Title

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

Journal

The Oncologist, 24(11)

ISSN

1083-7159

Authors

Klempner, Samuel J
Madison, Russell
Pujara, Vivek
et al.

Publication Date

2019-11-01

DOI

10.1634/theoncologist.2019-0121

Peer reviewed

The Oncologist®

Gastrointestinal Cancer

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

Samuel J. Klempner,[a,b,†] Russell Madison,[c,†] Vivek Pujara,[a] Jeffrey S. Ross,[c,d] Vincent A. Miller,[c] Siraj M. Ali,[c] Alexa B. Schrock,[c] Seung Tae Kim,[e] Steven B. Maron,[f] Farshid Dayyani,[g] Daniel V.T. Catenacci,[h] Jeeyun Lee,[e] Joseph Chao[i]

[a]The Angeles Clinic and Research Institute, Los Angeles, California, USA; [b]Cedars-Sinai Medical Center, Samuel Oschin Comprehensive Cancer Institute, Los Angeles, California, USA; [c]Foundation Medicine, Inc., Cambridge, Massachusetts, USA; [d]Upstate Medical University, Syracuse, New York, USA; [e]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [f]Division of Solid Tumor Oncology, Memorial Sloan Kettering Cancer Center, New York, New York, USA; [g]Division of Hematology-Oncology, Department of Medicine, University of California Irvine, Orange, California, USA; [h]Department of Medicine, Division of Hematology-Oncology, University of Chicago School of Medicine, Chicago, Illinois, USA; [i]Department of Developmental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, California, USA

[†]Contributed equally.

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Fibroblast growth factor receptor 2 • Gastric cancer • Gastroesophageal junction adenocarcinoma • Heterogeneity • Receptor tyrosine kinase

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.

Correspondence: Samuel J. Klempner, M.D., The Angeles Clinic and Research Institute, 11800 Wilshire Blvd., Los Angeles, California 90025, USA. Telephone: 310-231-2167; e-mail: sklempner@theangelesclinic.org Received February 12, 2019; accepted for publication May 15, 2019; published Online First on June 27, 2019. http://dx.doi.org/10.1634/theoncologist.2019-0121

Introduction

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 intertumoral 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 exists 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.

Subjects, Materials, and Methods

We interrogated the Foundation Medicine database of more than 200,000 solid tumor samples to identify samples with the associated diagnoses of gastroesophageal adenocarcinoma. Owing to known molecular differences, squamous cancers were excluded. Basic demographic data including histology, age, sex, and biopsy sample location were collected and annotated to genomic profiling results. Approval for this study, including a waiver of informed consent and a Health Insurance Portability and Accountability Act waiver of authorization, was obtained from the Western Institutional Review Board (Protocol 20152817).

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 *FGFR2*amp

Table 1. Sex, age, and TMB among *FGFR2*-altered gastric and esophageal adenocarcinomas from a large cohort of 6,667 gastroesophageal adenocarcinoma samples

Characteristics	FGFR2 WT (*n* = 6,398)	FGFR2 SV (*n* = 40)	*p* value	FGFR2 amp (*n* = 209)	*p* value	FGFR2 RE (*n* = 37)	*p* value
Male:Female	2.8:1	1.2:1	**.01**	1.6:1	**.0003**	1.6:1	.14
Median age, years	62	64	.34	59	**.04**	62	.88
TMB, median	4.35	4.78	.49	3.60	.79	3.48	.41
TMB, mean	6.06	11.1	.06	4.49	.17	4.28	.52
% MSI-H	3.07%	16.22%	**.0009**	0.00%	**.01**	0.00%	.99
RTK amp	24.0%	10%	**.04**	13.9%	**.0005**	24.3%	.99
ERRB2 amp	14.7%	7.5%	.26	6.70%	**.0006**	13.5%	.99
EGFR amp	6.51%	2.5%	.52	7.66%	.48	10.8%	.30
MET amp	4.61%	0%	.26	2.87%	.31	5.41%	.69
Multiple FGFR2	0%	10%	NP	7.66%	NP	37.8%	NP

Bolded *p* values are statistically significant ($p < .05$). All *p* values are based off comparison with *FGFR2* WT.
Abbreviations: amp, amplification; EGFR, epidermal growth factor receptor; FGFR2, fibroblast growth factor receptor 2; MSI-H, microsatellite instability-high; NP, not performed; RE, rearrangement; SV, short variant; TMB, tumor mutational burden; WT, wild type.

