromothripsis** and **chromoplexy**, which are now recognized as important cancer driver processes, further contribute to the complexity seen in cancer genomes [30,31].

Although *FGFR* rearrangements account for only 5-10% of all *FGFR* alterations, they have attracted considerable attention in recent years due to their distinct oncogenic mechanisms of action, clinical actionability, and relevance to emerging molecular classification and treatment paradigms [24,25,27,28].

Canonical in-frame FGFR fusions

The most well-studied *FGFR* rearrangements are gene fusions involving other protein-coding partners, particularly those occurring in-frame to produce functional chimeric transcripts. FGFR fusions can be classified into type I (**Figure 1C**) or type II (**Figure 1D**), based on whether the C- or N-terminal region of the FGFR is retained in the fusion protein [13,32].

Type I fusions, in which FGFR is the 3′ partner, are more commonly associated with hematological malignancies and involve replacement of the N-terminal portion of FGFR – including the extracellular and transmembrane domains – by a fusion partner, leading to loss of the membrane anchor and consequent altered subcellular localization and dysregulated signaling (**Figure 1C**). The kinase domain becomes constitutively active in aberrant intracellular compartments, escaping normal ligand dependence, endocytic downregulation, and membrane-specific spatial feedback controls that normally restrain FGFR activation [15]. Examples of type I fusions include *BCR::FGFR1*, *ZMYM2::FGFR2* and *ETV6::FGFR3*.

In contrast, type II fusions, in which FGFR is the 5′ fusion partner, are more common in solid tumors. Here, the FGFR extracellular, transmembrane, and kinase domains are typically retained, whereas the C-terminal tail is truncated – commonly at intron 17 (I17) or E18 of the gene – and replaced by the fusion partner (**Figure 1D**). Examples of type II fusions are *FGFR2::BICC1* and *FGFR3::TACC3*, which are established oncogenic drivers in intrahepatic **cholangiocarcinoma** (iCCA) and glioblastoma, respectively, among other tumor types [5–7,33]. In most type II FGFR fusions, the fusion partner contributes self-association domains such as coiled-coil (e.g., FGFR3::TACC3), sterile alpha motif (e.g., FGFR2::BICC1), Lissencephaly-1-homology (LisH) domain, IRSp53/MIM homology domain (IMD), and caspase domains, which promote ligand-independent dimerization or oligomerization through specific protein-protein interactions [5–7,13]. These fusions typically show ligand-independent and constitutive FGFR autophosphorylation and activation of downstream signaling pathways [6,7].

FGFR fusion-positive cancers usually contain few concurrent driver alterations [34–36] and are mutually exclusive with *FGFR* hotspot mutations and amplifications [6,7,37,38], suggesting that *FGFR* fusions function as primary oncogenic drivers and thus represent actionable targets. *FGFR* fusions have also emerged as mechanisms of acquired resistance to targeted therapy, such as EGFR inhibitors in nonsmall cell lung cancer (NSCLC) [20,34,39–41].

Tumor spectrum of FGFR fusions

FGFR fusions involve a broad spectrum of partner genes across a wide range of tumor types [6,7,24,25,27,28]. Type I *FGFR1* fusions, involving partners such as *ZMYM2*, *BCR*, *FOP1*,

and *CNTRL*, are associated with rare but aggressive hematological neoplasms [13,32]. In solid tumors, *FGFR1* fusions are much less common, with only sporadic cases reported in breast, lung, glioma, and salivary gland cancers [13,28,32]. *FGFR2* fusions, in particular type II fusions, are most common in iCCA and may occur in up to 50% of all iCCA cases, but they have also been recurrently observed in breast, lung, ovarian, and pancreatic cancers, among others [6,13,28]. To date, more than a hundred distinct *FGFR2* fusion partners have been identified, with *BICC1*, *TACC2*, *AHCYL1*, and *KIAA1217* being among the most frequent [6,13,28]. *FGFR3* type II fusions are frequently observed in urothelial, brain, lung, and breast cancers, with *TACC3* being the single most recurrent partner (~85%) [7]. Other partners, such as *TNIP2*, *ADD1*, and *JAKMIP1* have also been identified, albeit at much lower frequencies [7,13,24,27,28,42]. In contrast to *FGFR1-3*, *FGFR4* is rarely involved in gene fusions or other structural rearrangements, consistent with the low frequency of *FGFR4* alterations across cancers as compared with *FGFR1-3* (7% for *FGFR4* versus 49% for *FGFR1*, 19% for *FGFR2*, and 26% for *FGFR3*) [24]. The few reported *FGFR4* fusion events have been predominantly found in NSCLC and typically involve type I fusions with partners such as *ANO3*, *NSD1*, and *ZNF346* [24,27,28,34,42].

