Clinical Cancer Research

The FGFR Landscape in Cancer: Analysis of 4,853 Tumors by Next-Generation Sequencing

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Abstract

Purpose: Molecular profiling may have prognostic and predictive value, and is increasingly used in the clinical setting. There are more than a dozen fibroblast growth factor receptor (FGFR) inhibitors in development. Optimal therapeutic application of FGFR inhibitors requires knowledge of the rates and types of FGFR aberrations in a variety of cancer types.

Experimental Design: We analyzed frequencies of FGFR aberrations in 4,853 solid tumors that were, on physician request, tested in a Clinical Laboratory Improvement Amendments (CLIA) laboratory (Foundation Medicine) using next-generation sequencing (182 or 236 genes), and analyzed by N-of-One.

Results: FGFR aberrations were found in 7.1% of cancers, with the majority being gene amplification (66% of the aberrations), followed by mutations (26%) and rearrangements (8%). *FGFR1* (mostly amplification) was affected in 3.5% of 4,853 patients; *FGFR2* in 1.5%; *FGFR3* in 2.0%; and *FGFR4* in 0.5%. Almost every type of malignancy examined showed some patients with FGFR aberrations, but the cancers most commonly affected were urothelial (32% FGFR-aberrant); breast (18%); endometrial (∼13%), squamous lung cancers (∼13%), and ovarian cancer (∼9%). Among 35 unique FGFR mutations seen in this dataset, all but two are found in COSMIC. Seventeen of the 35 are known to be activating, and 11 are transforming.

Conclusions: FGFR aberrations are common in a wide variety of cancers, with the majority being gene amplifications or activating mutations. These data suggest that FGFR inhibition could be an important therapeutic option across multiple tumor types.
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Introduction

Fibroblast growth factor receptors (FGFRs) are highly conserved, widely distributed transmembrane tyrosine kinase receptors. They are involved in development, differentiation, cell survival, migration, angiogenesis, and carcinogenesis (1). In humans, there are four such FGFRs that are typical tyrosine kinase receptors (FGFR1-4), and one that lacks an intracellular tyrosine kinase domain (FGFRL1 or FGFR5). There are also 18 human ligands for FGFRs, which are known as fibroblast growth factors (1). When FGFs bind to their cognate receptors, the receptors dimerize, leading to intracellular phosphorylation of receptor kinase domains, a cascade of intracellular signaling, and gene transcription (2). FGF/FGFRs signal through several intracellular pathways, including the Ras/Raf/MEK and the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)–Akt pathway (1). All four FGFRs share structural homology with vascular endothelial growth factor receptors (VEGFR), platelet-derived growth factor receptors (PDGFR), and other tyrosine kinase receptors, which has implications for pharmacologic therapy (2).

Specific FGFR aberrations have been observed in a proportion of certain cancers [e.g., *FGFR3* mutations in bladder cancer (3) and *FGFR1* amplification in squamous cell lung cancer (4)]. Some of these FGFR abnormalities are likely to be "driver" aberrations. There is also evidence that changes in specific FGFR expression may be related to prognosis or sensitivity to cancer treatments (5–7).

Because the majority of FGFR aberrations identified to date lead to gain-of-function, it is reasonable to hypothesize that targeting these cancers with FGFR inhibitors would be therapeutically beneficial (8). *In vitro* data suggest that this is indeed the case (9). Several tyrosine kinase inhibitors (TKI) have been identified as FGFR inhibitors, including ponatinib (AP24534), regorafenib (BAY 73-4506), lenvatinib (E7080), dovitinib (TKI258), lucitanib (E3810), nintedanib (BIBF 1120), and others. Some FGFR inhibitors also suppress VEGFRs and additional growth factor receptors, whereas others are more selective for FGFR inhibition (e.g., NVP-BGJ398, AZD4547, JNJ-42756493, etc.). At this time, four FGFR inhibitors are FDA approved for treatment of cancer. The most recently FDA-approved FGFR-inhibiting drug is lenvatinib, which is approved for iodine-refractory, well-differentiated thyroid carcinoma. Other FDA-approved FGFR-inhibiting drugs include regorafenib, approved for advanced colorectal carcinoma and drug-resistant gastrointestinal stromal tumors (GIST), ponatinib, approved for drug-resistant chronic myelogenous leukemia (CML) and Philadelphia chromosome-positive acute lymphocytic leukemia (ALL), and pazopanib, approved for renal cell carcinoma and sarcoma. None of these are FDA approved on the basis of targeting FGFR (or any other molecular phenotype). The hypothesis that selecting for FGF/FGFR aberration might increase response rates or other clinical benefits is being tested in several ongoing trials that require FGF/FGFR aberrations for eligibility.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

Cancer is fundamentally a disease of disordered genes. The paradigm of precision oncology hypothesizes that we understand the genetic abnormalities that drive cancer, that drugs successfully target the products of these abnormal genes, and that we can detect abnormal genes in individual patients. Considering cancer treatment development more broadly, the challenge lies in defining population(s) for which new therapeutics will be most effective. Currently, there are more than a dozen anti-fibroblast growth factor receptor (FGFR) drugs in development for cancer, but which patients or patient populations will benefit most from these drugs? To facilitate answering this question, we present an analysis of next-generation sequencing data from a very large database of nearly 5,000 cancers of diverse histologies. Our data provide robust evidence of frequencies and characteristics of FGFR aberrancies in cancer. These data will aid design of studies to further define the role of FGFR inhibitors in cancer.

