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REVIEW

Rationale for targeting fibroblast growth factor receptor signaling in breast cancer

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Abstract Fibroblast growth factor receptor (FGFR) signaling is involved in multiple biological processes, including cell proliferation, survival, differentiation, migration, and apoptosis during embryonic development and adult tissue homeostasis. Given its role in the activation of critical signaling pathways, aberrant FGFR signaling has been implicated in multiple cancer types. A comprehensive search of PubMed and congress abstracts was conducted to identify reports on FGFR pathway components in breast cancer. In breast cancers, *FGFR1* and *FGFR4* gene amplification and single nucleotide polymorphisms in *FGFR2* and *FGFR4* have been detected. Commonly, these FGFR aberrations and gene amplifications lead to increased FGFR signaling and have been linked with poor prognosis and resistance to breast cancer treatments. Here, we review the role of FGFR signaling and the impact of FGFR genetic amplifications/aberrations on breast tumors. In addition, we summarize the most recent preclinical and clinical data on FGFR-targeted therapies in breast cancer. Finally, we highlight the ongoing clinical trials of the FGFR-targeted agents dovitinib, AZD4547, lucitanib, BGJ398, and JNJ-42756493, which are selected for patients with FGFR pathway-amplified breast cancer. Aberrant FGFR pathway amplification may drive some breast cancers. Inhibition of FGFR signaling is being explored in the clinic, and data from these trials may refine our ability to select patients who would best respond to these treatments.

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Role of FGFR signaling

The fibroblast growth factor receptor (FGFR) family comprises four transmembrane tyrosine kinase receptors (FGFR1-4). Each FGFR has an extracellular ligand-binding domain containing three immunoglobulin (Ig)-like domains and an acidic box, a single-pass transmembrane domain, and an intracellular tyrosine kinase domain [1]. Twenty-two FGF ligands bind to the second and third Ig-like domains of the different FGFRs and their splice variants, creating ligand-binding specificity [2–4]. Ligand binding induces receptor dimerization, enabling transphosphorylation of intracellular kinases, and phosphorylation of intracellular signaling proteins.

FGFR signaling is involved in cell proliferation, survival, differentiation, migration, and apoptosis during embryonic development and adult tissue homeostasis [1]. Signaling is regulated in part by the spatial and temporal expression patterns of the different ligands and receptors, leading to distinct cell type-specific functions. For example, during embryogenesis, FGFR signaling plays a key role in the development of the nervous system, limbs, midbrain, lungs, and mammary glands. In contrast, FGFR signaling in the adult drives tissue repair, angiogenesis, and inflammation.

FGFR genetic aberrations in breast cancer

Multiple genetic aberrations in FGFRs leading to increased pathway activation have been identified in breast cancer. The

most common aberration is *FGFR1* gene amplification (one of several putative oncogenes on 8p11-12), which is present in 7.5–17 % of all breast cancer and in 16–27 % of luminal B-type breast cancer (although variability in these numbers is expected, given the different methods used to assess amplification) [5–13]. In addition to *FGFR1* gene amplification, elevated mRNA is detected in 22 % of tumor cell lines and breast-tumor samples [14], and gene amplification is robustly associated with FGFR1 overexpression [7, 10, 13]. Amplification of other FGFRs has also been observed. For example, amplification of *FGFR2* (10q26) was identified in 4 % of triple-negative breast cancers (TNBCs) [15], and two TNBC cell lines (SUM52PE, MFM223) with *FGFR2* amplification showed constitutive activation of FGFR2. Interestingly, survival of SUM52PE and MFM223 was dependent on FGFR2 expression and tyrosine kinase activity. *FGFR4* amplification has been detected in $\approx$10 % of breast cancer samples and was associated with estrogen receptor (ER) and progesterone receptor (PR) positivity and lymph node metastases [16]. In a separate study, elevated FGFR4 mRNA levels were detected in 32 % of breast cancer samples [14].

