OncoTargets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Targeting FGFR2 Positive Gastroesophageal Cancer: Current and Clinical Developments

Anderley Gordon, Edwina Johnston, David K Lau, Naureen Starling

Gastrointestinal and Lymphoma Unit, Royal Marsden NHS Foundation, London, UK

Correspondence: Naureen Starling, Gastrointestinal and Lymphoma Unit, The Royal Marsden Hospital, Downs Road, Sutton, Surrey, SM2 5PT, United Kingdom, Tel +44 2086426011, Email Naureen.Starling@rmh.nhs.uk

Abstract: Despite recent advances in the systemic treatment of gastroesophageal cancers, prognosis remains poor. Comprehensive molecular analyses have characterized the genomic landscape of gastroesophageal cancer that has established therapeutic targets such as human epidermal growth factor receptor 2 (HER2), vascular endothelial growth factor receptor (VEGFR) and programmed death ligand 1 (PD-L1). The aberrant fibroblast growth factor receptor 2 (FGFR2) pathway is attractive for targetable therapy with FGFR inhibition based on preclinical data showing a pivotal role in the progression of gastric cancer (GC). *FGFR2* amplification is the most common *FGFR2* gene aberration in gastroesophageal cancer, and most associated with diffuse GC, which is often linked to poorer prognostic outcomes. There has been considerable progress with drug development focused on FGFR inhibition. At present, there is no approved FGFR inhibitor for FGFR2 positive gastroesophageal cancer. A selective FGFR2b monoclonal antibody bemarituzumab is currently being investigated in the first phase III randomized trial for patients with first line advanced GC, which may change the treatment paradigm for FGFR2b positive GC. The role of FGFR signalling, specifically *FGFR2*, is less established in oesophageal squamous cell cancer (ESCC) with a paucity of evidence for clinical benefit in these patients. Precision medicine is part of the wider approach in gastrointestinal cancers; however, it can be challenging due to heterogeneity and here circulating tumour DNA (ctDNA) for patient selection may have future clinical utility. In our review, we outline the FGFR pathway and focus on the developments and challenges of targeting FGFR2 driven gastroesophageal cancers.

Keywords: gastric cancer, gastroesophageal cancer, FGFR2, molecular targets, novel therapies

Introduction

Gastroesophageal cancer encompasses three major subdivisions which are histologically, epidemiologically, and pathologically different: gastric adenocarcinoma, gastroesophageal junctional (GEJ) adenocarcinoma and oesophageal cancer, which is further classified into squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). Gastric and oesophageal cancers are the fifth and seventh most common cancers globally, however fourth and sixth leading cause for cancer mortality.[1]

Gastroesophageal cancer is aggressive and challenging to treat due to molecular heterogeneity, limited selective biomarkers and approved targeted therapies. Fluoropyrimidine and platinum-based chemotherapy remains at the forefront of systemic treatment in gastroesophageal cancer, with taxanes, irinotecan, trifluridine/tipiracil[2] used in subsequent lines. There are limited targeted therapies available but targeted monoclonal antibodies including trastuzumab and trastuzumab deruxtecan for HER2[3] and ramucirumab for VEGFR2[4] have been approved for GC. Recently, immune checkpoint inhibitors (ICIs) including nivolumab and pembrolizumab have been approved for select patients with advanced gastroesophageal cancer due to positive results from pivotal phase III trials.[5–11] Despite these advances prognosis remains poor and there may be further opportunities through understanding the molecular biology for development of novel drug targets.

The Cancer Genome Atlas (TCGA) network provided a comprehensive molecular analysis and helped identify the genomic landscape of each major subtype. Gastric adenocarcinoma was classified into four subtypes: microsatellite instability (MSI), Epstein-Barr virus (EBV)-positive, chromosomal instability (CIN) and genomically stable (GS) tumours.[15] Oesophageal adenocarcinoma is strongly characterized by CIN, noting some oesophageal adenocarcinomas were more

Received: 15 March 2022
Accepted: 29 August 2022
Published: 11 October 2022

enriched with DNA hypermethylation, and ESCC were divided into three molecular subclasses: ESC1, ESC2 and ESC3.[11] Whilst these comprehensive analyses are useful for providing a molecular roadmap, there is yet to be therapeutic exploitation based on these broader groups, hitherto drug development is still focused on individual molecular targets.