These and other clinical trials will shed light on the specific patient populations that would benefit from FGFR-inhibiting drugs and possibly on specific molecular aberrations that predict response to these drugs.

In fact, it is highly likely that optimizing the clinical utility of FGFR-targeting therapies will depend on appropriate selection of patient populations. To that end, developing a clear understanding of the landscape of FGFR aberrations in various cancer types is relevant and necessary for more effective use of these pharmaceutical agents. Next-generation sequencing technology makes rapid and accurate identification of these aberrations feasible. Herein, we describe the landscape of FGFR abnormalities, including mutations, amplifications, and rearrangements in 4,853 patient samples from diverse cancers.

Materials and Methods

We collected sequencing data from 4,853 cancers of various types (specific cancer types and numbers of cases are listed in Supplementary Tables S2 and S3) from patients whose formalin-fixed, paraffin-embedded (FFPE) tumor samples were submitted to a CLIA-certified lab for genomic profiling (Foundation Medicine). Samples were required to have a surface area $\geq$25 mm^2, volume $\geq$1 mm^3, nucleated cellularity $\geq$80%, and tumor content $\geq$20% (10). The methods used in this assay have been validated and previously reported (10–12). Briefly, 50 to 200 ng of genomic DNA was extracted and purified from the submitted FFPE tumor samples. This whole-genome DNA was subjected to shotgun library construction and hybridization-based capture before paired-end sequencing on the Illumina HiSeq2000 platform. Hybridization selection is performed using individually synthesized baits targeting the exons of 182 or 236 cancer-related genes and the introns of 14 or 19 genes frequently rearranged in cancer (Supplementary Table S1). The samples collected for this study were assayed between December 16, 2011 and November 14, 2013. Sequence data were processed using a customized analysis pipeline (10). Sequencing was performed with an average sequencing depth of coverage greater than 250×, with >100× at >99% of exons. This method of sequencing allows for detection of copy number alterations, gene rearrangements, and somatic mutations with 99% specificity, and >99% sensitivity for base substitutions at $\geq$5 mutant allele frequency and >95% sensitivity for copy number alterations. A threshold of $\geq$6 copies for gene amplification (except for *ERRB2*, which is considered amplified with $\geq$5 copies) was used. The submitting physicians provided specification of tumor types. The database was de-identified with only diagnosis available. Next-generation sequencing data were collected and interpreted by N-of-One. For this study, the dataset of 4,853 sequenced tumors was queried for alterations in *FGFR1-4* and coaberrant genes. Data were analyzed in accordance with UCSD IRB guidelines. Here, we report on the prevalence and frequencies of these aberrations in human cancers.

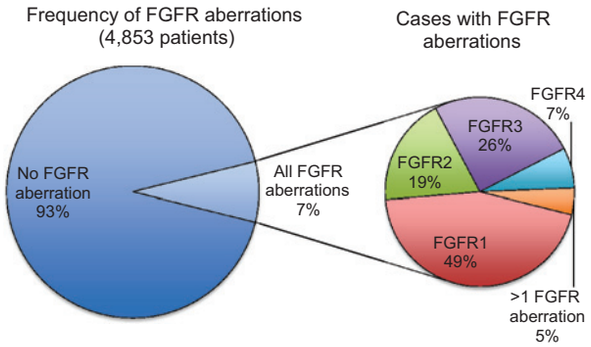

Figure 1.
All FGFR aberrations. Frequency of FGFR aberrations among all cases (left) and relative proportion of FGFR aberrations by FGFR gene among all cases with FGFR alterations (right). Sixteen cases had more than one aberration, so the total of the right chart is more than 100%.

Results

Of the 4,853 cancers sequenced, we observed 360 FGFR aberrations in 343 cases (17 cancers had more than one FGFR alteration), for an overall frequency of 7.1%. *FGFR1* alterations were more common than alterations in *FGFR2–4* (Figs. 1 and 2). The majority of the FGFR aberrations were gene amplifications (66% of 360 FGFR aberrations), with gene mutations being less common (26%) and gene rearrangements rare (8%; Fig. 2). These proportions were similar across all four FGFRs (Supplementary Figs. S1–S4); however, *FGFR1* and *FGFR4* showed high rates of gene amplification (89% and 78% of all *FGFR1* or *FGFR4* alterations, respectively; Supplementary Figs. S1A and S4) and *FGFR2* and *FGFR3* had relatively more frequent gene rearrangements (16% and 19%, respectively; Supplementary Figs. S2A and S3A). The percentages of 343 patients with an aberrant FGFR that had any anomaly in *FGFR1*, *FGFR2*, *FGFR3*, and *FGFR4* were 49, 19, 26 and 7, respectively (Fig. 1).