Noncanonical FGFR rearrangements

FGFR gene fusion studies have traditionally focused on protein-coding gene-gene rearrangements. This has left rearrangements involving noncoding regions of the genome largely unexplored, partly because of sequencing methods that target coding regions only, such as whole-exome sequencing or targeted gene panels. Rearrangements with noncoding regions have also been neglected because they have been considered incapable of generating chimeric transcripts. However, recent studies have demonstrated that structural alterations outside gene bodies can play important roles in tumor development and therapeutic response, in particular, in cancers that show aberrant kinase signaling [6,43,44]. The prevalence and potential significance of these events are underscored by the fact that up to 62% of all rearrangements found pan-cancer involve breakpoints in intergenic regions [43]. These rearrangements may drive tumorigenesis through two distinct mechanisms. First, gene-intergenic and intergenic-intergenic rearrangements can result in the repositioning of distant promoters or enhancers, boosting mRNA expression of oncogenes (known as promoter or enhancer "swapping" or "hijacking") [43]. Second, intergenic sequences can give rise to pseudoexons that lead to the formation of functional transcripts by providing splice donor or acceptor sites and thereby maintaining reading frames or creating new junctions [45].

Next-generation sequencing (NGS) technologies have greatly improved the detection of rare and complex noncanonical rearrangements, with recent studies showing that these events are of particular clinical relevance for *FGFR*s [6,7,46]. For instance, noncanonical intragenic or "tail-to-tail" rearrangements within or near the *FGFR1* gene can generate ectodomain-deficient (N-terminally truncated) proteins that preserve kinase activity

(**Figure 1F**) and drive squamous cell lung cancer through ligand-independent dimerization [46]. Analysis of paired whole-genome sequencing (WGS) and RNA-sequencing data from a pan-cancer cohort also uncovered a substantial fraction of tumors harboring functionally relevant noncanonical rearrangements in E18 of *FGFR2* (**Figure 1E**) [6]. These include events in which the reading frame of the partner gene is unknown (potentially out of frame), the partner gene is out of strand, or the rearrangement involves intergenic or internal *FGFR* gene sequences instead of a partner gene.

Oncogenic mechanisms behind *FGFR* rearrangements

Truncation of *FGFR2* at E18 – its last exon encoding the C-terminal tail – acts as a potent oncogenic driver alteration in cancer [6]. Importantly, this tumor-driver potential is independent of a specific fusion partner, indicating that truncation or loss of E18 itself is the critical pathogenic event (**Figure 3A**). E18-truncated *FGFR2* (*FGFR2*$^{\Delta E18}$) transcripts can result from different types of genomic alterations, including gene rearrangements or gene fusions, E1-17 partial amplifications, as well as E18 nonsense and frameshift mutations (**Figure 3A**). Notably, in a large real-world cohort of tumor sequencing profiles, among the 1,367 tumor samples that contained *FGFR2* alterations potentially generating E18-truncated transcripts, 44.6% were noncanonical rearrangements. Analysis of RNA-sequencing profiles from a subset of these cases confirmed the generation of functional *FGFR2*$^{\Delta E18}$ transcripts [6]. These findings suggest that noncanonical rearrangements that would have previously been classified as variants of unknown significance can give rise to functional oncogenic *FGFR2*$^{\Delta E18}$ isoforms, positioning them as bona fide tumor drivers and actionable targets for FGFR-targeted therapies. The tumor-driving effect of E18 loss in FGFR2 was recently attributed to the disruption of a phenylalanine-serine motif that is located in the proximal part of the C-tail [47]. These two residues are essential for binding of the FGFR2 C-tail to the kinase domain and for restraining kinase activity, and have therefore been termed the kinase domain-binding and suppression (KDBS) motif. Functional *in vitro* assays, together with *in vivo* mammary tumor modeling in mice, demonstrated that the C-terminal tail suppresses FGFR2 oncogenicity through this KDBS motif and the concurrent regulation of endocytosis and the PI3K/ extracellular signal-regulated kinase (ERK) negative-feedback loop.

Perturbation of E18 of *FGFR3*, which encodes the FGFR3 C-terminal tail akin to FGFR2, is also recurrent in cancer, resulting in the expression of *FGFR3*$^{\Delta E18}$ transcripts that lack (part of) E18 and thus have dysfunctional C-terminal tails [7]. However, in contrast to FGFR2, FGFR3 requires both E18 truncation and fusion to a partner gene that retains the expression of a dimerizing domain for full oncogenic competence (**Figure 3B**). Interestingly, the KDBS motif is not fully conserved in FGFR3 (phenylalanine-alanine instead of phenylalanine-serine), which might explain the differential impact of C-terminal truncation on FGFR2 versus FGFR3 oncogenicity and the selective pressure for FGFR3 to preferably fuse with partners that contain dimerization domains. Notably, 95% of partner genes involved in