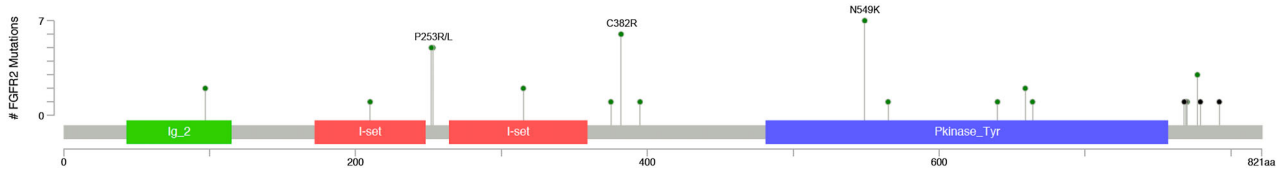

Figure 1. Lollipop plot demonstrating the relative frequency and protein location among cases of *FGFR2* mutant gastroesophageal cancer. Recurrent activating N549K mutations at codon 549 in the kinase domain represent 16.2% of all *FGFR2* mutations (*n* = 40). The most common codon locations are labeled. Figure adapted from Cbioportal (www.cbioportal.org) [48, 49].

and *FGFR2*re were exclusively microsatellite stable, whereas 16% of *FGFR2* SV cases were MSI-high. The most common fusion partner was *TACC2* (22%), and the activating N549K 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 overread 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