Frequencies of aberrations and relative distribution of types of aberration for histologies with $\geq$75 cases are shown in Fig. 2 and Supplementary Table S2. A summary of cases with FGFR aberration(s) in cancer types with fewer than 75 cases is presented in Supplementary Table S3. As expected, some cancer types had a higher frequency of FGFR alteration than others, and are discussed in greater detail below. It should be noted that no clinical data about the study population is available other than the submitting physician's indication of tumor type. For some tumor types, for example, urothelial carcinoma, frequencies, or types of FGFR

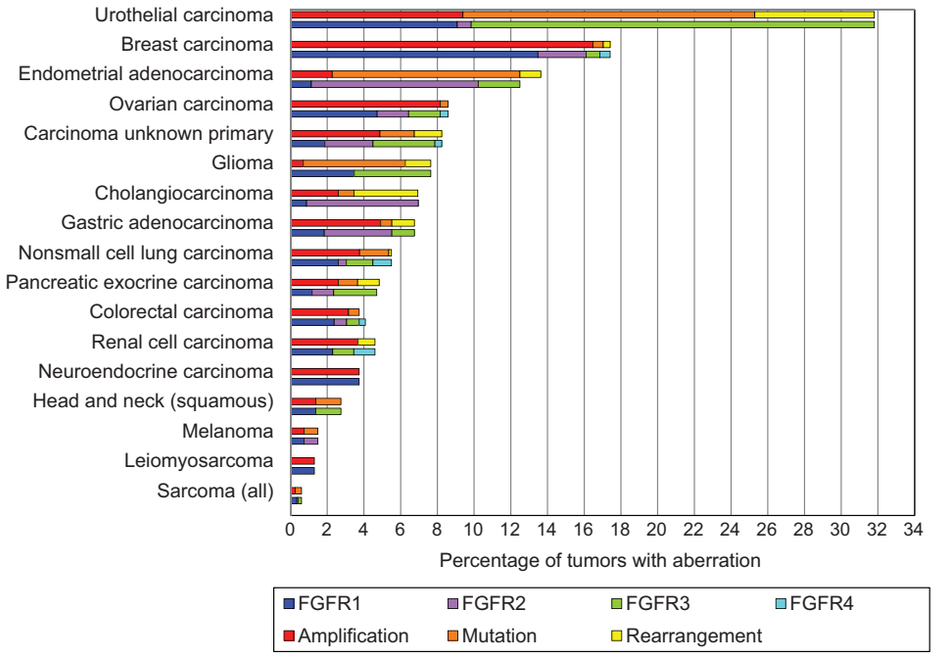

Figure 2.
Frequencies and distributions of FGFR aberrations for all cancers with ≥75 cases analyzed. Within each cancer, the frequency of FGFR aberrations is reported as percentage of all cases of that cancer analyzed. The distributions of FGF receptors altered and types of alterations are normalized to 100% for each cancer type. See Supplementary Table S2 for additional information.

aberrations may depend upon grade and/or stage of cancer. For instance, FGFR3 mutations are seen in >50% of bladder cancer cases with low-grade, noninvasive disease, but drop in frequency, once one looks at higher grade/stage (13). Because we do not have this information for our dataset, we are not able to provide analysis of this issue. For more information, see section "Urothelial Cancers."

Non–small cell lung cancer

There were 675 cases of non–small cell lung cancer (NSCLC) in the dataset (Figs. 2 and 3, Supplementary Tables S2 and S6). There was a marked difference between squamous cell histology ($N = 93$), adenocarcinoma ($N = 408$), and other non–small cell types (e.g., large cell carcinoma). In particular, squamous cell lung carcinoma was most notable for its 9% frequency of *FGFR1* amplification, which is in contrast to only 4% of lung adenocarcinomas harboring *any* FGFR abnormality (Fig. 3). Interestingly, 3% of squamous cell lung carcinomas had somatic *FGFR2* and *FGFR3* mutations identical to those seen in inherited dwarfism syndromes (14), including *FGFR2–P253R*, *FGFR2–S252W*, *FGFR3–G370C*, *FGFR3–K650E*, *FGFR3–R248C*, and *FGFR3–S249C*. See below for a discussion of the functional significance of these activating mutations.

Urothelial cancers

There were 126 cases of urothelial cancers in the dataset (Figs. 2 and 4, Supplementary Tables S2 and S6), and urothelial (transitional cell) cancer of the bladder, renal pelvis, and ureter were represented. This dataset does not include cases of bladder sarcoma, small cell carcinoma, squamous cell carcinoma, or neuroendocrine carcinoma. In urothelial tumors, 15% of aberrations were somatic mutations in *FGFR3* that are known to be activating (Supplementary Table S4). Another 7% of urothelial cancers had *FGFR1* amplifications, 6% had gene fusions, and 3% had *FGFR3* amplifications.

Among the seven urothelial cases with gene fusions, six were fusions with *FGFR3* and one was with *FGFR1*. The most common fusion was *FGFR3–FGFR3–TACC3* (4 cases, 3%), which results from 4p16.3 rearrangements. The *TACC3* gene is located within 48 kb of *FGFR3* on 4p16.3, so this spatial proximity may support recombination. See below for discussions of these aberrations. All other FGFR gene fusions are listed in Supplementary Table S5.