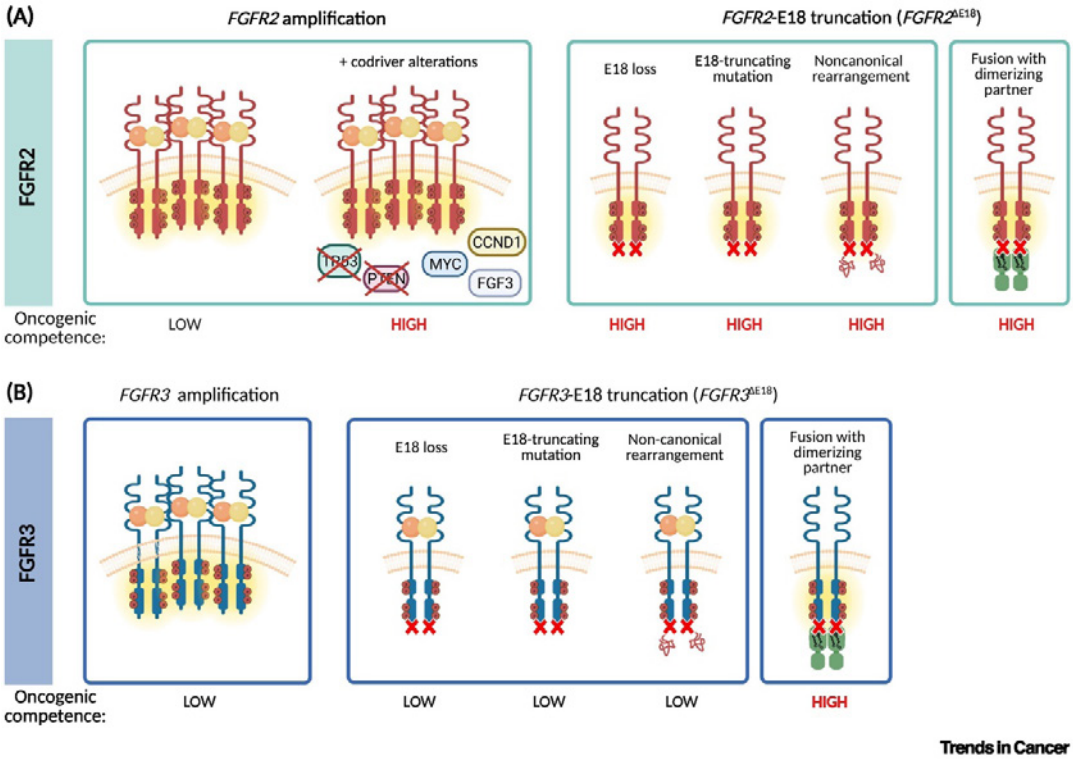


Figure 3. Differential oncogenic competence of amplified full-length versus E18-truncated FGFR2/3.

(**A**) The oncogenic competence of full-length FGFR2 relies on cooperating codriver alterations such as TP53 or PTEN loss, or overexpression of MYC, CCND1, or FGF3. In contrast, E18-truncated variants promote tumorigenesis without requiring additional alterations. The key pathogenic event is disruption of E18, whether through exon loss, truncating mutations, noncanonical rearrangements, or fusion with a partner harboring a dimerizing domain. (**B**) For FGFR3, full oncogenic competence requires E18 truncation combined with fusion to a dimerizing partner. *FGFR3* amplification, E18 loss, E18-truncating mutations, and noncanonical rearrangements exhibit limited oncogenic activity and might depend on cooperating cancer driver mutations to enhance their oncogenic potential. Created in https://BioRender.com. CCND1: cyclin D1; FGFR: fibroblast growth factor receptor; MYC: v-myc myelocytomatosis viral oncogene homolog; PTEN: phosphatase and tensin homolog; TP53: tumor protein 53.

FGFR3$^{\Delta 18}$ fusions encode self-interacting domains, with the coiled-coil motif being the most frequent. TACC3 contains two coiled-coil domains that are typically preserved in FGFR3$^{\Delta E18}$::TACC3 fusions. The FGFR3 fusion partner oligomerization domains mediate constitutive, ligand-independent receptor dimerization, thus driving aberrant FGFR3 kinase activation and downstream signaling [5–7,32]. Nevertheless, a sizable subset of all tumors harbor E18-truncating mutations (12.3%), potentially resulting in *FGFR3*$^{\Delta E18}$ transcripts. These alterations are devoid of fusion partners, suggesting that FGFR3$^{\Delta E18}$ might display oncogenic activity in specific comutational and/or cellular contexts [7].