The FGFR pathway has emerged as an attractive target for novel therapies in several cancers. It is known to mediate multiple processes including cell proliferation, survival, and differentiation through activation of the downstream signalling RAS, RAF and MAPK pathways.[12] Dysregulation of FGFR signalling can culminate in tumorigenesis and cancer progression. *FGFR2* amplification is the most common *FGFR2* gene aberration and is associated with GC, specifically the diffuse subtype and accounts for 2% to 9% of GC.[13–17] FGFR2 overexpression varies from 31 to 61% and correlates with aggressive features including higher grade T stage, more frequent lymph node dissemination and inferior overall survival.[18–20] In ESCC, a distinct role for FGFRs remains to be elucidated.

This review article focuses on the relevance of *FGFR2* signalling in GC and highlights the potential for *FGFR2* as a target. We outline the evolution of FGFR drug development from a tumour-agnostic and GC viewpoint based on the current clinical evidence and discuss future developments as well as challenges pertaining to FGFR positive gastro-esophageal cancer.

The FGFR Signalling Pathway

The FGFR family is comprised of four transmembrane receptor tyrosine kinase (RTKs); FGFR1, FGFR2, FGFR3 and FGFR4. A fifth related receptor (FGFRL1) exists however lacks a tyrosine kinase domain which may negatively regulate signalling.[12] FGFR1-4 share a similar configuration, being composed of three major elements including a large extra-cellular ligand binding domain, a single transmembrane helix, and an intra-cellular tyrosine kinase domain. The extra-cellular domain includes three immunoglobulin-like sub-units (D1, D2 and D3).[21] FGFRs are expressed on the cell membrane, where they are activated by their native ligand FGFs.[22] Upon binding with the ligand FGF, FGFRs dimerise causing conformational shifts in structure, which activate the intracellular kinase domain, resulting in phosphorylation of the intracellular domain. Through the recruitment of FRS2, SOS and GRB2 signalling molecules, there is downstream activation of the RAS and the MAPK pathways. The PI3K-mTOR-AKT and STAT3 signalling pathways are also activated by FGFR (Figure 1).[12] FGFRs play a key role in the development and physiology of multiple organ systems and drive key signalling pathways which are responsible for cell proliferation, survival, migration as well as wound healing and angiogenesis.[12,23]

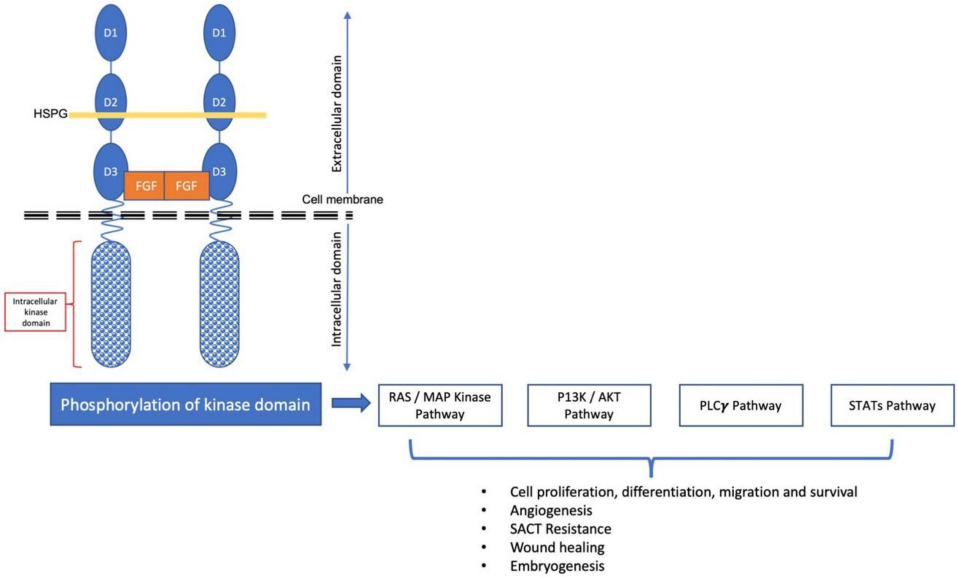

Figure 1 The FGF – FGFR complex and downstream signalling pathways. Two FGFs, two FGFRs and a heparin sulphate proteoglycan (HSPG) form the FGF-FGFR complex. The phosphorylation of the intra-cellular kinase domain results from FGF binding and FGFR dimerization. Consequent activation of multiple downstream pathways, including the RAS-RAF-MAP kinase pathway, P13K-AKT pathway, PLCγ pathway and STAT pathway results. Triggering these signaling pathways cumulates in the FGFRs role in cell proliferation, differentiation, migration and survival. Additionally, FGFR signaling is pivotal in angiogenesis, would healing and embryogenesis.