The high prevalence of FGFR gene abnormalities in urothelial carcinomas not only suggests that anti-FGFR therapies may be effective for these patients, but also raises the question of whether there are coaberrant genes that could also be targeted by additional therapies. One such gene of interest is *PIK3CA*. The overall frequency of *PIK3CA* mutation among urothelial tumors was 20.6% (25 cases, 1 case had two mutations). Among the 32 urothelial tumors with *FGFR3* abnormalities, 6 (24%) had coexisting *PIK3CA* gene abnormalities, suggesting that combination therapy with anti-FGFR and anti-PIK3CA drugs could be evaluated. The frequencies of aberration in these two genes is likely an independent occurrence (χ^2 P value = 0.86 in this dataset), which is in contrast to two other published studies (15, 16) in which *PIK3CA* mutation was positively correlated with FGFR aberration. However, it should be noted that in the first study, 77% were stage T_a/T_1 and 57% were grade G_1/G_2, and in the second study 75% were stage T_a/T_1 and grade G_1/G_2, and both studies reported a stronger correlation between *PIK3CA* and FGFR abnormalities in earlier stage and lower grade tumors. Other genes of interest that were coaberrant with *FGFR3* amplification include *CDKN2A* (8 cases), *TSC1* (5 cases), *ARID1A* (5 cases), and *TP53* (4 cases). To facilitate exploration of coaberrant genes, we listed all urothelial and other tumor types from our dataset that had any FGFR aberration and all coexisting gene aberrations in Supplementary Table S6.

We grouped all urothelial carcinomas together for this analysis, although it is possible that there are differences in molecular phenotype according to where in the genitourinary tract the

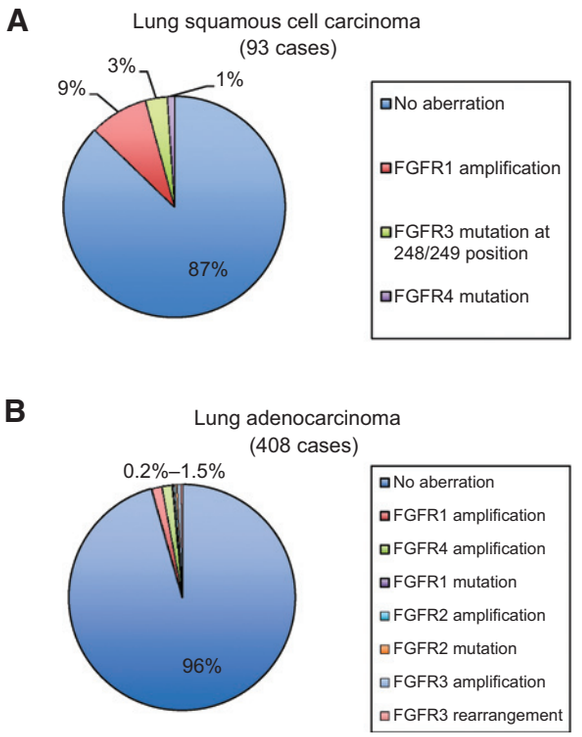

Figure 3.
Relative frequencies of FGFR aberrations in non–small cell lung carcinoma. A, lung squamous cell carcinoma, 93 cases. Frequencies are reported as percentage of all 93 cases. B, lung adenocarcinoma, 408 cases. Frequencies are reported as percentage of all 408 cases. Non–small cell lung carcinomas not otherwise specified were excluded from this analysis.

urothelial tumors arise. Among the 126 urothelial cancers we evaluated, 22 of 90 bladder carcinomas, 11 of 21 renal pelvis carcinomas, 3 of 6 ureteral carcinomas, and 4 of 9 urothelial carcinomas not otherwise specified (NOS) had FGFR aberrations. Although these data may suggest that FGFR gene aberrations are least frequent among urothelial carcinomas arising from the lower urinary tract, our dataset is not equipped to make this determination because of small numbers of patients in certain subsets. To avoid sample size bias, we chose to analyze only those tumor types with at least 75 representative cases, and bladder is the only site in the urothelial tract that meets this requirement with 90 cases (renal pelvis had 21, urothelial not otherwise specified 9, and ureter 6 cases).

Among urothelial tumors, *FGFR3* mutations are very frequent among tumors of low-malignant potential, papillomas, low-grade, and low-stage tumors. Di Martino and colleagues showed that the most common *FGFR3* mutations seen in urothelial cancers are able to transform NIH-3T3 cells, but have less potent effects on normal bladder cells (TERT-NHUC) (13). These data suggest that *FGFR3* mutations may confer a selective proliferative advantage to early urothelial lesions, but that they may also have cell-type–specific effects that may explain the observed differences in mutation frequencies among urothelial tumors.

In our dataset, we do not have grade or stage information for any of the tumor samples, including the urothelial tumors. This means that we cannot say whether they are superficial or invasive nor whether they are low- or high-grade tumors. We therefore cannot draw conclusions about the significance of FGFR aberration frequencies in this dataset.

Breast cancer

There were 522 cases of breast cancer in the dataset (Fig. 2, Supplementary Tables S2 and S6), and included invasive ductal carcinoma, invasive lobular carcinoma, and invasive metaplastic carcinoma. Breast sarcoma, neuroendocrine breast cancer, and noninvasive breast cancer are not included. Estrogen receptor and progesterone receptor protein expression are not measured by the NGS assay used. In contrast, *ERBB2* (Her2) amplification of $\geq$5-fold is detected by the assay. Only 4 of 72 breast cancer cases with any FGFR aberrations also had *ERBB2* amplification measured in this fashion.

