FGFR2-Altered Gastroesophageal Adenocarcinomas Are an Uncommon Clinicopathologic Entity with a Distinct Genomic Landscape

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ABSTRACT

Background. With the exception of trastuzumab, therapies directed at receptor tyrosine kinases (RTKs) in gastroesophageal adenocarcinomas (GEA) have had limited success. Recurrent fibroblast growth factor receptor 2 (FGFR2) alterations exist in GEA; however, little is known about the genomic landscape of FGFR2-altered GEA. We examined FGFR2 alteration frequency and frequency of co-occurring alterations in GEA.

Subjects, Materials, and Methods. A total of 6,667 tissue specimens from patients with advanced GEA were assayed using hybrid capture-based genomic profiling. Tumor mutational burden (TMB) was determined on up to 1.1 Mb of sequenced DNA, and microsatellite instability was determined on 95 or 114 loci. Descriptive statistics were used to compare subgroups.

Results. We identified a total of 269 (4.0%) FGFR2-altered cases consisting of FGFR2-amplified (amp; 193, 72% of FGFR2-altered), FGFR2-mutated (36, 13%), FGFR2-rearranged (re; 23, 8.6%), and cases with multiple FGFR2 alterations (17, 6.3%). Co-occurring alterations in other GEA RTK targets including ERBB2 (10%), EGFR (8%), and MET (3%) were observed across all classes of FGFR2-altered GEA. Co-occurring alterations in MYC (17%), KRAS (10%), and PIK3CA (5.6%) were also observed frequently. Cases with FGFR2amp and FGFR2re were exclusively microsatellite stable. The median TMB for FGFR2-altered GEA was 3.6 mut/mb, not significantly different from a median of 4.3 mut/mb seen in FGFR2 wild-type samples.

Conclusion. FGFR2-altered GEA is a heterogenous subgroup with approximately 20% of FGFR2-altered samples harboring concurrent RTK alterations. Putative co-occurring modifiers of FGFR2-directed therapy including oncogenic MYC, KRAS, and PIK3CA alterations were also frequent, suggesting that pretreatment molecular analyses may be needed to facilitate rational combination therapies and optimize patient selection for clinical trials. The Oncologist 2019;24:1462–1468

Implications for Practice: Actionable receptor tyrosine kinase alterations assayed within a genomic context with therapeutic implications remain limited to HER2 amplification in gastroesophageal adenocarcinomas (GEA). Composite biomarkers and heterogeneity assessment are critical in optimizing patients selected for targeted therapies in GEA. Comprehensive genomic profiling in FGFR2-altered GEA parallels the heterogeneity findings in HER2-amplified GEA and adds support to the utility of genomic profiling in advanced gastroesophageal adenocarcinomas.

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The molecular complexity of gastroesophageal adenocarcinoma (GEA) is increasingly understood as a determinant of response to both cytotoxic therapies and, more importantly, receptor tyrosine kinase (RTK)-directed therapies [1–5]. Several series have now clearly demonstrated intratumoral and intratumoral heterogeneity of the actionable RTKs human epidermal growth receptor 2 (HER2), epidermal growth factor receptor (EGFR), and MET. Molecular heterogeneity exists at baseline and evolves over time, as demonstrated by HER2 loss and acquired receptor coamplifications in GEA [4, 6–8]. Prior small series have demonstrated that pathogenic alterations in fibroblast growth factor receptor 2 (FGFR2) including short variant mutations (SV), amplifications (amp), and rearrangements (re) exist recurrently in GEA [9–12].

FGFR2 is a transmembrane RTK, and overexpression has been associated with a poor prognosis in gastric cancer [9, 13]. Substantial preclinical work has suggested higher-level clonal FGFR2 amplification predicts response to FGFR2 inhibitors across several tumor types, including GEA [14–16]. Within GEA, FGFR2 activation promotes invasion, migration, and disease progression, suggesting FGFR2 is a potential therapeutic target in GEA [17, 18]. Although the therapeutic activity of targeting FGFR2 alterations is established in biliary tract cancers and urothelial cancers, the results have been disappointing in the limited GEA literature [15, 19–22]. A small phase II trial using the pan-FGFR tyrosine kinase inhibitor AZD4547 versus paclitaxel in the second-line treatment of FGFR2-amplified GEA failed to demonstrate a progression-free survival benefit [19, 23]. In the limited correlative work, there was no clear association between degree of receptor amplification and responsiveness, unlike a phenomenon that has been observed with HER2 and EGFR. However, this trial failed to examine the genomic context of the FGFR2-altered samples and is limited by small sample size.