Single nucleotide polymorphisms (SNPs) have also been detected in FGFR genes in breast tumors. For example, SNPs were identified in *FGFR2* intron 2 [17–22] and, in some studies, were more common in ER-positive (ER^+) tumors [18, 22]. Intron 2 of *FGFR2* contains putative transcription factor binding sites, and one of the SNPs, rs2981578, increased Oct-1/Runx2 and C/EBPβ transcription factor binding, which led to increased FGFR2 expression [21]. In the transmembrane region of *FGFR4*, a SNP involving the conversion of Gly to Arg was identified, and *FGFR4Arg388*-expressing MDA-MB-231 mammary tumor cells showed increased motility in comparison with cells expressing the *FGFR4Gly388* allele [23]. Additionally, introduction of the *FGFR4Arg388* allele in a transgenic mammary tumor model induced more rapid tumor formation and progression than did the *FGFR4Gly388* allele [24] and was shown to promote tumor progression through membrane type-1 matrix metalloproteinase-induced extracellular matrix degradation involving the epithelial-to-mesenchymal transition at the tumor/stromal border [25].

Point mutations are rare; however, they have been detected in human breast tumors, including S125L in *FGFR1* and R203C in *FGFR2* [26]. An activating point mutation in *FGFR4* (Y367C), which causes constitutive receptor dimerization and activation of MAPK, was identified in the MDA-MB-453 breast cancer cell line [27].

Prognostic significance of FGFR aberrancy

Various studies have investigated the role of the FGFR pathway as a predictive/prognostic marker, with several suggesting that aberrant FGFR expression is associated with an increased risk of breast cancer and is correlated with a poor prognosis. For example, *FGFR1* and *FGFR2* are preferentially amplified in ER^+ breast cancer and TNBC, respectively [28], and *FGFR1* amplification was an independent predictor of overall survival and poor outcome in patients with ER^+ breast cancer [9, 29]. However, these results may be confounded by other potential oncogenes on 8p11–12, which may also contribute [30–33]. Therefore, amplification status of 8p11-12 may not be a sufficient screening mechanism for clinical trials of FGFR-targeted drugs. Other genes on different chromosomes may also have an impact. For example, co-amplification of *cyclin D1* (*CCND1;* chromosome 11) and *FGFR1* were associated with a significant reduction in patient survival [34].

The prognostic role of FGFR2 has also been reported. Indeed, increased expression of FGFR2 is associated with poor overall survival and disease-free survival [35]. Following the detection of FGFR2 and FGFR3 constitutive activation in hormone-independent murine mammary tumors, FGFR expression levels were determined in tumor samples from patients with breast cancer ($n = 58$) [36]. This analysis detected a strong association between FGFR2 and FGFR3, with weaker associations between FGFR2 or FGFR3 and ER. The study also found that FGFR4 expression correlated with human epidermal growth factor receptor 2 (HER2) overexpression. Other studies have shown that the *FGFR2* SNPs rs2981582, rs1219648, rs2420946, and rs2981579 were significantly associated with an increased risk of breast cancer [37, 38]. Women with all three SNPs had a 1.36-fold greater chance of getting breast cancer than did those with no or no more than two SNPs, and the risk was greater in women with ER^+ and/or PR^+ cancer, premenopausal women, and women who gave birth to their first child at a later age.

The *FGFR4Arg388* allele has been correlated with significantly reduced disease-free survival [23], and, in a meta-analysis and pooled analysis of patients with cancer, including breast, a significant association between the *FGFR4Arg388* allele and nodal involvement was identified [39]. Additionally, carriers of the *FGFR4Arg388* allele had an increased hazard of poor overall survival compared with carriers of the *FGFR4Gly388* allele.

Role of FGFR in resistance mechanisms

Various studies support the role of the FGFR pathway in endocrine resistance. For example, in patients with ER^+ breast cancer treated with tamoxifen, high *FGFR4* mRNA levels were associated with poor clinical benefit and shorter progression-free survival [40]. Additionally, evidence suggests that resistance to HER2-targeted therapy may

result from a switch in dependency on the ER/HER2 signaling pathway to the FGFR signaling pathway [41]. In that study, *FGFR2* was highly amplified, FGFR2 was overexpressed, and HER2 expression was reduced in a lapatinib-resistant cell line (UACC812/LR). The survival of UACC812/LR cells appeared dependent on FGFR2, because inhibition of FGFR2 induced cell apoptosis.