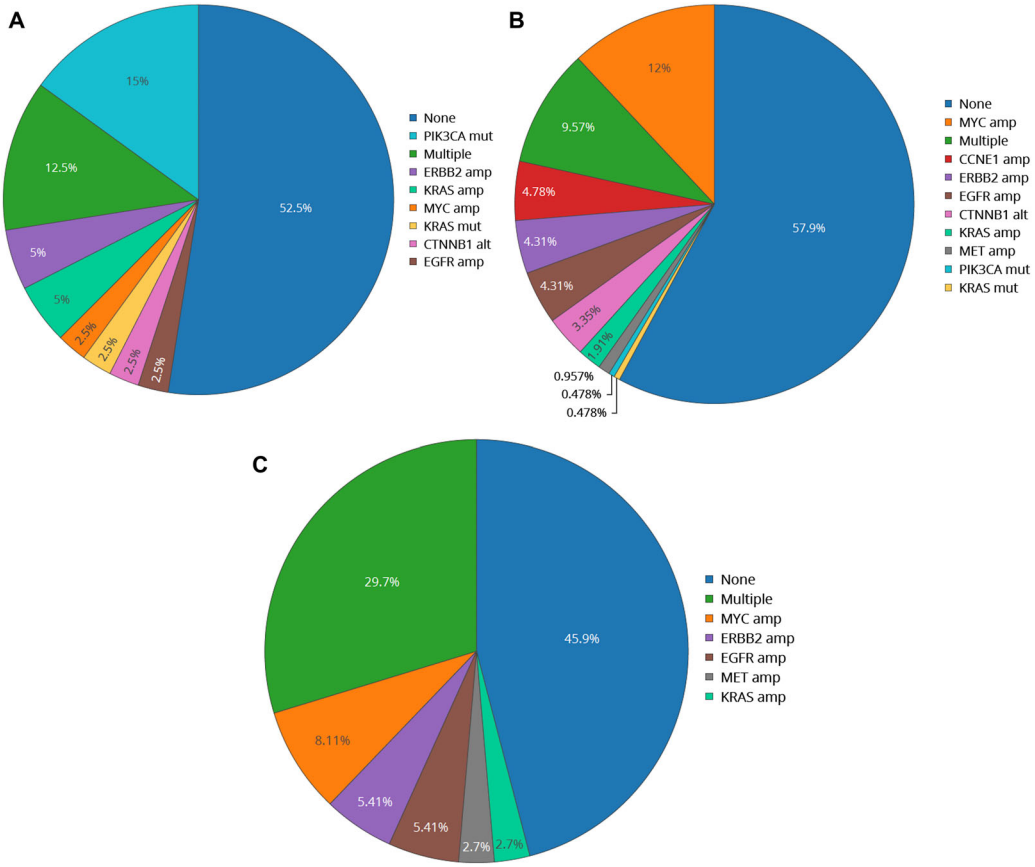

Figure 2. Differential frequency of co-occurring alterations predicted to decrease sensitivity to *FGFR2*-directed therapies among a large cohort of *FGFR2*-altered gastroesophageal adenocarcinomas. Coexisting alterations are broken out among the major classes of *FGFR2* genomic alterations. **(A):** *FGFR2* short variant cases (*n* = 40). **(B):** FGFR-amplified cases (*n* = 209). **(C):** *FGFR2*-rearranged cases (*n* = 37).

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 (*HER2*amp/*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 *FGFR2*amp/pan-WT tumors (*n* = 121, 58% of *FGFR2*amp; 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].