Beyond partner-driven dimerization, *FGFR* fusions and noncanonical rearrangements can disrupt transcriptional or translational regulatory elements of the *FGFR* loci, thereby altering protein expression or stability. Additionally, they can introduce premature stop codons or delete negative regulatory regions (e.g., the KDBS motif in FGFR2) or extracellular domains, resulting in the loss of inhibitory signals and enhanced FGFR signaling [13,46,47]. Some rearrangements can also result in aberrant subcellular localization of the fusion protein, with retention in the cytoplasm rather than the plasma membrane, thereby disrupting normal signaling regulation (**Figure 1C**) [48].

FGFR rearrangements as predictive biomarkers for FGFR targeted therapy

The implication of FGF/FGFR signaling in the pathogenicity of cancer has prompted the development of a range of FGFR-targeted therapeutic approaches, several of which have achieved regulatory approval for specific *FGFR*-altered tumor indications, and many more are currently being evaluated in clinical trials (**Table 1**).

Small-molecule FGFR inhibitors

The first generation of FGFR inhibitors consisted of multikinase small molecules that target the ATP-binding pocket of FGFR1-4, as well as other RTKs with highly structurally conserved tyrosine kinase domains (derazantinib, dovitinib, tasurgratinib, lenvatinib, lucitanib, nintedanib and, ponatinib) [83,84]. These molecules have shown considerable toxicity at the dosage required for full FGFR inhibition (likely due to multi-RTK inhibition), thus limiting their utility in clinical practice. This spurred the development of next-generation FGFR inhibitors, which have demonstrated improved potency and selectivity. They include pan-FGFR inhibitors (erdafitinib, rogaratinib, futibatinib, and resigratinib), as well as selective inhibitors of FGFR1-3 (pemigatinib, infigratinib, fexagratinib, and zoligratinib), FGFR2 (lirafugratinib), FGFR3 (LOXO-435), and FGFR4 (roblitinib and fisogatinib) [83–85]. Erdafitinib, pemigatinib, infigratinib, rogaratinib, and zoligratinib block FGFR kinase activity in an ATP-competitive and noncovalent manner, comparable to first-generation inhibitors. Conversely, futibatinib, resigratinib, lirafugratinib, roblitinib, and fisogatinib are covalent inhibitors that form irreversible bonds with specific cysteine residues within the ATP-binding pocket, resulting in stronger target engagement, enhanced selectivity, and less susceptibility to on-target resistance mutations [49,57,86].

To date, four FGFR inhibitors – three noncovalent (erdafitinib, infigratinib, and pemigatinib), and one covalent (futibatinib) – have received clinical approval for second- or later-line treatment in advanced solid tumors harboring specific *FGFR* gene alterations. Based on the phase 2 BLC2001 trial (NCT02365597), erdafitinib received accelerated FDA approval in 2019 for the treatment of *FGFR2/3* fusion- and *FGFR3* mutation-positive urothelial carcinoma [50,51]. The follow-up phase 3 THOR trial (NCT03390504) demonstrated that erdafitinib meaningfully improves objective response rates compared with standard-of-care

Table 1. Small-molecule FGFR inhibitors in clinical use or under development

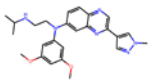
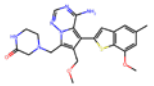
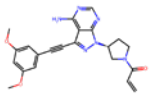
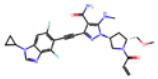
Inhibitor	Structure	Binding mode	Resistance-associated FGFR mutations[a]	Indication	Clinical status	Refs
Pan-FGFR						
Erdafitinib (JNJ-42756493)		Reversible	• FGFR2: N550K, V565F/L, C632Y, and D651Y • FGFR3: N540K, V555L/M, E587Q, and L608V	Urothelial carcinoma	Approved	[49–56]
				Glioma	Phase 2	
				Solid tumors	Phase 2	
Rogaratinib (BAY 1163877)		Reversible	• FGFR2: N550K and V565F/L	Urothelial carcinoma	Phase 1/2/3	[49]
				Squamous cell lung cancer	Phase 2	
				Sarcoma	Phase 2	
Futibatinib (TAS-120)		Covalent (binds FGFR2 C492)	• FGFR2: C492F and V565F Retained potency against: • FGFR2: N550D/H/K, V565I/L, E566A/G, M583I, L618V, K660M/N, and H683L	Cholangiocarcinoma	Approved	[49,54,57–61]
				Urothelial carcinoma	Phase 2	
				Colorectal cancer and other solid tumors	Phase 2	
				Bladder cancer	Phase 2	
				Advanced biliary cancer	Phase 3	
Resigratinib (KIN-3248)		Covalent (binds FGFR2 C492)	• FGFR2: C492F Retained potency against: • FGFR2: N550H/K, V565F, and K660M • FGFR3: N540K, V555M, and K650M	Advanced solid tumors with *FGFR2* and/or *FGFR3* alterations	Phase 1b	[62]