Several studies suggest that FGFR signaling mediates resistance to hormonal therapies through activation of the MAPK and PI3K pathways. For example, in *FGFR1*-amplified breast cancer cell lines, FGFR signaling caused persistent MAPK activation followed by cyclin D1 expression, which led to tamoxifen resistance [13]. This activated signaling occurred in both an ER-dependent and -independent manner, and the FGFR1-induced tamoxifen resistance was reversible following treatment with FGFR1-directed siRNA. Additionally, constitutive activation of FGFR3 in MCF-7 cells reduced sensitivity to tamoxifen in an ER-independent manner through stimulation of the MAPK and PI3K pathways [42]. In this study, activation of phospholipase Cγ was critical for activation of MAPK and PI3K and subsequently for tamoxifen resistance.

FGFR signaling may also mediate resistance to chemotherapy in breast cancer. In patients with node-positive breast cancer receiving chemotherapy as an adjuvant therapy, presence of the *FGFR4Arg388* allele was significantly associated with poor disease-free survival and overall survival [43]. Additionally, FGFR4 is upregulated in MDA-MB-453 breast cancer cells that are resistant to doxorubicin and cyclophosphamide, and FGFR4 overexpression leads to upregulation of the anti-apoptotic molecule Bcl-xl through MAPK activation [27].

Targeting the FGFR pathway in preclinical studies

The evidence supporting a role of the FGFR pathway in breast cancer has led to preclinical investigation of FGFR pathway-targeting agents, and several approaches have been explored. For example, FP-1039 is an FGF ligand trap consisting of the extracellular domain of FGFR1 fused to the Fc region of IgG [44]. In xenograft models using JIMT-1, an FGFR1-amplified and -overexpressing cell line [13], FP-1039 blocked tumor formation. In another approach, monoclonal antibody GP369 targets the epithelial-expressed FGFR2-IIIb receptor isoform, whose overexpression can drive tumorigenesis [45, 46]. In a xenograft model with MFM-223 breast cancer cells (a cell line with 287 genomic copies of FGFR2), GP369 induced tumor stasis.

More commonly, the FGFR pathway has been targeted using small molecule inhibitors. SU5402, an FGFR1 small molecule inhibitor, reduced cell survival in several breast cancer cell lines; the sensitivity was greatest in MDA-MB-134 cells [47].

PD173074 is a selective FGFR1 and FGFR3 inhibitor that has shown activity in numerous breast cancer cell lines. For example, it inhibited FGFR tyrosine kinase activity and autophosphorylation and caused G1 growth arrest in MDA-MB-415, MDA-MB-453, and SUM52 [48]. The study also showed that FGFR inhibition led to the downregulation of cyclin D1/2 expression, inhibition of cyclin D/cdk4 activity, and reduced pRB phosphorylation. In the FGFR1-, FGFR2-, and FGFR3-expressing cell line 4T1, PD173074 demonstrated concentration-dependent apoptosis, inhibited tumor growth and metastases to the lung, and increased CD4 and CD8 T cell infiltration to the spleen and tumors in xenograft models [49]. Other studies have shown that PD173074 treatment inhibited MAPK and PI3K/AKT signaling and induced cell-cycle arrest and apoptosis in 47 % of TNBC cell lines and significantly reduced the growth of CAL51 basal-like breast cancer cell line-containing xenografts [15, 50]. Finally, decreased phosphorylation of FGFR2 and induction of apoptosis was observed in a lapatinib-resistant breast cancer cell line (UACC812/LR) following treatment with PD173074 [41].

Brivanib alaninate (BMS-582664) inhibits VEGFR2, VEGFR3, and FGFR3 (and to a lesser extent FGFR1 and FGFR2) [51] and has caused decreased receptor autophosphorylation, inhibited FGF2-induced tyrosine kinase activity, and reduced phosphorylation of ERK and AKT in breast cancer cell lines with amplification of *FGFR1* [52]. Additionally, brivanib inhibited the growth of human H3396 breast-tumor xenografts [53] and elicited tumor growth regression in tamoxifen-sensitive (MCRF-7 E2) and tamoxifen-stimulated (MCF-7 Ral, MCF-7 Tam) breast cancer cell lines [54].

Lucitanib (E-3810)—a small molecule inhibitor of VEGFR1-3, FGFR1-2, and colony stimulating factor 1 receptor—has demonstrated anti-angiogenic and anti-tumor activity in preclinical models [55]. Additionally, in combination with paclitaxel, lucitanib caused long-lasting tumor regressions in xenografts of the TNBC cell line MDA-MB-231 [56].