Owing to the rarity of FGFR2 alterations, it is unknown whether coamplification and concurrent putative resistance alterations exist in FGFR2-altered GEA. Prior studies, including The Cancer Genome Atlas (TCGA) and Asian Cancer Research Group, contained limited numbers of FGFR2-altered samples [11, 24]. Using a large genomic database, we sought to characterize the genomic landscape of FGFR2-altered GEA with a focus on concurrent alterations that may impact sensitivity to FGFR2-directed therapies in development for multiple tumor types including GEA.

Comprehensive genomic profiling (CGP) was conducted using a hybrid capture-based genomic profiling assay as previously described [25]. All classes of genomic alterations including base pair substitutions, insertions/deletions (together “short variants”), copy number alterations, and rearrangements were captured. Tumor mutational burden (TMB) was determined on up to 1.1 megabase pairs (Mb) of sequenced DNA and microsatellite instability (MSI) was determined on 95 or 114 loci using validated methods [26]. Descriptive statistics were used to compare among subgroups.

Pathogenic alterations in FGFR2 were defined by literature review as genomic changes known to be oncogenic including amplification (predicted copy number ≥6), rearrangements, and short variants deposited in the Catalog of Somatic Mutations in Cancer (v62) [27]. Short variants were cross-referenced against the Onco-KB database to highlight mutations predicted to be activating (supplemental online Table 1) [28]. As there is a well-reported relationship between FGFR2 expression by immunohistochemistry (IHC) and FGFR2 amplification, IHC was not explored [9]. Prespecified focus on concurrent amplifications in other established RTK targets in GEA included FGFR2, HER2, MET, and EGFR. As there are limited preclinical and clinical data exploring innate FGFR2 resistance in GEA, we expanded the list of putative genomic alterations predicted to decrease responsiveness to FGFR2-directed therapies based on literature review in other tumor types. Beyond concurrent RTK amplification, we prespecified amplifications in the cell cycle genes MYC and CCNE1, the Wnt pathway gene CTNNB1, amplification or pathogenic mutation in KRAS, and oncogenic PIK3CA mutations as putative resistance alterations that have been observed in HER2-amplified GC [29–31]. In rare cases where there were multiple samples from a single patient, the earliest sample was used to avoid biasing. Programmed death-ligand 1 (PD-L1) status tested by Foundation Medicine using the combined positive score, and 22c3 antibody clone was abstracted when available. Descriptive statistics were used to compare across groups, and p < .05 was the threshold to determine statistical significance.

**Results**

**Detection of Pathogenic FGFR2 Alterations by CGP**

Out of 6,667 individual GEA samples, we identified a total of 269 (4.0%) FGFR2-altered cases consisting of FGFR2 amplification (193, 72% of FGFR2-altered), FGFR2 SV mutation (36, 13%), FGFR2 rearrangement (23, 8.6%), co-occurring FGFR2 amp with re (13, 4.8%), amp with SV (3, 1.1%), or SV with re (1, 0.37%). Baseline demographic information is shown in Table 1. More than 66% of samples originated from primary tumors, and a complete list of sample site is provided in supplemental online Table 2. FGFR2 amplification was the most common pathogenic FGFR2 alteration and was enriched in tumors from female patients compared with FGFR2 wild-type (WT) cases (p = .0003). There were no significant differences in TMB as a function of the class (SV, amp, re) of FGFR2 alterations. The median TMB was low (<5 mutations/Mb) across all classes of FGFR2 alterations (Table 1). Cases with FGFR2amp
and FGFR2 were exclusively microsatellite stable, whereas 16% of FGFR2 SV cases were MSI-high. The most common fusion partner was TACC2 (22%), and the activating NS49K mutation in the kinase domain of FGFR2 represented 16% of short variant FGFR2 mutations (Fig. 1; supplemental online Fig. 1). The observed FGFR2 rearrangements in 14% (37/269) of FGFR2-altered cases are previously undescribed in GEA.

Receptor Tyrosine Kinase Amplifications Coexist in FGFR2-Altered GEA
RTK coamplification and concurrent amplification are known to influence responsiveness to targeted therapies in HER2-amplified GEA. Co-occurring alterations in other GEA RTK targets including HER2 (10%), EGFR (8%), and MET (3%) were observed in all types of FGFR2-altered GEA (Table 1; Fig. 2A–C; supplemental online Fig. 2). Within a given class of FGFR2 alteration, there were differential frequencies of concurrent RTK amplifications, with FGFR2-rearranged cases demonstrating the greatest frequency of concurrent RTK alterations (24%, p > .1). Across FGFR2-altered cases, HER2 and EGFR were the most common RTKs with concurrent amplification (Fig. 2A–C). FGFR2-rearranged GEA cases had a high rate (35%) of concurrent FGFR2 amplification, confirmed by manual overview of sequencing data.