Eighteen percent of breast cancers analyzed had any FGFR aberration, the most common of which was *FGFR1* amplification ($\sim$14%), whereas amplification of *FGFR2–4* was much less frequent (0.5%–2.3%). Because *PIK3CA* alterations are among the most commonly seen in breast cancer (17–19), it is interesting to note that 26.4% (19/72) of cases with *FGFR1* amplification also harbored aberrations in the *PIK3CA* gene, nearly all of which are activating alterations: gene amplification ($N = 2$), *PIK3CA–E545K* ($N = 7$), *PIK3CA–H1047R* ($N = 7$), and one case each with *PIK3CA–N345K*, *PIK3CA–E542K*, *PIK3CA–E545Q*, *PIK3CA–Q546K*, and *PIK3CA–M1043L* (likely an activating mutation). The total number of *PIK3CA* aberrations listed is greater than 19 because one case had three distinct aberrations. This overall frequency of $\sim$30% is similar to what we observed in the entire set of 522 breast cancer cases (28.9%) and to the reported rates of *PIK3CA* mutations in breast cancer not selected for FGFR aberration, which range from 22% to 34.5% for hormone receptor positive and Her2-positive breast cancers (17–19), perhaps suggesting that there is no relationship to *FGFR* aberration. In fact, the χ^2 *P* value is 0.61, so it is very likely that these two genes are independently selected for in the breast cancer cases analyzed.

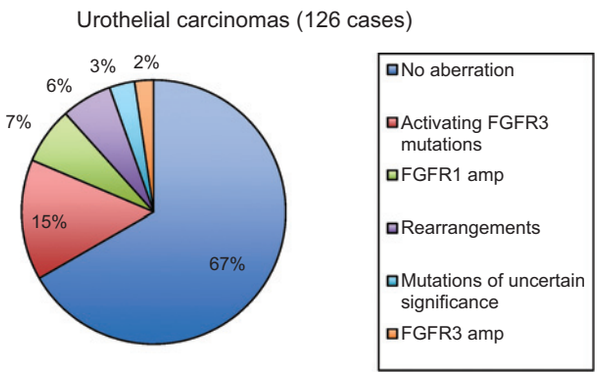

Figure 4.
Distribution of FGFR aberrancies in urothelial cancers. Cancers included urothelial carcinomas (transitional cell carcinomas) of the bladder, renal pelvis, ureter, and not specified. The majority of aberrations were activating mutations in *FGFR3*, including S249C (8 instances), R248C (6 instances), Y373C (2 instances), G370C (2 instances), and K650M (1 instance). Three of these *FGFR3* mutations are also about to transform cells *in vitro* (S249C, S248C, Y737C; Supplementary Table S4). Frequencies are expressed as percentages of all 126 cases. There were 44 aberrations in 40 cases (4 cases had more than one aberration), so the total is greater than 100%.

Other genes of interest that were coaberrant in the *FGFR1*-amplified subset of breast cancers include *CCND1* amplification (21 cases), *MYC* amplification (21 cases), and mutations or loss of *TP53* (31 cases). See Supplementary Table S6 for a list all co-aberrant genes for all cases with any FGFR abnormality.

Endometrial carcinoma

About 11% of 80 cases harbored FGFR abnormalities, most of which occurred in *FGFR2* (Fig. 2, Supplementary Tables S2 and S6). These *FGFR2* mutations included S252W (2 cases), P253R (2 cases), C382R and N549K (1 case each). All of these are gain-of-function mutations that are able to transform cells *in vitro* (Supplementary Table S4). Their functional significance is discussed below.

Non–lung squamous cell carcinomas

All non–lung squamous cell carcinomas were analyzed together. There were 273 cases, including esophageal, bladder, cervical, cutaneous, gallbladder, head and neck, ocular, penile, vulvar, vaginal, urethral, and rectal carcinomas; 5.1% of these cases harbored any FGFR aberration, and the majority (6 of 14 aberrations) were *FGFR1* amplifications.

Other cancers

A wide variety of other cancers harbored FGFR aberrations in a subset of patients, ranging from 1% to 9% (Supplementary Tables S2 and S6). These cancers include, but are not limited to, ovarian cancer (∼9%), gliomas (∼8%), pancreatic, renal, colorectal cancer, and neuroendocrine (about 4% to 5% each), and sarcomas (∼4%).

Specific Aberrations and Their Functional Significance: Preclinical Work and Implications for Drug Development

***FGFR1* amplification**

FGFR1 amplification is one of the most common FGFR alterations seen in this dataset (Supplementary Fig. S1A). It was observed in 151 cases (3% of all cases, or about 42% of all observed FGFR aberrations). It was common in breast carcinoma (∼14% of patients with breast cancer), squamous cell lung carcinoma (∼9%), and ovarian carcinoma (∼5%), but was also seen in significant proportions of urothelial carcinoma (7% of cases; 20% of FGFR aberrations), gastric/gastroesophageal junction carcinoma (∼2% of cases; 25% of FGFR aberrations), colorectal carcinoma (2% of cases; 64% of FGFR aberrations), carcinoma of unknown primary (2% of cases; 23% of FGFR aberrations), and squamous non-lung tumors (2% of cases, 43% of FGFR aberrations). Presumably, *FGFR1* (and other FGFR gene) amplification leads to protein overexpression and dependence on FGFR signaling. This assumption is borne out in preclinical models of squamous cell lung carcinoma in which *FGFR1* amplification correlates with protein overexpression and increased sensitivity to FGFR-inhibiting drugs (20, 21). Similar findings are seen in breast cancer preclinical models for both *FGFR1* (9, 22) and *FGFR2* (23). These *in vitro* data suggest that *FGFR1* and *FGFR2* amplification could serve as biomarkers for efficacy of FGFR inhibiting drugs.