Table 1. continued

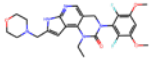
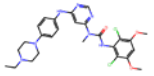
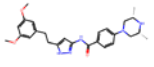
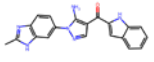
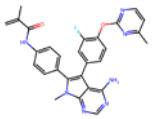
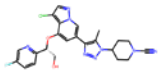
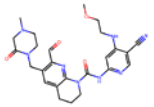
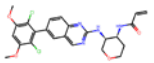
Inhibitor	Structure	Binding mode	Resistance-associated FGFR mutations[a]	Indication	Clinical status	Refs
FGFR1-3						
Pemigatinib (INCB-054828)		Reversible	• FGFR1: N546K and V561L/M • FGFR2: M537I, N550D/H/K/T, V565F/I/L, E566A, L617V, K641R, and K659M • FGFR3: N540K and V555L/M	Cholangiocarcinoma Myeloid/lymphoid neoplasms Solid tumors Hematologic malignancies	Approved Approved Phase 1/2 Phase 1/2	[49,54,63–68]
Infigratinib (BGJ398)		Reversible	• FGFR1: V561M • FGFR2: N550D/H/K, V565F/L, L618V, and K660M • FGFR3: V555M Retained potency against: • FGFR2: M538I and H683L, which induce clinical resistance to zoligratinib •	Cholangiocarcinoma Bladder cancer	Discontinued[b] Discontinued[b]	[49,57,69–72]
Fexagratinib (AZD4547)		Reversible	• FGFR1: V561M • FGFR2: I567S, N568H/T, V581L, E584G, S587L, K660R, and K678M	Solid tumors, lymphoma, and multiple myeloma Breast cancer	Phase 2 Phase 2	[71,73,74]
Zoligratinib (Debio1347)		Reversible	• FGFR2: N550K, V565L, L618F/V, and K660M Retained potency against: • FGFR2: V565F	Breast cancer	Phase 1b/2	[49,57]

Table 1. continued

Inhibitor	Structure	Binding mode	Resistance-associated FGFR mutations[a]	Indication	Clinical status	Refs
FGFR2						
Lirafugratinib (RLY-4008)		Covalent (binds FGFR2 C492)	• FGFR2: C492F Retained potency against: • FGFR2: N550D/K/T, V565F/I/L, E566G, and K660M	Cholangiocarcinoma and other solid tumors	Phase 1/2	[54,75–77]
FGFR3						
LOXO-435 (LY3866288)		Reversible	Designed to preserve activity against resistance-associated FGFR3 mutations Retained potency against: • FGFR3: V555M	FGFR3-altered solid tumors	Phase 1	[78,79]
FGFR4						
Roblitinib (FGF401)		Covalent (binds FGFR4 C552)	• FGFR4: V550E Retained potency against: • FGFR4: N535K	Hepatocellular carcinoma and other FGFR4-altered solid tumors	Phase 1/2	[80,81]
Fisogatinib (BLU-554)		Covalent (binds FGFR4 C552)	• FGFR4: V548L/M, V550E/L/M, C552F/R/W/Y, and A553P/V	Hepatocellular carcinoma	Phase 1/2	[82]

[a]Resistance-associated FGFR mutations:
FGFR1: N546K (molecular brake), V561L/M (gatekeeper).
FGFR2: C492F (covalent binding site, P-loop), N550D/H/K/T (molecular brake), V565F/I/L (gatekeeper), E566A/G (molecular brake), E584G (hinge), K660M/N/R (activation loop), K678M (activation loop).
FGFR3: N540K (molecular brake), V555L/M (gatekeeper), K650M (activation loop).
FGFR4: N535K (molecular brake), V550E/L/M (gatekeeper), C552F/R/W/Y (covalent binding site, hinge-1).
[b]Infigratinib (BGJ398) FDA approval was voluntarily withdrawn by its sponsor in May 2024.

chemotherapy in *FGFR2/3*-altered urothelial carcinoma patients previously treated with an immune checkpoint inhibitor (ICI) [52], which led to its full approval in 2024. However, no differentiation versus the next-line ICI pembrolizumab was observed [53]. Pemigatinib [63,64], infigratinib [69], and futibatinib [57,58] also received accelerated FDA approval for the treatment of advanced iCCA harboring *FGFR2* fusions and/or rearrangements in 2020, 2021, and 2022, respectively. In 2022, pemigatinib was also approved for patients with myeloid/lymphoid neoplasms harboring *FGFR1* fusions [65,66].