FGFR2 in Gastric Cancer

Gene abnormalities in *FGFR2* can lead to activation of *FGFR2* signalling. In a hybrid capture-based genomic profiling study using 6667 tissue specimens from advanced GC patients, *FGFR2* gene aberrations were found in 269 (4%) with the most frequent alteration being amplification (72%) followed by mutations (13%), translocations (8.6%) and co-occurring alterations (6.3%).[24] Rare (<1%) fusions (*FGFR2-TACC2)*, and single point mutations (N549K) have been discovered however their clinicopathological characteristics and targeting potential remain unclear.[24]

Amongst GC, gene amplification is the most common aberration of the *FGFR2* gene which leads to FGFR2 protein overexpression and constitutive signalling of the FGFR pathway. The prevalence of *FGFR2* gene amplification ranges from 2% to 9%[13–17] depending on the clinical characteristics of the cohort, and the method used to detect amplification. Detection of *FGFR2* amplifications to date been based upon tissue-based methods. In the largest case-series (n=961) of resected GC, *FGFR2* gene amplification by fluorescent in situ hybridisation (FISH) was observed in 5.6% of cases, with minor differences in the prevalence noted according to geographical location (China 4.6%, Korea 4.2%, and UK 7.4%).[25] Amongst early-stage GC, *FGFR2* amplifications are associated with higher grade T stage, more frequent lymph node dissemination and inferior overall survival.[14,15,25,26] There does not appear to be any association with age, gender, histological subtype, or anatomical location.[25] The association with Lauren histological subtype is controversial with some case series suggesting enrichment amongst diffuse type compared to intestinal type.[15,25,26] In the metastatic setting, *FGFR2* amplifications are also associated with inferior progression free survival (PFS) and overall survival (OS) in patients receiving platinum and fluoropyrimidine chemotherapy.[18,27,28] *FGFR2* and *HER2* amplifications are mutually exclusive,[25,28] however rare cases have been reported.[24] Nevertheless, approximately 40% of *FGFR2* altered gastroesophageal cancers harbour other mutations (*KRAS, MYC*) which may render it resistant to FGFR pathway targeted therapy.[25] *FGFR2* amplification occurs in microsatellite stable (MSS) tumours and does not enrich for PD-L1 expression.[25]

FGFR2 overexpression by immunohistochemistry (IHC) has been reported in a large proportion of GC (31–61%).[18–20] Overexpression of the FGFR2 receptor promotes aberrant signalling through downstream pathways ultimately leading to tumour cell proliferation. In GC, FGFR2 overexpression correlates with more aggressive clinical features such as higher-grade T stage, lymph node and distant metastases which can lead to poorer patient outcomes.[18] Similar to *FGFR2* amplified cases, FGFR2 overexpression has been associated with worse survival in junctional[18] and gastric tumours.[29–31] IHC is a relatively inexpensive test and is available in most laboratories, offering a more cost-effective approach than FISH analysis.

FGFR2 has two isoforms (IIIb and IIIc) which are based upon alternate splicing of exon 8 and 9, respectively leading to differing binding affinities of FGFs.[12] *FGFR2b* is the IIIb splice isoform of *FGFR2*. It is expressed in epithelial cells and is the more prevalent in *FGFR2* amplified GC.[32] While *FGFR2* amplified tumours exhibit evidence of ligand-independent signalling, the natural ligand for *FGFR2b*, FGF7, plays a role in GC progression where FGFR2 expression is elevated.[33] Paracrine secretion of FGF7 by fibroblasts contribute to proliferation,[34] migration and invasion in *FGFR2* expressing cells.[35] Small cohorts have suggested *FGFR2b* expression is associated with worse survival[36] and therapeutic targeting of *FGFR2b* is currently under active clinical investigation as discussed later in the review.

As a result of its association with aggressive clinical features potentially leading to poorer patient outcomes, therapeutic targeting of *FGFR2* in GC is of interest in those harbouring *FGFR2* amplifications or FGFR2b over-expression. We highlight the relevance of these potential targets later in this review with parallel evaluation from supporting clinical studies.