FGFR mutations

In our dataset, there were five unique *FGFR1* mutations (Supplementary Table S4). All five have been reported previously in the COSMIC database (Catalogue of Somatic Mutations In Cancer, http://cancer.sanger.ac.uk/cosmic, accessed June 2015). The functional effects of three of them are unknown, but two of them (N546K and K656E) are known to be both activating and transforming. Both lie in the intracellular kinase domain. Lew and colleagues (24) showed that formation of the Fgfr1 monophosphorylated receptor is 25 times faster with N546K than with wild-type and that the mutant receptor is capable of transforming Rat-1 cells *in vitro*. The *FGFR1 K656E* mutation causes constitutively active receptor signaling in an analogous mutation in *FGFR3* (25). This activating mutation in *FGFR1* not only induces phosphorylation of downstream effectors, but is also capable of transforming NIH3T3 cells *in vitro* (25). These data suggest that both of these mutations are likely pathogenic *in vivo* and represent valid targets for drug development.

FGFR2 has a higher missense mutation rate in our dataset (12 unique mutations, all but one of which are reported in the COSMIC database; see Supplementary Table S4). Seven are known to be activating mutations. *FGFR2* S252W, P253R, and N549K were the most commonly seen *FGFR2* alterations. *FGFR2* S252W and P253R lie in the receptor's extracellular linker region between the two immunoglobulin-like domains, a key site for ligand binding (26), and are thought to differentially increase ligand binding affinity, thereby increasing receptor signaling (27). Both are also capable of transforming NIH3T3 cells despite the fact that the mutant receptor is expressed at lower levels than the wild-type (26). Furthermore, knockdown of the S252W mutant receptor by specific shRNA inhibits both transformation and survival of MFE-280 cells *in vivo* (26), strongly suggesting that the *FGFR2* S252W mutation and possibly also the P253R mutation are compelling targets for drug therapy. The *FGFR2* N549 residue is associated with a "molecular brake" that keeps the kinase in an auto-inhibited state (28). The N549K mutation presumably disrupts this inhibition, leading to increased kinase activity. It also transforms NIH3T3 cells (26). Among the other *FGFR2* mutations known to be activating (A315T, Y375C, C382R, and K659E), only C382R and K659E are known to transform NIH3T3 cells (26, 29). We are unaware of data regarding the transformational ability of the other *FGFR2* mutations in our dataset.

FGFR3 also had a high rate of mutation, with 13 unique mutations identified in the dataset (Supplementary Table S4). All but one have been reported in the COSMIC database. Eight of them are known to be activating and four of them are able to transform cells *in vitro*. The most common missense mutations in *FGFR3* were S249C (17 cases), R248C (9 cases), G370C (4 cases), K650E (4 cases), R399C (3 cases), and Y373C (3 cases). All other mutations were observed in single cases. The *FGFR3* S249C mutation is both activating and transforming. It lies between the two extracellular immunoglobulin-like domains. In 293T cells, *FGFR3* S249C induces ligand-independent dimerization and increased receptor basal phosphorylation (30) and leads to anchorage independent growth (31) and xenograft tumors in mice (32). Furthermore, gene knockdown of this mutant receptor abolishes transformation (33). The nearby *FGFR3* R248C mutation, which is the second most common *FGFR3* mutation in our dataset, is similarly activating and transforming. For both of these mutations, the creation of a new, unpaired cysteine residue results in formation of intermolecular disulfide bones, increased homodimerization and signaling (34). *In vitro, FGFR3* R248C promotes increased cell

numbers at confluence, induces proliferation, induces morphologic transformation, reduces apoptosis, and decreases attachment to fibronectin, but does not alter migration (34, 35). *FGFR3* G370C lies in the extracellular juxtamembrane region. In 293T cells, it leads to ligand-independent dimerization and phosphorylation (30). We are unaware of data regarding the ability of this mutation to transform cells *in vitro*. *FGFR* K650E also shows ligand independent activation, although by undefined mechanism(s) (35, 36) and is able to transform NIH3T3 cells (37, 38). *FGFR3* Y373C is also thought to induce disulfide bond formation causing constitutive activation of the receptor (32, 35). It is a strong inducer of transformation, which can be abrogated by siRNA-mediated knockdown or SU5402 (a potent FGFR inhibitor; refs. 32, 37), suggesting that this mutation represents a valid drug target. We are unaware of data regarding functional significance or transformational ability of *FGFR3* R399C.

Among the five unique mutations observed in *FGFR4*, all were previously reported in the COSMIC database, but to our knowledge none of them have been characterized to date.

FGFR gene fusions

Fusions of FGFR genes with other genes or parts of genes were observed mostly with *FGFR2* (10 cases) and *FGFR3* (18 cases). By far, the most common fusion partner was *TACC3* (Transforming Acidic Coiled-Coil Containing Protein 3; 12 cases). Other fusion partners included three cases with *NPM1*, two with *TACC2*, two with *BICC1*, and single cases with *NTM*, *C10orf68*, *KIAA1598*, *NCALD*, *NOL4*, *PPAPDC1A*, *JAKMIP1*, *TNIP2*, and *WHSC1*. Four of our cases that had gene fusions were urothelial carcinomas, two were glioblastomas, and the rest were single cases of cholangiocarcinoma, cervical adenocarcinoma, cervical squamous cell carcinoma, endometrial carcinoma, non–small cell lung carcinoma, pancreatic carcinoma, gallbladder carcinoma, renal cell carcinoma, and carcinoma of unknown primary. All gene fusions are listed in Supplementary Table S5.