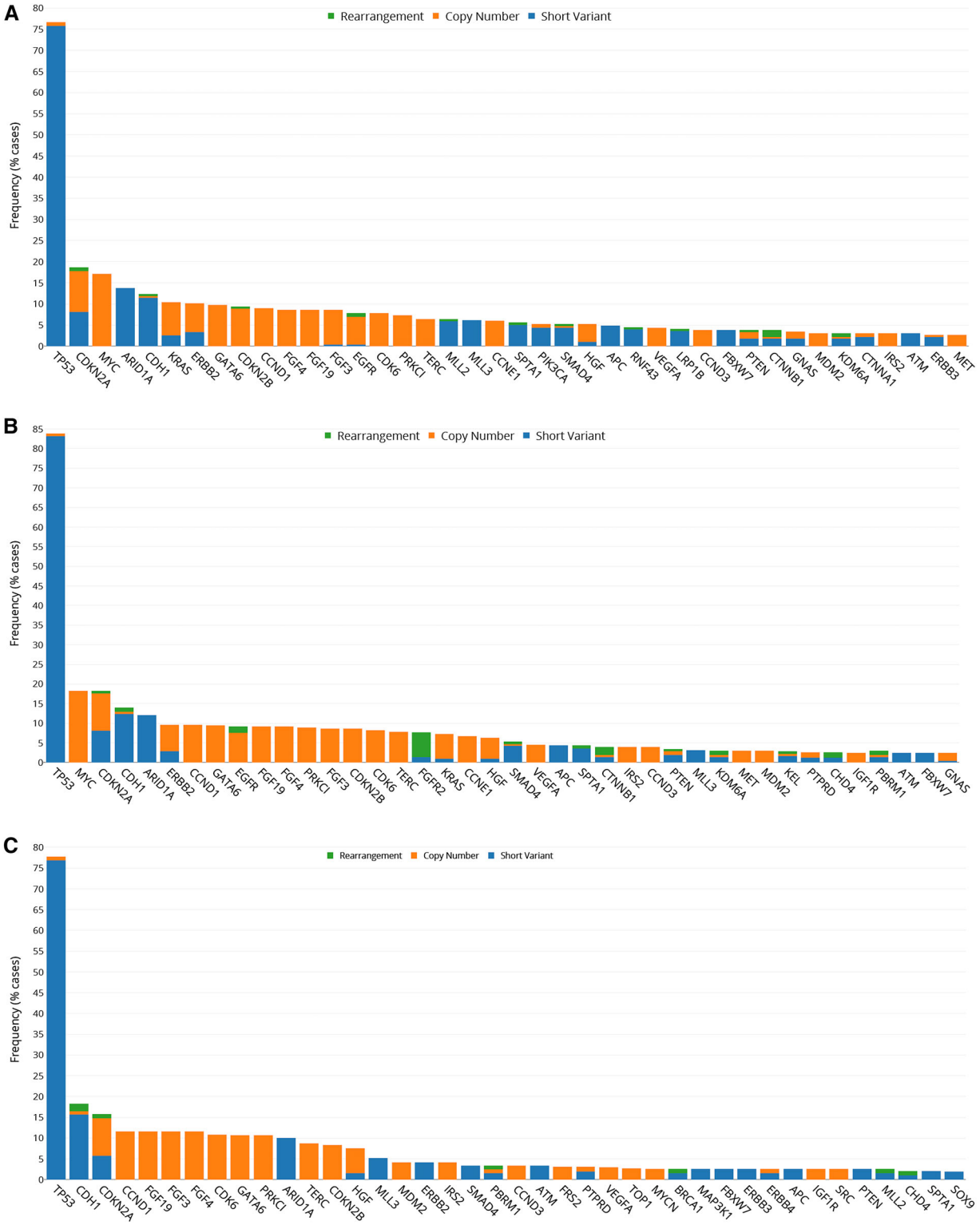

Figure 3. Long tail plots for *FGFR2*-altered gastroesophageal adenocarcinomas **(A)**. **(B):** Concurrent genomic alterations among *FGFR2*-amplified cases (*n* = 209). **(C):** Concurrent genomic alterations among *FGFR2*-amplified cases (*n* = 121) with no putative resistant alterations.

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].

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 tumoral heterogeneity. Interestingly, and different from *HER2*, *EGFR*, and *MET*, *FGFR2*amp 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 genomically [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.

Acknowledgments

We acknowledge the authors whose work could not be cited because of space limitations. S.J.K. is supported by the Howard H. Hall fund for esophageal cancer research. S.B.M. is supported by an ASCO Young Investigator Award and an AACR Gastric Cancer Fellowship. D.V.T.C. is partly supported by the UCCCC (University of Chicago Comprehensive Cancer Center) Award in Precision Oncology—CCSG (Cancer Center Support Grant; P30CA014599), Castle Foundation, LLK (Live Like Katie) Foundation Award, Ullman Scholar Award, and the Sal Ferrara II Fund for PANGEA. J.L. is supported by funding from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI14C3418).

Author Contributions

Conception/design: Samuel J. Klempner, Jeeyun Lee, Joseph Chao
Provision of study material or patients: Samuel J. Klempner, Russell Madison, Alexa B. Schrock, Steven B. Maron, Farshid Dayyani, Daniel V.T. Catenacci, Jeeyun Lee, Joseph Chao
Collection and/or assembly of data: Samuel J. Klempner, Russell Madison, Vivek Pujara, Jeffrey S. Ross, Vincent A. Miller, Siraj M. Ali, Alexa B. Schrock, Seung Tae Kim, Steven B. Maron, Farshid Dayyani, Daniel V.T. Catenacci, Jeeyun Lee, Joseph Chao
Data analysis and interpretation: Samuel J. Klempner, Russell Madison, Vivek Pujara, Jeffrey S. Ross, Vincent A. Miller, Siraj M. Ali, Alexa B. Schrock, Seung Tae Kim, Steven B. Maron, Farshid Dayyani, Daniel V.T. Catenacci, Jeeyun Lee, Joseph Chao
Manuscript writing: Samuel J. Klempner, Russell Madison, Alexa B. Schrock, Steven B. Maron, Daniel V.T. Catenacci, Jeeyun Lee, Joseph Chao
Final approval of manuscript: Samuel J. Klempner, Russell Madison, Vivek Pujara, Jeffrey S. Ross, Vincent A. Miller, Siraj M. Ali, Alexa B. Schrock, Seung Tae Kim, Steven B. Maron, Farshid Dayyani, Daniel V.T. Catenacci, Jeeyun Lee, Joseph Chao