Notably, in the phase 2 FIGHT-202 trial (NCT02924376) evaluating pemigatinib in CCA, objective and durable responses were observed exclusively in patients with *FGFR2* fusions or rearrangements involving the I17/E18 hotspot region of *FGFR2*, with an objective response rate of 35.5%. In contrast, no objective responses were observed in patients with *FGF/FGFR* alterations other than fusions/rearrangements or in those who were *FGF/FGFR* wild type [63]. A retrospective analysis of the FIGHT-202 trial data revealed that stratifying patients by *FGFR2* E18-truncating rearrangement type (in-frame fusions versus noncanonical rearrangements involving intergenic regions or frame-unknown events) had no impact on the trial outcome; both groups of patients responded to pemigatinib and achieved comparable **progression-free survival (PFS)** benefit, irrespective of the fusion/rearrangement type [6]. Preclinical data suggest that E18-truncating *FGFR2* fusions and rearrangements generate a constitutively active receptor that acts as a potent tumor driver, thereby conferring a strong dependence on FGFR2 signaling that translates into sensitivity to FGFR-targeted agents [6,87]. In contrast, wild-type *FGFR2* and *FGFR2* alterations that retain E18, such as amplifications, produce FGFR2 that remains ligand dependent and is not constitutively active [6]. As the oncogenic driver landscape of iCCA and other cancers suggests, tumors harboring non-E18-truncating *FGFR2* alterations are shaped by additional driver alterations and may therefore be less reliant on FGFR2 signaling [6,88,89]. Ultimately, this may account for the lack of objective responses to pemigatinib in patient cohorts that are devoid of I17/E18 hotspot-rearranged *FGFR2*, as observed in FIGHT-202 [63]. Together, these data suggest that *FGFR2* fusions and noncanonical rearrangements that involve E18 are predictive biomarkers for response to pemigatinib and, likely, for other FGFR-targeted therapies.

Conceivably, clinical outcomes in patients with select genomic *FGFR* alterations may also be improved by the use of FGFR inhibitors in earlier lines. It is noteworthy that two phase 3 trials in CCA evaluating infigratinib (NCT03773302) and pemigatinib (FIGHT-302, NCT03656536) in first-line treatment versus standard-of-care chemotherapy were terminated prematurely. In 2024, FDA approval of infigratinib was withdrawn by its sponsor due to challenges in recruiting patients, making continued commercial viability for the second-line indication unfeasible. Changes in the first-line standard-of-care for CCA also led to the discontinuation of FIGHT-302 in 2025. Efforts that are currently underway to advance next-generation FGFR-targeted medicines are centered on optimizing patient selection,

reducing class-related toxicities (i.e. hyperphosphatemia and ocular, nail, dermatologic, and gastrointestinal adverse events), and improving selectivity and safety profiles [85,90].

Other FGFR-targeted therapeutic approaches

While small-molecule FGFR inhibitors are the most clinically advanced, other modalities targeting the FGF/FGFR axis are also being explored. These include monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs), ligand traps targeting FGFs, and DNA/RNA-based aptamers, among others (reviewed in detail by Katoh *et al.* [84]). Among these, bemarituzumab (FPA144), an FGFR2b-specific mAb engineered to enhance antibody-dependent cellular cytotoxicity, is the most clinically advanced. Bemarituzumab showed promising activity in a phase 2 trial in patients with FGFR2b-overexpressing gastric and gastroesophageal junction cancers [91], and the corresponding phase 3 trials are currently ongoing (NCT05052801 and NCT05111626). In addition, SIM0686 (SCR-A002), an FGFR2b-targeted and topoisomerase I inhibitor payload-conjugated ADC, has demonstrated potent antitumor activity in several preclinical models, including those that show bemarituzumab resistance [92], and is currently being evaluated in a phase 1 trial (NCT07050459). Collectively, these emerging strategies broaden the therapeutic options for FGFR-driven malignancies.

Comutational landscape

Extending the clinical utility of FGFR-targeted therapies will require a deeper understanding of the interplay between *FGFR* alterations and the broader comutational landscape to inform rational combination strategies. Notably, 94% of cancers that contain alterations affecting components of the FGF/FGFR axis harbor one or more additional pathogenic coalterations [89]. These most commonly affect *TP53*, as well as p53 pathway members, cell cycle regulators, other RTKs, and components of the MAPK and PI3K pathways [6,7,24,67,68,88,89,93,94].