Drug Development in FGFR Driven Cancer

Oncogenic signalling via the FGFR pathway has emerged as a targetable site in multiple cancers, including GC. FGFR inhibition is established in urothelial carcinomas and cholangiocarcinoma, with FGFR inhibitors only approved for clinical practice in these tumour types. (Table 1) Extensive assessment of the structure of FGFRs and development of FGFR inhibitors is ongoing. This section provides an overview of FGFR drug development from a tumour agnostic viewpoint before focusing on the specific developments within FGFR2 gastroesophageal cancer. FGFR inhibitors can be sub-divided into small-molecule oral tyrosine kinase inhibitors (TKIs), monoclonal antibodies and ligand traps.[37]

Table 1 Approved FGFR Inhibitors to Date

Drug	Cancer Type; Indication	Gene Target	Trial Results	Approval
Infigratinib	Advanced CCA; ≥ 2nd line	*FGFR2* rearrangement or fusion	n=108; ORR 14.8% (95% CI, 7.0 to 26.2), mDOR 7.5 months (95% CI, 5.6 to 7.6)[43]	FDA May 2021
Futibatinib	Advanced CCA; ≥ 2nd line	*FGFR2* rearrangement or fusion	n=67, ORR 34%, mDOR 6.2mo[47]	FDA breakthrough therapy designation April 2021
Pemigatinib	Advanced CCA; ≥ 2nd line	*FGFR2* rearrangement or fusion	n=107, ORR 36% (95% CI 26·5–45·4), mDOR 7.5mo (95% CI 5.7–14.5)[42]	FDA April 2020 EMA March 2021
Erdafitinib	Metastatic urothelial carcinoma; ≥ 2nd line	*FGFR3* mutations or *FGFR2* fusions	n=87, ORR 40% (95% CI 31–50%), mDOR 5.6mo (95% CI 4.2–7.2)[41]	FDA April 2019

Abbreviations: CCA, cholangiocarcinoma; CI, confidence interval; EMA, European Medicines Agency; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; mDOR, median duration of response; ORR, objective response rate.

Oral TKIs

Oral TKIs were part of the first approach for targeting FGFR. TKIs have a similar structure to adenosine triphosphate (ATP) and compete for the ATP binding cleft of the kinase domain on the FGFR receptor. Competitive, reversible inhibition reduces tyrosine kinase phosphorylation, causing blockade of multiple downstream pathways thereby inhibiting cancer cell proliferation.[38] First generation FGFR TKIs were non-selective (eg dovitinib, lenvantinib, anolotinib, pontinib) and inhibited multiple other kinase pathways including VEGFR, KIT and RET.[39] These TKIs lacked kinase selectivity and were less potent against the FGFR pathway resulting in significant toxicities during initial trials, ultimately limiting their application in clinical practice.[40]

Refining FGFR TKIs to specifically and selectively act on the tyrosine kinase domain led to the development of selective TKIs. Selective TKIs achieve clinical benefit whilst minimising the significant toxicities associated with non-selective TKIs. The benefit of targeting FGFR has been demonstrated in urothelial cancers and cholangiocarcinoma. Erdafitinib, an oral reversible inhibitor of FGFR1 to FGFR4, has been FDA approved for use in second line advanced or metastatic urothelial carcinoma with *FGFR2* or *FGFR3* alterations.[41] Pemigatinib, a potent FGFR1-4 inhibitor, was granted FDA and EMA approval in second line treatment for patients with advanced cholangiocarcinoma harbouring *FGFR2* mutations.[42] Infigratinib (BGJ398), a FGFR1-3 inhibitor was FDA approved in May 2021 for second line treatment in advanced cholangiocarcinoma with *FGFR2* fusions,[43] and is being compared to chemotherapy in the randomised phase III PROOF trial (NCT03773302). Derazantinib (ARQ087), a competitive pan FGFR inhibitor, predominantly targeting FGFR1-3 but also colony stimulating factor-1-receptor (CSF1R) and VEGFR2 has been granted orphan drug designation by FDA and EMA in second line patients with intrahepatic cholangiocarcinoma harbouring FGFR2 abnormalities.[44] It is currently under investigation in the FIDES-02 trial (NCT03230318) for advanced urothelial cancers and FIDES-03 for advanced GC (NCT04604132).