Disclosures

Samuel J. Klempner: Lilly Oncology, Astellas, Foundation Medicine, Inc., Merck (C/A), TP Therapeutics (OI), Merck, Leap Therapeutics, Incyte (RF); **Russell Madison:** Foundation Medicine, Inc. (E), Roche (OI); **Jeffrey S. Ross:** Foundation Medicine, Inc. (E, OI); **Vincent A. Miller:** Foundation Medicine, Inc. (E), Revolution Medicines (C/A); **Siraj M. Ali:** Foundation Medicine, Inc. (E, OI), Incysus (SAB); **Alexa B. Schrock:** Foundation Medicine, Inc. (E); **Farshid Dayyani:** Genentech, Exelixis, Eisai (C/A), Merck, AstraZeneca, Bristol-Myers Squibb (RF), Bayer, Sirtex, Genentech, Amgen, Ipsen (H); **Daniel V.T. Catenacci:** Five Prime, Taiho, Astellas, Merck, Bristol-Myers Squibb, Gritstone, Eli Lilly and Company, Genentech/Roche, Amgen, Foundation Medicine, Inc., Guardant Health, Tempus (C/A, H); **Joseph Chao:** Lilly Oncology, Merck, Foundation Medicine, Inc., AstraZeneca, Boston Biomedical, Daiichi-Sankyo, Taiho (C/A), Merck (RF, H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

References

1. Maron SB, Alpert L, Kwak HA et al. Targeted therapies for targeted populations: Anti-EGFR treatment for EGFR-amplified gastroesophageal adenocarcinoma. Cancer Discov 2018;8:696–713.

2. Klempner SJ, Chao J. Toward optimizing outcomes in Her2-positive gastric cancer: Timing and genomic context matter. Ann Oncol 2018;29:801–802.

3. Pectasides E, Stachler MD, Derks S et al. Genomic heterogeneity as a barrier to precision medicine in gastroesophageal adenocarcinoma. Cancer Discov 2018;8:37–48.

4. Kwak EL, Ahronian LG, Siravegna G et al. Molecular heterogeneity and receptor coamplification drive resistance to targeted therapy in MET-amplified esophagogastric cancer. Cancer Discov 2015;5:1271–1281.

5. Janjigian YY, Sanchez-Vega F, Jonsson P et al. Genetic predictors of response to systemic therapy in esophagogastric cancer. Cancer Discov 2018;8:49–58.

6. Kim ST, Banks KC, Pectasides E et al. Impact of genomic alterations on lapatinib treatment outcome and cell-free genomic landscape during HER2 therapy in HER2+ gastric cancer patients. Ann Oncol 2018;29:1037–1048.

7. Sanchez-Vega F, Hechtman JF, Castel P et al. EGFR and MET amplifications determine response to HER2 inhibition in ERBB2-amplified esophagogastric cancer. Cancer Discov 2019;9:199–209.

8. Klempner SJ, Catenacci DVT. Variety is the spice of life, but maybe not in gastroesophageal adenocarcinomas. Cancer Discov 2019;9: 166–168.

9. Ahn S, Lee J, Hong M et al. FGFR2 in gastric cancer: Protein overexpression predicts gene amplification and high H-index predicts poor survival. Mod Pathol 2016;29:1095–1103.

10. Ali SM, Sanford EM, Klempner SJ et al. Prospective comprehensive genomic profiling of advanced gastric carcinoma cases reveals frequent clinically relevant genomic alterations and new routes for targeted therapies. ***The Oncologist*** 2015;20:499–507.

11. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014;513: 202–209.

12. Cancer Genome Atlas Research Network; Analysis Working Group: Asan University, BC Cancer Agency et al. Integrated genomic characterization of oesophageal carcinoma. Nature 2017;541:169–175.

13. Dieci MV, Arnedos M, Andre F et al. Fibroblast growth factor receptor inhibitors as a cancer treatment: From a biologic rationale to medical perspectives. Cancer Discov 2013;3: 264–279.

14. Cha Y, Kim HP, Lim Y et al. FGFR2 amplification is predictive of sensitivity to regorafenib in gastric and colorectal cancers in vitro. Mol Oncol 2018;12:993–1003.

15. Pearson A, Smyth E, Babina IS et al. High-level clonal FGFR amplification and response to FGFR inhibition in a translational clinical trial. Cancer Discov 2016;6:838–851.

16. Jang J, Kim HK, Bang H et al. Antitumor effect of AZD4547 in a fibroblast growth factor receptor 2-amplified gastric cancer patient-derived cell model. Transl Oncol 2017;10:469–475.

17. Huang T, Liu D, Wang Y et al. FGFR2 promotes gastric cancer progression by inhibiting the expression of thrombospondin4 via PI3K-Akt-Mtor pathway. Cell Physiol Biochem 2018;50: 1332–1345.

18. Huang T, Wang L, Liu D et al. FGF7/FGFR2 signal promotes invasion and migration in human gastric cancer through upregulation of thrombospondin-1. Int J Oncol 2017;50:1501–1512.

19. Gavine PR, Mooney L, Kilgour E et al. AZD4547: An orally bioavailable, potent, and selective inhibitor of the fibroblast growth factor receptor tyrosine kinase family. Cancer Res 2012; 72:2045–2056.

20. Xie L, Su X, Zhang L et al. FGFR2 gene amplification in gastric cancer predicts sensitivity to the selective FGFR inhibitor AZD4547. Clin Cancer Res 2013;19:2572–2583.

21. Javle M, Lowery M, Shroff RT et al. Phase II study of BGJ398 in patients with FGFR-altered advanced cholangiocarcinoma. J Clin Oncol 2018; 36:276–282.

22. Helsten T, Elkin S, Arthur E et al. The FGFR landscape in cancer: Analysis of 4,853 tumors by next-generation sequencing. Clin Cancer Res 2016;22:259–267.

23. Van Cutsem E, Bang YJ, Mansoor W et al. A randomized, open-label study of the efficacy and safety of AZD4547 monotherapy versus paclitaxel for the treatment of advanced gastric adenocarcinoma with FGFR2 polysomy or gene amplification. Ann Oncol 2017;28:1316–1324.

24. Cristescu R, Lee J, Nebozhyn M et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat Med 2015;21:449–456.

25. Frampton GM, Fichtenholtz A, Otto GA et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol 2013; 31:1023–1031.

26. Chalmers ZR, Connelly CF, Fabrizio D et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med 2017;9:34.

27. Forbes SA, Beare D, Gunasekaran P et al. COSMIC: Exploring the world's knowledge of somatic mutations in human cancer. Nucleic Acids Res 2015;43:D805–D811.

28. Chakravarty D, Gao J, Phillips SM et al. OncoKB: A precision oncology knowledge base. JCO Precis Oncol 2017;2017.

29. Wheler JJ, Atkins JT, Janku F et al. Presence of both alterations in FGFR/FGF and PI3K/AKT/mTOR confer improved outcomes for patients with metastatic breast cancer treated with PI3K/AKT/mTOR inhibitors. Oncoscience 2016;3:164–172.

30. Diaz-Serrano A, Angulo B, Dominguez C et al. Genomic profiling of HER2-Positive gastric cancer: PI3K/Akt/mTOR pathway as predictor of outcomes in HER2-positive advanced gastric cancer treated with trastuzumab. ***The Oncologist*** 2018;23:1092–1102.