Strikingly, different *FGFR* alteration types co-occur with distinct codriver alterations. Across cancers, and in breast cancer specifically, *FGFR2* hotspot mutations and *FGFR2* E18-truncating alterations, including fusions, functionally cooperate with *PIK3CA* hotspot mutations [6,94]. Conversely, *FGFR2* E18-truncating alterations and *FGFR3* fusions are mutually exclusive with *TP53* hotspot missense mutations, *PTEN* loss-of-function, and *MYC*, *CCND1*, and *FGF3/4/19* amplification, whereas these driver gene alterations co-occur with *FGFR2* amplifications [6,68,95]. Functional *in vivo* annotation showed that the oncogenicity of full-length FGFR2 indeed depends on TP53 or PTEN loss or overexpression of MYC, CCND1, or FGF3, whereas FGFR2$^{\Delta E18}$ variants promote tumor formation independent of any coalterations (**Figure 3A**) [6]. Interestingly, although *FGFR2* and *FGFR3* E18-truncating fusions/rearrangements are mutually exclusive with *TP53* mutations, the subset of patients double positive for *FGFR2/3* and *TP53* mutation status exhibit particularly low response rates to FGFR inhibitors, manifesting in poor PFS [67,68,95] and **overall survival** [64,89].

Taken together, integrating *FGFR* status information with comutational profiles may guide combination treatment strategies to improve patient outcomes.

Preclinical studies have demonstrated convincing synergism between FGFR inhibitors and targeted approaches against PI3K [94,96–99], CDK4/6 [19] and EGFR/AXL [100]. In the clinic, FGFR targeted therapies are currently being evaluated in combination with PI3K inhibitors, CDK4/6 inhibitors, ICIs, chemotherapeutics, and DNA damage response-targeted agents. Initial reports suggest that such combinations may indeed yield superior clinical response rates compared with their respective monotherapies, particularly when combining FGFR inhibition with CDK4/6 blockade [89,101] or ICI [61,102]. Histology-agnostic clinical studies or **basket trials** could offer a valuable framework in this context, although the evaluation of larger patient cohorts will likely be necessary to more clearly define the therapeutic benefit and guide the integration of FGFR-based combinations into future precision oncology strategies.

Acquired resistance mechanisms

Despite the encouraging results of FGFR inhibitors in clinical trials, both primary and acquired resistance remain significant obstacles to achieving durable clinical benefit. To date, most insights into mechanisms of resistance come from studies in *FGFR2* fusion-positive iCCA [49,54,59,72,103,104] and *FGFR3*-altered urothelial carcinoma [55,56,70]. Recent basket trials have also uncovered resistance-associated mutations in indications other than iCCA or urothelial cancer, including NSCLC as well as pancreatic and gastroesophageal cancers [67]. In a recent study, Tangermann *et al*. used saturation mutagenesis in NCI-H1581 NSCLC cells to systematically interrogate all 11,520 possible point mutations across the kinase domains of *FGFR1-4* [105]. A total of 738 mutations conferring resistance to pemigatinib and futibatinib were identified, capturing 97% of the resistance mutations observed in clinical trials and substantially expanding the catalog of potential resistance mechanisms that may emerge in patients.

Across *FGFR1-FGFR3*, the most frequent mechanisms of acquired resistance to noncovalent ATP-competitive FGFR inhibitors involve secondary mutations in the **gatekeeper** and **molecular brake residues** within the *FGFR* kinase domain, which lead to steric hindrance of inhibitor binding and destabilization of the inactive kinase conformation, respectively [84] (Table 1). In a considerable fraction of cases, multiple polyclonal intratumoral mutations have been observed [49,55,67,72,106]. Pathway reactivation through the upregulation or mutation of other RTKs or downstream signaling components, including RAS/rapidly accelerated fibrosarcoma (RAF)/ERK and PI3K/AKT/mTOR, represents alternative mechanisms underlying both intrinsic and acquired resistance to FGFR inhibitors [49,55,74,84].

Low clinically achievable drug concentrations due to adverse effects can create a permissive environment for the outgrowth of resistant clones, as observed with the FGFR inhibitor infigratinib [57]. Next-generation isoform-selective FGFR2 and FGFR3 inhibitors may be dosed at higher concentrations, resulting in enhanced efficacy and reduced emergence of resistance. Moreover, covalent FGFR inhibitors retain efficacy in *FGFR*-driven cancers that are resistant to noncovalent ATP-competitive FGFR inhibitors via acquired kinase domain mutations [107]. For example, the FGFR3-selective inhibitor LOXO-435 (LY3866288) has shown promising initial results in *FGFR3*-altered advanced solid tumors [78], with preclinical data indicating efficacy against the *FGFR3* V555M gatekeeper mutation [79]. Similarly, the covalent pan-FGFR inhibitor futibatinib has demonstrated efficacy in four iCCA patients with *FGFR2* fusions who developed resistance to the reversible ATP-competitive inhibitors infigratinib and zoligratinib [57]. Another promising example is lirafugratinib (RLY-4008), a highly selective, covalent FGFR2 inhibitor that retains antitumor activity against a subset of *FGFR2* resistance mutations in iCCA [75–77].