Dovitinib (TKI258) is a small molecule inhibitor of FGFR1-3, VEGFR1-3, c-KIT, fms-related tyrosine kinase 3 (FLT3), platelet-derived growth factor receptor (PDGFR) β, c-KIT, and FLT3 [57]. In 4T1 and the FGFR2- and FGFR3-expressing cell line 67NR, dovitinib decreased FGFR substrate 2 (FRS2) phosphorylation; decreased the activity of ERK1/2, AKT, and phospholipase Cγ; and blocked proliferation [58]. Dovitinib also significantly reduced primary tumor outgrowth in xenograft models with these cell lines and reduced tumor-induced lung metastasis in the 4T1 model [58]. In other tumor models using these cell lines, combining dovitinib with the PI3K/mTOR inhibitor BEZ235 or the pan-ErbB inhibitor AEE788 blocked the FGFR/FRS2/Erk and PI3K/Akt/mTOR pathways and

further inhibited tumor growth and blocked tumor spread [59]. In experiments with FGFR-amplified cell lines, dovitinib decreased pFRS2 and pERK/MAPK and inhibited cell growth in MDA-MB-134 (FGFR1-amplified) and SUM52 (FGFR2-amplified) lines [60]. Furthermore, dovitinib caused tumor regressions in HBCx-2 (8 *FGFR1* copies) and HBCx-3 (10 *FGFR2* copies) xenograft models.

ACTB-1003—a multitargeted kinase inhibitor of FGFR1, VEGFR2, Tie-2, RSK, and p70S6K—demonstrated potent, low nanomolar activity in a variety of tumor models, including breast cancer [61]. Ponatinib, an oral multitargeted kinase inhibitor of Bcr-Abl as well as FGFR1-4 [62–64], inhibited cell growth in MDA-MB-134 and SUM52PE and in MFM-223—a cell line that also has *FGFR2* amplification [65].

Clinical trials with FGFR pathway-targeting agents in breast cancer

Data from the various preclinical studies clearly demonstrate the role of the FGFR pathway in breast cancer and have led to clinical trials exploring patients who may best benefit from targeted treatments (Table 1). Indeed, many of the clinical trials testing FGFR tyrosine kinase inhibitors in breast cancer are requiring molecular prescreening prior to study entry to enable correlation between response and FGFR pathway activation or are only enrolling patients with FGFR pathway activation.

In a phase 2 trial of dovitinib (NCT00958971), patients with metastatic $HER2^-$ breast cancer were grouped based on hormone receptor (HR) status and FGFR1 amplification (as assayed by silver in situ hybridization) [60]. Dovitinib was reasonably well tolerated in the heavily pretreated patients ($n = 81$), and unconfirmed partial response and/or stable disease at $\geq$24 weeks were observed in 25 % of the 20 evaluable patients with HR^+ *FGFR1*-amplified breast cancer (3 % in the 31 evaluable patients with *FGFR1* nonamplified, HR^- disease). In preplanned analyses, amplifications of *FGFR1/2* by quantitative polymerase chain reaction (PCR) were found to be associated with anti-tumor activity in patients with HR^+. These data led to the initiation of a phase 2 study of dovitinib in combination with fulvestrant in postmenopausal patients with locally advanced or metastatic $HER2^-$, HR^+ breast cancer who have progressed during or following endocrine therapy (NCT01528345) [66]. Of interest, the study requires molecular prescreening prior to study entry, with patients grouped based on FGFR pathway amplification status (*FGFR1*, *FGFR2*, or *FGF3* by quantitative PCR). Additional ongoing studies include a phase 2 study of dovitinib as salvage therapy in patients with relapsed stage IV $HER2^-$ inflammatory breast cancer (NCT01262027) and a phase 1/2 study of dovitinib in combination with aromatase inhibitors in patients with metastatic breast cancer with evidence of resistance to prior aromatase inhibitor therapy (NCT01484041). The latter study also requires tumor availability for determination of *FGFR1* amplification for study inclusion.