Chromosomal translocations in cancers that lead to fusion proteins exert their oncogenic effects through overexpression of an otherwise normal gene or creation of a chimeric gene in which parts of two genes are fused together. In the case of *FGFR3–TACC3*, the entire *FGFR3* kinase domain is fused with the *TACC3* domain that mediates microtubule binding (31, 39). These fusion proteins activate the MAPK pathway when transfected into normal human urothelial cells, suggesting that they retain active signaling. Furthermore, cell lines harboring the fusion proteins are very sensitive to a selective FGFR inhibitor (PD173074), indicating that the fusion protein represents a valid therapeutic target in cancer cells (31). Similar *FGFR–TACC3* fusions that are also sensitive to PD173074 have been reported in glioblastoma (39).

Coexistent FGFR mutation and amplifications

Ten of the 17 tumors that had more than one *FGFR* gene aberration had amplifications concurrent with either mutation or fusion events, 8 of them involved *FGFR3*, and 2 involved *FGFR2*. The tumor types involved were urothelial carcinoma ($N = 3$), endometrial carcinoma ($N = 2$), and single cases of cervical carcinoma, gallbladder carcinoma, non–small cell lung carcinoma, pancreatic exocrine carcinoma, and renal cell carcinoma. All concurrent aberrations are listed in Supplementary Table S6.

Discussion

This study represents a comprehensive overview of FGFR aberrations in a large cancer genomic database. About 7% of cancers had FGFR aberrations, with the most common abnormality being *FGFR1* amplification. Overall, 5% of 4,853 patients had FGFR amplifications; 2% of patients had mutations; and 0.5% of patients had rearrangements. *FGFR1* was affected in 3.5% of 4,853 patients; *FGFR2* was affected in 1.5% of patients; *FGFR3* was affected in 2.0% of patients, and *FGFR4* was affected in 0.5% of patients (Fig. 1). Almost every histology included individuals who harbored FGFR aberrations, but the cancers most commonly affected were urothelial (32% FGFR-aberrant), breast (18%), endometrial (∼13%), squamous cell lung (∼13%; Fig. 3), ovarian (∼9%), carcinoma of unknown primary (∼8%), glioma (∼89%), and cholangiocarcinoma (7%; Fig. 2 and Supplementary Tables S2 and S6).

FGFR aberrations did not appear to segregate well by histology. However, some aberrations were found more frequently in certain cancers. For example, *FGFR1* amplifications predominated in squamous cell lung, breast, ovarian, and urothelial cancers, observed in 5% to 14% of patients with these malignancies; *FGFR3* mutations predominated in bladder and other urothelial tumors, observed in 15% of individuals. Others (20, 21, 40, 41) also reported high rates of *FGFR1* amplification in squamous cell lung cancer (13%–22%). Squamous cell cancers originating in other organs were analyzed together and showed FGFR aberrations in 5.1% of cases (most frequently *FGFR1* amplification). There were insufficient small cell lung cancers (43 cases) in our dataset to report.

Although therapies targeting the aberrant proteins produced by mutated *EGFR* or rearranged *ALK* have been applied successfully in lung adenocarcinoma and the FDA recently approved nivolumab for squamous cell lung carcinoma, no therapy based on molecular phenotype is currently approved for squamous cell or other non-adenocarcinoma types of lung cancers. However, FGFR inhibitors are being developed for NSCLC, including squamous cell carcinomas. For example, the results of at least two phase III clinical trials of the multikinase inhibitor nintedanib (which targets FGFR, VEGFR, and PDGFR) in NSCLC showed statistically significant, albeit modest, benefit (42, 43). These studies did not select for FGFR aberrations, so it would be of interest to determine the correlation between response and the presence of FGFR abnormalities.

Fifteen percent of urothelial malignancies (Fig. 4) also harbored somatic mutations in *FGFR3*, which are known to be activating and transforming. Because these activating mutations are easy to detect and are frequent, they represent attractive targets for drug development. There are several ongoing trials of FGFR inhibiting drugs in urothelial carcinoma, some of which are reporting early success. For example, preliminary analysis of a phase I trial of BGJ398, a potent, selective pan-FGFR inhibitor, showed tumor regression in four of five patients with urothelial carcinomas with *FGFR3*-activating mutations (with tumor reductions ranging from 27% to 48%; ref. 44).

Eighteen percent of breast cancers had an FGFR aberration, the most frequent being *FGFR1* amplification (14% of cases), whereas amplification of *FGFR2–4* was much less common (0.5–2.3%). *FGFR1* amplification may be a strong independent predictor of overall survival in patients with breast cancer (45) and may also correlate with endocrine therapy resistance (6), suggesting

prognostic value for assessing *FGFR1* status. It is also possible that patients with *FGFR1*-amplified breast cancer might benefit from the administration of FGFR inhibitors. In fact, lucitanib, a dual kinase inhibitor (FGFR/VEGFR), has shown activity in *FGFR1*-amplified breast cancer, with an overall response rate of 50% (46), and other studies are ongoing.