Concluding remarks and future perspectives

FGFR rearrangements, particularly in-frame gene fusions, have emerged as actionable oncogenic drivers in a subset of tumor indications. Several FGFR inhibitors have achieved regulatory approval based on their clinical benefits and have established *FGFR* rearrangements as predictive biomarkers. Nevertheless, major challenges remain (see **Outstanding questions**). Not all *FGFR* alterations carry equal clinical relevance; therefore, optimizing patient selection for FGFR-targeted therapies requires systematic evaluation of rare canonical and noncanonical rearrangements, which are increasingly uncovered through advances in NGS. Functional characterization of these *FGFR* rearrangements is essential to inform the rational design of next-generation targeted therapies, as only a subset act as true oncogenic drivers. Currently, integrating WGS with matched transcriptomic and/or proteomic data provides the most reliable means of identifying functionally expressed drivers, including those generated through noncanonical rearrangements involving pseudoexon, frameshift, or antisense events. However, robust computational frameworks capable of distinguishing true oncogenic driver events from passenger alterations need to be further developed and implemented into routine clinical practice. Current machine-learning models based on background breakpoint distribution analysis represent a promising start, but further refinement is needed, particularly through the incorporation of genomic features (e.g., replication timing, chromatin state) across all tissue types [45]. In parallel, the influence of co-occurring genetic alterations on *FGFR*-driven oncogenesis and therapeutic response needs to be further investigated. Finally, acquired resistance to FGFR inhibitors continues to pose a significant obstacle, underscoring the need for next-generation agents designed to prevent or overcome resistance, as well as to mitigate adverse events.

OUTSTANDING QUESTIONS

- What are the key determinants of oncogenicity in fibroblast growth factor receptor (FGFR) rearrangements?
- Which FGFR rearrangements act as standalone oncogenic drivers versus those that require cooperating co-driver alterations to achieve full oncogenicity?
- How do co-occurring (epi)genetic alterations influence *FGFR*-driven oncogenesis, therapeutic response, and resistance evolution?
- How can we systematically assess the clinical significance of rare canonical and non-canonical *FGFR* rearrangements?
- Which biomarkers can be robustly implemented to reliably predict patient response and resistance to FGFR-targeted therapies across tumor types?
- How should biomarker testing be standardized to ensure consistent detection of *FGFR* rearrangements across tumor types and clinical laboratories?
- How should basket studies be designed to effectively evaluate FGFR-targeted therapies across tumor types and (rare) *FGFR* variants?

GLOSSARY

- **Basket trial**: a clinical study design that evaluates the efficacy of a targeted therapy across multiple cancer types that share the same molecular alteration, rather than being restricted to a single tissue of origin. Patients are "pooled" into molecularly defined baskets (e.g., specific *FGFR* mutations or fusions).
- **Cholangiocarcinoma (CCA)**: malignant tumor that originates from the epithelial cells of the bile ducts, occurring either within the liver (intrahepatic; iCCA) or along the extrahepatic biliary tree.
- **Chromoplexy**: complex DNA rearrangement event characterized by interdependent and balanced chromosomal translocations involving multiple chromosomes, creating chains of rearrangements that disrupt and fuse several genes simultaneously.
- **Chromothripsis**: catastrophic mutational process in which one or more chromosomes are shattered into tens to hundreds of fragments in a single cellular event, followed by error-prone DNA repair mechanisms that reassemble the fragments in random order, resulting in clustered complex chromosomal rearrangements.
- **Gatekeeper residue**: conserved amino acid within the kinase domain that sits at the entry of a hydrophobic pocket adjacent to the ATP-binding site. Its mutation can modify pocket accessibility and thereby alter kinase activity and sensitivity to reversible ATP-competitive inhibitors.
- **Microhomology-mediated end joining**: error-prone DNA double-strand break repair pathway that aligns and joins broken DNA ends using short microhomologous sequences (typically 5-25 base pairs), usually resulting in deletions at the repair site.

- **Molecular brake residues**: conserved amino acid residues within the kinase domain that stabilize its inactive conformation and limit basal kinase activity; their mutation leads to increased kinase activation.
- **Nonhomologous end joining**: error-prone DNA double-strand break repair mechanism that directly ligates the broken DNA ends together without requiring an homologous template.
- **Overall survival**: length of time from the start of treatment or randomization in a clinical trial until death from any cause, considered the gold standard endpoint for measuring treatment benefit in oncology.
- **Progression-free survival (PFS)**: length of time during and after treatment in a clinical trial that a patient lives with the disease without it worsening, measured from treatment start until disease progression or death from any cause, and is commonly used as a surrogate endpoint to assess the effectiveness of targeted therapies in oncology trials.

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DECLARATION OF INTERESTS

D.Z. is an employee of Genentech, Inc. and holds equity in Roche. The other authors declare no competing interests.

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