Alterations Predicted to Reduce Responsiveness to FGFR2-Directed Therapies Are Common in FGFR2-Altered GEA
Beyond co-occurring RTK alterations, changes in cell cycle genes, PI-3-kinase, and MAP-kinase pathway genes are implicated in innate and acquired resistance to HER2-targeted therapies in GEA [30, 31]. We observed alterations in MYC (17%), KRAS (10%), and PIK3CA (5.6%) frequently across FGFR2-altered cases, paralleling HER2 observations (Fig. 2A–C). When all prespecified putative resistance alterations were pooled, more than 40% of all FGFR2-altered GEA samples contained at least one co-occurring genomic alteration predicted to decrease responsiveness to FGFR2-directed therapies. We also explored the “pan-wild-type” subset of FGFR2-amplified cases with no predicted resistance changes. Within this group (n = 121), TP53 mutation was the predominant alteration with recurring amplifications of unknown clinical significance across cell cycle genes (CCND1, CDK6) and FGF-family genes (Fig. 3A–C), likely reflecting TCGA chromosome instability molecular subtype [11].

In the patients with available PD-L1 immunohistochemistry, there was no difference in rates of PD-L1 positivity between FGFR2-altered and FGFR2-wild-type samples. Specifically, 3/32 (9%) FGFR2-altered cases demonstrated PD-L1 expression in tumor cells and 3/28 (11%) in tumor-associated lymphocytes. In the FGFR2-wild-type samples, rates were 94/891 (11%) in tumor cells and 93/891 (11%) in tumor-associated lymphocytes.

## DISCUSSION
In this descriptive series, we provide improved understanding of the landscape of FGFR2-altered GEA and focus on therapeutically relevant coexisting genomic alterations. This is the largest study to examine FGFR2-altered GEA and the
first to delve into the frequency of changes that may affect responsiveness to targeted therapies. Although heterogeneity and coexisting alterations are established in HER2- and MET-amplified GEA, much less is known about FGFR2. The potential actionability of FGFR2 alterations, including data in other tumor types, has spawned several trials in advanced GEA including the phase III FIGHT trial combining the antibody bemarituzumab with modified FOLFOX6 in gastric cancer with FGFR2 amplification or overexpression (NCT03694522). Other agents including the small-molecule FGFR inhibitors dovitinib and TAS-120 continue in earlier-phase development. Our analyses suggest that roughly 20% of all FGFR2-altered GEA have at least one coexisting genomic event predicted to decrease the sensitivity to FGFR2-directed therapies. Recurrent RTK coamplifications are relatively unique to GEA among tubular gastrointestinal cancers, and our results are consistent with studies of other RTKs of interest [32]. The frequency of coexisting alterations is a cautionary tale for developing FGFR2-directed therapies, particularly monotherapies, in GEA and suggests a need for comprehensive baseline genomic characterization [33, 34]. Composite biomarkers (HER2amp/MET WT/EGFR WT for example) and concordance between tissue-based and plasma-based biomarker assessment are important for optimal patient selection in targeted GEA trials [1, 2, 6]. Within our series, we would anticipate the FGFR2amp/pan-WT tumors \( n = 121, 58\% \text{ of FGFR2amp; Fig. 3A–C} \) to have the genomic background most likely to respond to FGFR2-directed therapies, although prospective data are needed to validate this hypothesis. This concept is supported by prior observations that RTK activation may attenuate AZD4547 in FGFR2-amplified gastric cancer models [35, 36]. Although the SHINE trial, which selected patients with FGFR2 amplification for treatment with AZD4547, did not pursue genomic analyses to enable identification of co-occurring alterations, the study did observe significant heterogeneity of intratumoral subclonal populations with and without amplification of FGFR2 [23]. Furthermore, the subclonal preponderance of FGFR2 amplification may have accounted for variability in FGFR2 mRNA expression transcripts level in which the authors observed in human tumors, in stark contrast to a homogeneously FGFR2-amplified and -expressed SNU16 cell line model. However, the SHINE investigators were unable to draw clear correlation between analysis of subclonal heterogeneity of FGFR2 amplification alone and clinical response to AZD4547. As such, our data set further supports identification of genomic coalterations providing an additional facet in whether single agent FGFR2-targeted strategies should continue to be prospectively tested. It is likely that dual targeting or sequential approaches will be needed for the patients with GEA with non-pan-WT tumors [37, 38]. We also observed FGFR2 rearrangements not previously reported in GEA in 14% of cases, and FGFR2 fusions are known to be responsive to FGFR2 agents in multiple other tumor types, although heterogeneity in those tumor types is not well described [21].