About 11% of endometrial cancers were found to have FGFR abnormalities, mostly activating mutations in or amplification of *FGFR2* (∼9% of patients). As described in the "Results," the *FGFR2*–S252W mutation increases affinity for the FGF ligands, in particular FGF9, which may be especially important for endometrial cancer because it is found in abundance in the endometrial stroma (47). Also intriguing is that *FGFR2* and *KRAS* mutations seem to be mutually exclusive in endometrial cancers, suggesting redundancy with regard to activation of the MAPK pathway (48).

We also noted FGFR gene fusions (usually involving *FGFR2* or *FGFR3*) in a minority of the cases. The most common fusion partner was *TACC3* (31), perhaps because *FGFR3* and *TACC3* are close together on chromosome 4p16 (39). Fusion of *FGFR3* with *TACC3* leads to ligand-independent signaling activation in glioblastoma and bladder cancer (31, 39, 49). Mice-harboring FGFR-*TACC3*–associated gliomas respond to administration of an FGFR inhibitor (39).

Stratifying by type of abnormality, *FGFR1* amplification was one of the most common FGFR anomalies observed (Supplementary Fig. S1A; 3% of all cases, or approximately 42% of FGFR aberrations). *FGFR1* amplification was frequent in breast carcinoma (∼14% of cases), squamous cell lung carcinoma (∼9%), urothelial carcinoma (∼7%), and ovarian carcinoma (∼5%), as well as other malignancies. Of interest, at this time there are at least five ongoing clinical trials of FGFR inhibitors that include *FGFR1* amplification in their eligibility criteria (NCT01948141, NCT01283945, NCT01349296, NCT01202591, NCT02053636, see clinicaltrials.gov).

At this time, there are four FGFR inhibiting drugs approved by the FDA: ponatinib, regorafenib, pazopanib, and most recently lenvatinib. All are multikinase inhibitors, but there are also specific FGFR inhibitors in development as well. None of the approved FGFR inhibiting drugs were approved specifically for FGFR-selected populations, but several FGFR inhibiting agents are currently in clinical trials that require FGF/FGFR aberrations for eligibility. For example, dovitinib (TKI-258), a potent multikinase inhibitor (FGFR, VEGFR, and PDGFR), is being used in phase II trials for *FGFR1*-amplified squamous non–small cell lung cancer (NCT01861197), *FGFR1*- or *FGFR2*-amplified breast cancer (NCT01528345), and refractory urothelial carcinoma with *FGFR3* mutations or overexpression (NCT01732107). Lucitanib (E-3810), a multikinase inhibitor (FGFR, VEGFR, and PDGFR), is being tested in a phase I/IIa trial in patients with solid tumors (NCT01283945), phase II studies of *FGFR1*-amplified lung cancer (NCT02109016) and *FGFR1*-amplified breast cancer (NCT02202746 and NCT02053636). Results of these and other trials will clarify the utility and safety of FGFR-inhibiting drugs, the advantages or disadvantages of drug specificity for FGFR, and refine appropriate biomarkers for response to these drugs.

There are some limitations to these data. First, the dataset was not annotated and therefore correlation with clinical characteristics (e.g., stage, phenotype, etc.) was not possible, which may have greater importance for some tumor types than for others (see "Urothelial cancers"). Second, the number of patients with each cancer was dependent on the number of cases submitted by physicians for next-generation sequencing analysis, which introduces the possibility of sample size bias. Finally, pathologic diagnosis was designated based on the determination of the submitting attending physician/pathologist.

Our observed frequency of primarily activating FGFR aberrations in diverse cancers, along with preclinical and early clinical data already reported suggest that targeting FGFR alterations with cognate inhibitors has therapeutic potential. There is also evidence that there are FGFR alterations that confer resistance to other types of cancer treatment (6, 7) and that some specific FGFR aberrations may demonstrate differential sensitivity/resistance to distinct FGFR inhibitors (50). Intriguingly, some *FGFR2* and *FGFR3* somatic mutations were identical to mutations that, in germline form, are associated with dwarfism. However, there are no published epidemiologic data to suggest that individuals with germline FGFR aberrations and dwarfism have an increased incidence of cancer, suggesting that developmental compensatory mechanisms can mitigate the oncogenic potential of these aberrations. FGFR may also have prognostic value. Indeed, in breast cancer, *FGFR1* amplification was independently associated with poor survival (45). Further study will be needed to elucidate the impact of each of the FGFR aberrations on cancer phenotype, prognosis, and response to treatment. Because many FGFR changes appear to activate signaling, it is also important to characterize the clinically relevant effects of the many potent FGFR inhibitors that are currently in clinical trials. Based on the frequent finding of FGFR abnormalities in diverse malignancies, especially in urothelial, breast, ovarian, endometrial, and squamous lung cancers, molecular interrogation of patients for FGFR aberrations in the clinical research and practice setting is warranted.

Disclosure of Potential Conflicts of Interest

S. Elkin and J. Carter have ownership interest (including patents) in N-of-One. R. Kurzrock reports receiving research funding from Foundation Medicine, Genentech, Merck Serono, and Pfizer; is a consultant/advisory board member for Sequenom, and has ownership interest (including patents) in RScueRX. No potential conflicts of interest were disclosed by the other authors.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): T. Helsten, S. Elkin, E. Arthur, B.N. Tomson
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