AZD4547 is an inhibitor of FGFR1-3 and VEGFR2 [67]. A phase 1/2 study of AZD4547 in combination with the estrogen receptor antagonist fulvestrant in patients with ER^+ breast cancer with high levels of *FGFR1* is currently ongoing (NCT01202591). Tumor biopsy must be available to confirm *FGFR1* polysomy or amplification for study inclusion. Another ongoing phase 1/2 study is comparing AZD4547 in combination with letrozole or anastrozole versus exemestane in patients with ER^+ breast cancer who relapsed during adjuvant endocrine therapy with anastrozole or letrozole (NCT01791985). Enrollment in the expansion phase of this study requires tumor biopsy for confirmation of *FGFR1* status by fluorescence in situ hybridization (FISH). Additionally, an ongoing phase 2 study is evaluating AZD4547 in patients with *FGFR1*- or *FGFR2*-amplified tumors (NCT01795768) [68]. Patients with breast cancer must have *FGFR1* amplification and are required to provide archival or fresh tumor biopsy for confirmation of FGFR amplification, with a second biopsy planned on days 10–14.

A phase 1/2 study testing lucitanib in patients with advanced solid tumors is currently ongoing (NCT01283945) [69]. In dose expansion, patients with *FGFR1* or 11q12-14 amplification per FISH or comparative genomic hybridization array were enrolled; of nine evaluable patients with breast cancer, four achieved PR sustained over four to six courses, three achieved stable disease, and two had progressive disease [70]. A phase 2 study of lucitanib is also ongoing in patients with ER^+ FGFR1-amplified and -nonamplified metastatic breast cancer (NCT02053636).

The pan-FGFR inhibitor BGJ398 is being tested in patients with tumors containing *FGFR1* or *FGFR2* amplifications or *FGFR3* mutations (NCT01004224). In this study, reductions in tumor volume were observed with single-agent BGJ398 in some patients with breast cancer [71]. BGJ398 is also being studied in a phase 1b trial in combination with the α-selective PI3K inhibitor BYL719 in patients whose tumors have PIK3CA mutations and *FGFR1-3* alterations (NCT01928459).

In a dose-escalation study, the pan-FGFR inhibitor JNJ-42756493 also demonstrated reductions in tumor volume in a patient with breast cancer (NCT01962532) [72]. In a second phase 1 trial in patients with advanced or refractory solid tumors or lymphoma, the dose-expansion phase will include a cohort of patients with breast cancer with *FGFR1*, *FGFR2*, or *FGFR4* gene amplifications (NCT01703481).

Other FGFR-targeted agents have been explored in clinical trials, but without requiring FGFR testing at study entry. For example, orantinib (TSU-68)—an inhibitor of VEGFR2, PDGFR, and FGFR—had no activity as a single

Table 1 Breast cancer clinical trials of FGFR pathway-targeting agents

Agent	Targets	Phase	Trial number/status	Clinical trials
Dovitinib	FGFR1-3, VEGFR1-3, c-KIT, FLT3, PDGFRβ	2	NCT00958971 completed	Dovitinib in *FGFR1*-amplified and -nonamplified metastatic or advanced HER2$^-$ breast cancer [60]
		2	NCT01528345 ongoing	Dovitinib + fulvestrant in HR$^+$/HER2$^-$ LA/mBC following progression on or after endocrine therapy [66]
		2	NCT01262027 ongoing	Dovitinib as salvage in stage IV HER2$^-$ inflammatory breast cancer
		1/2	NCT01484041 active (not recruiting)	Dovitinib + aromatase inhibitor in HR$^+$/HER2$^-$ mBC resistant to an aromatase inhibitor
AZD4547	FGFR1-3, VEGFR2	1/2	NCT01202591 active (not recruiting)	AZD4547 + fulvestrant vs fulvestrant alone in ER$^+$ breast cancer with *FGFR1* polysomy or gene amplification following progression after endocrine therapy
		1/2	NCT01791985 ongoing	AZD4547 + (anastrozole or letrozole) versus exemestane in ER$^+$ breast cancer progressing on anastrozole or letrozole
		2	NCT01795768 ongoing	AZD4547 in patients with *FGFR1*- or *FGFR2*-amplified tumors (including HER2$^-$, *FGFR1*-amplified LA/mBC) [68]
Lucitanib	FGFR1, VEGFR1-3, CSF1R	1/2	NCT01283945 ongoing	Lucitanib in patients with advanced solid tumors (including, in dose expansion, *FGFR1*-amplified breast cancer with at least one prior chemotherapy or at least one prior endocrine therapy if ER$^+$) [69, 70]
		2	NCT02053636 ongoing	Lucitanib in *FGFR1*-amplified or -nonamplified ER$^+$ mBC
BGJ398	FGFR1-4	1	NCT01004224 ongoing	BGJ398 in patients with advanced solid tumors with *FGFR1* or *FGFR2* amplification or *FGFR3* mutation
		1	NCT01928459 ongoing	BGJ398 + BYL719 in solid tumors (including mBC with PIK3CA mutations and *FGFR1-3* alterations)
JNJ-42756493	FGFR1-4	1	NCT01703481 ongoing	JNJ-42756493 in patients with advanced or refractory solid tumors or lymphoma (includes a cohort with breast cancer)
		1	NCT01962532 ongoing	JNJ-42756493 in patients with advanced or refractory solid tumors or lymphoma (includes a cohort with FGFR-amplified, -mutated, or -translocated breast cancer)
Orantinib	FGFR1, VEGFR2, PDGFRβ	2	NR	Orantinib in patients with mBC progressing despite prior anthracycline-containing regimen and taxane [73]
		2	NR	Orantinib + docetaxel in mBC patients with anthracycline resistance [74]
Brivanib	FGFR3, VEGFR2, VEGFR3	1	NCT00798252 active (not recruiting)	Brivanib + chemotherapy in advanced solid tumors
Nintedanib	FGFR1-3, VEGFR1-3, PDGFRα, PDGFRβ, FLT3	2	NCT01658462 ongoing	Docetaxel ± nintedanib as second-line chemotherapy for HER2$^-$ LA/mBC
		1/2	NCT01484080 active (not recruiting)	Neoadjuvant paclitaxel versus nintedanib followed by nintedanib + paclitaxel in early HER2$^-$ breast cancer