**Figure 2.** Differential frequency of co-occurring alterations predicted to decrease sensitivity to FGFR2-directed therapies among a large cohort of FGFR2-altered gastroesophageal adenocarcinomas. Coexisting alterations are broken out among the major classes of FGFR2 genomic alterations. (A): FGFR2 short variant cases \( n = 40 \). (B): FGFR-amplified cases \( n = 209 \). (C): FGFR2-rearranged cases \( n = 37 \).
The large size of our series (total $n = 6,667$ GEA samples from unique patients) is an advantage, and prior bioinformatic work has suggested sample sizes of 600 or more are needed to accurately capture genomic variants [39]. Additionally, the frequencies of HER2, MET, and EGFR amplification closely parallel those reported in independent studies, suggesting that our data set is representative of the overall GEA population.

Although limited to a smaller subset, PD-L1 expression was seen to exist at similar frequencies between FGFR2-altered and FGFR2-wild-type cases. With the recent abstract presenting very high response rates for pembrolizumab with the anti-HER2 antibody trastuzumab in HER2-positive GEA, our observation raises the possibility for similar approaches in FGFR2-altered disease [5, 40].

Figure 3. Long tail plots for FGFR2-altered gastroesophageal adenocarcinomas (A). (B): Concurrent genomic alterations among FGFR2-amplified cases ($n = 209$). (C): Concurrent genomic alterations among FGFR2-amplified cases ($n = 121$) with no putative resistant alterations.
There are inherent weaknesses in retrospective genomic analyses, primarily including the lack of detailed clinical annotation. Based on clinical practice, sample submission patterns, and lack of clear clinical utility in nonmetastatic GEA, nearly all samples examined here are expected to be from patients with advanced GEA. From limited studies, the rates of RTK amplification do not appear significantly different between nonmetastatic and advanced GEA, but less is known about changes in coexisting alterations [5, 11, 24, 41–43]. Furthermore, if a large proportion of advanced GEA cases are based on sequencing of small endoscopic biopsies or limited sampling of metastatic sites, one may argue that coexisting alterations may be underestimated because of intrapatient tumor heterogeneity. Interestingly, and different from HER2, EGFR, and MET, FGFR2amp is well described in the often genomically stable TCGA subtype, a group commonly difficult to assess by next-generation sequencing (NGS) owing to very low tumor cellularity [9, 11]. Thus, NGS-based evaluation may underestimate the true frequency of FGFR2-amplified GEA. Although acquired RTK coamplification is known as a resistance mechanism to targeted therapies in GEA, the probability that a significant portion of our samples had received prior FGFR2-directed therapies is minimal owing to the lack of approved agents and real-world sample set [44]. Similarly, FGFR2 amplification has been observed as an infrequent mechanism of trastuzumab resistance, and “contamination” from post-trastuzumab samples is not expected to play a major role in our findings [5, 44]. Furthermore, we did not observe prior mechanisms of FGFR2 inhibitor resistance among our samples, adding further indirect support that we are representing an FGFR2-directed-therapy-naive population [45, 46]. Although prior publication has suggested HER2 by IHC may be altered by chemoradiotherapy, it is less clear if this applies when the alteration is defined genetically [47]. Finally, owing to pooled DNA used for NGS assays, we cannot determine whether the coexisting alterations exist within the FGFR2-altered cell population or represent a different subclone, underscoring the potential role for single cell technologies in future GEA studies. It is likely that both situations exist: concurrent resistance alterations within the same cell, and cases with intra- and intertumoral subclonal populations harboring varying resistance alterations.

CONCLUSION

Overall, potentially actionable FGFR2 alterations exist in roughly 4% of GEA samples, similar to the frequencies of alterations in MET and EGFR. Coexisting alterations that may attenuate responsiveness to FGFR2-directed therapies were found in 40% of samples; thus, prospective inclusion of baseline comprehensive profiling is warranted to inform optimal patient selection for FGFR2-directed therapies in GEA.

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DISCLOSURES

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