31. Pietrantonio F, Fuca G, Morano F et al. Biomarkers of primary resistance to trastuzumab in HER2-positive metastatic gastric cancer patients: The AMNESIA case-control study. Clin Cancer Res 2018;24:1082–1089.

32. Liu Y, Sethi NS, Hinoue T et al. Comparative molecular analysis of gastrointestinal adenocarcinomas. Cancer Cell 2018;33:721–735.e8.

33. Catenacci DV. Next-generation clinical trials: Novel strategies to address the challenge of tumor molecular heterogeneity. Mol Oncol 2015; 9:967–996.

34. Gillies RJ, Verduzco D, Gatenby RA. Evolutionary dynamics of carcinogenesis and why targeted therapy does not work. Nat Rev Cancer 2012;12:487–493.

35. Chang J, Wang S, Zhang Z et al. Multiple receptor tyrosine kinase activation attenuates therapeutic efficacy of the fibroblast growth factor receptor 2 inhibitor AZD4547 in FGFR2 amplified gastric cancer. Oncotarget 2015;6: 2009–2022.

36. Lau WM, Teng E, Huang KK et al. Acquired resistance to FGFR inhibitor in diffuse-type gastric cancer through an AKT-independent PKC-mediated phosphorylation of GSK3beta. Mol Cancer Ther 2018;17:232–242.

37. Apicella M, Migliore C, Capeloa T et al. Dual MET/EGFR therapy leads to complete response and resistance prevention in a MET-amplified gastroesophageal xenopatient cohort. Oncogene 2017;36:1200–1210.

38. Gallaher JA, Enriquez-Navas PM, Luddy KA et al. Spatial heterogeneity and evolutionary dynamics modulate time to recurrence in continuous and adaptive cancer therapies. Cancer Res 2018;78:2127–2139.

39. Lawrence MS, Stojanov P, Mermel CH et al. Discovery and saturation analysis of cancer genes across 21 tumour types. Nature 2014;505:495–501.

40. Zehir A, Benayed R, Shah RH et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med 2017;23:703–713.

41. Bang YJ, Van Cutsem E, Feyereislova A et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. Lancet 2010;376:687–697.

42. Silva ANS, Coffa J, Menon V et al. Frequent coamplification of receptor tyrosine kinase and downstream signaling genes in japanese primary gastric cancer and conversion in matched lymph node metastasis. Ann Surg 2018;267:114–121.

43. Nagatsuma AK, Aizawa M, Kuwata T et al. Expression profiles of HER2, EGFR, MET and FGFR2 in a large cohort of patients with gastric adenocarcinoma. Gastric Cancer 2015;18:227–238.

44. Sanchez-Vega F, Hechtman JF, Castel P et al. EGFR and MET amplifications determine response to HER2 inhibition in ERBB2-amplified esophagogastric cancer. Cancer Discov 2019;9:199–209.

45. Sase H, Nakanishi Y, Aida S et al. Acquired JHDM1D-BRAF fusion confers resistance to FGFR inhibition in FGFR2-amplified gastric cancer. Mol Cancer Ther 2018;17:2217–2225.

46. Lee SY, Na YJ, Jeong YA et al. Upregulation of EphB3 in gastric cancer with acquired resistance to a FGFR inhibitor. Int J Biochem Cell Biol 2018;102:128–137.

47. Chan E, Duckworth LV, Alkhasawneh A et al. Discordant HER2 expression and response to neoadjuvant chemoradiotherapy in esophagogastric adenocarcinoma. J Gastrointest Oncol 2016;7:173–180.

48. Gao J, Aksoy BA, Dogrusoz U et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 2013;6:pl1.

49. Cerami E, Gao J, Dogrusoz U et al. The cBio cancer genomics portal: An open platform for exploring multidimensional cancer genomics data. Cancer Discov 2012;2:401–404.

See http://www.TheOncologist.com for supplemental material available online.