CSF1R colony stimulating factor 1 receptor, *ER* estrogen receptor, *FGFR* fibroblast growth factor receptor, *FLT3* fms-related tyrosine kinase 3, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *LA/mBC* locally advanced or metastatic breast cancer, *NR* not registered, *PDGFR* platelet-derived growth factor receptor, *VEGFR* vascular endothelial growth factor receptor

agent in patients with metastatic breast cancer progressing despite treatment with a prior anthracycline-containing regimen and taxane [73]. However, in patients with anthracycline resistance, orantinib in combination with docetaxel achieved an overall response rate of 21 % [74]. Additional ongoing studies not requiring FGFR testing at entry include a study of brivanib alaninate in combination with chemotherapy in patients with advanced cancer (NCT00798252) and a study of docetaxel with or without nintedanib (BIBF 1120)—an inhibitor of FGFR1-3, VEGFR1-3, PDGFRα, PDGFRβ, and FLT3 [75]—as second-line chemotherapy in patients with HER2$^-$ metastatic or locally recurrent breast cancer (NCT01658462).

Bioassays

Challenges remain in identifying the patient population that may benefit from FGFR pathway-targeted therapy. For example, definitions of FGFR pathway amplification vary both

in the methods used and the threshold copy number. For example, amplicons may not accurately reflect the level of amplification of the component genes and be confounded by other potential oncogenes in the amplicon. Additionally, measurement of gene amplification may not reflect protein expression or activity. Conversely, detection of activating mutations may not be relevant unless the gene is expressed. The best method is yet unknown, but analyses comparing screening methods with efficacy can be informative. For example, in a phase 2 study with dovitinib, tumor reduction was greater in patients with FGF pathway amplification identified by quantitative PCR than in those with FGF pathway amplification identified by in situ hybridization [60]. However, no consensus has been reached, and ongoing trials are using different methods for detecting FGFR pathway activation/aberration, which will complicate cross-study data interpretation. Careful analyses of the biomarker data from clinical trials may improve the ability to identify the optimal patient population that will benefit from FGFR-targeted therapies.

Conclusions

The FGFR pathway is involved in multiple cellular processes, and research has shown that aberrant pathway amplification is observed in multiple tumor types, including breast cancer. As research advances toward targeted treatment of cancer, it is increasingly important to understand how the FGFR pathway is driving the disease and, more importantly, how it can be targeted. Multiple agents that target FGFR pathway components are being investigated. Results from these trials are also expected to help refine our ability to identify patients with FGFR pathway-amplified tumors who may best respond to these treatments.

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