Further refinement includes the development of irreversible FGFR inhibitors. These inhibitors form a covalent bond and cannot be readily displaced by ATP which aims to provide longer duration of activity.[45] Futibatinib (TAS-120) is an example of this, binding covalently to ATP resulting in irreversible inhibition of FGFR1 to FGFR4.[46] Following the Phase II FOENIX-CCA2 trial, futibatinib was granted break through designation by the FDA for use in previously treated locally advanced or metastatic cholangiocarcinoma with FGFR fusion or rearrangement.[47]

The frequently reported toxicities associated with TKIs comprise hyperphosphataemia, stomatitis, palmar-plantar syndrome, nail toxicity, ocular toxicities including retinal detachment, alopecia, fatigue, and gastro-intestinal toxicity including nausea, abdominal pain or altered bowel habit.[39] In general, these are manageable with phosphate binders and supportive interventions.[46]

Monoclonal Antibodies

Another strategy for inhibiting the FGFR pathway is targeting the extra-cellular domain using monoclonal antibodies or antibody drug conjugates (ADC). Monoclonal antibodies target a certain FGFR and interferes with ligand binding and receptor dimerization. Bemarituzumab (FPA144), is a humanised monoclonal antibody (IgG1 isotype) which targets the FGFR2b receptor, specifically targeting the third immunoglobulin region of the FGFR2b receptor isoform, which is responsible for ligand specificity.[48] Bemarituzumab blocks FGF ligands from binding to the receptor, inhibiting downstream pro-tumour signalling by preventing receptor dimerization, decreasing FGFR2b phosphorylation and subsequent phosphorylation of the downstream effector, FRS2.[49] Unlike small molecule FGFR TKIs, blocking signalling via this route may improve the side effect profile for bemarituzumab as monotherapy or in combination with chemotherapy. Additionally, bemarituzumab promotes antibody-dependent cell (ADCC) mediated toxicity which is another mechanism of action that small molecule FGFR TKIs do not have.[50]

Ligand Traps

The last approach to FGFR inhibition is to prevent FGF ligand binding to the receptor by developing ligand traps. The production of decoy receptors that expresses the extracellular kinase domain only, facilitates binding and trapping of FGF ligands, therefore suppressing FGF pathway activation and signalling.[51] For example, FP-1039 is a ligand trap composed of a fusion between the FGFR1 extra-cellular domain and the human IgG1 Fc fragment, which in pre-clinical studies showed in vivo action against *FGFR2* mutated endometrial cells and lung cancer cells exhibiting *FGFR1* amplification.[52]

In summary, the landscape of FGFR inhibitors has considerably evolved with an immensity of ongoing clinical development. FGFR inhibition continues to move toward increasing TKI kinase selectivity, creating stronger binding kinetics and interrupting FGF ligand binding and/or receptor dimerization. The sites of action on the FGF-FGFR pathway are outlined in Figure 2.

Targeting FGFR2 in Gastroesophageal Cancer: Clinical Evidence

In gastroesophageal cancer, *FGFR2* has emerged as a therapeutic target with numerous preclinical studies suggesting anti-tumour efficacy of FGFR inhibitors in *FGFR2* amplified GC models. There have been several phase II clinical trials, with some showing promising results and the first phase III trial is currently active. Despite these developments, no FGFR targeted treatment has been approved for *FGFR2* amplified gastroesophageal cancer to date. In this section we review past, current and potential future developments of *FGFR2* as a therapeutic target in gastroesophageal cancer.

Non-Selective TKIs

Dovitinib, an anti-angiogenic agent that inhibits multiple RTKs including FGFRs, PDGFRs and VEGFRs, has shown antitumour potential in preclinical models for various solid tumours.[53,54] In a preclinical GC cell model study, dovitinib in combination with nab-paclitaxel exhibited an additive effect on tumour growth inhibition, resulting in tumour regression and improved survival in vivo models. In contrast, dovitinib monotherapy did not prolong survival. The synergistic effect of dovitinib in combination with cytotoxic chemotherapy may support a potential future treatment strategy.[55] The phase II trial, GASDOVI-1 trial (NCT01719549) evaluated the safety and efficacy of dovitinib in patients with chemorefractory metastatic gastric cancer whose tumours had *FGFR2* amplification. At present, there is no preliminary data despite closing several years ago.

Selective TKIs

AZD4547 is a pan FGFR-1,2,3 TKI that exhibited potent antitumour activity in *FGFR2* amplified GC in preclinical studies. AZD4547 inhibited phosphorylation of FGFR2 and its downstream signalling molecules, inducing apoptosis in gastric cell lines, resulting in tumour regression in vivo models.[56] The SHINE study, a small phase II randomized trial (n=71) evaluated the efficacy of AZD4547 versus paclitaxel in second-line treatment of gastroesophageal adenocarcinoma harbouring *FGFR2*-gene amplifications or *FGFR* polysomy detected by FISH. The trial did not meet the primary endpoint as it failed to demonstrate a PFS benefit in patients randomized to AZD4547 compared to paclitaxel (1.8 vs 3.5 months, HR 1.57, p=0.95).[57] An exploratory analysis revealed marked subclonal heterogeneity of the tumour sections

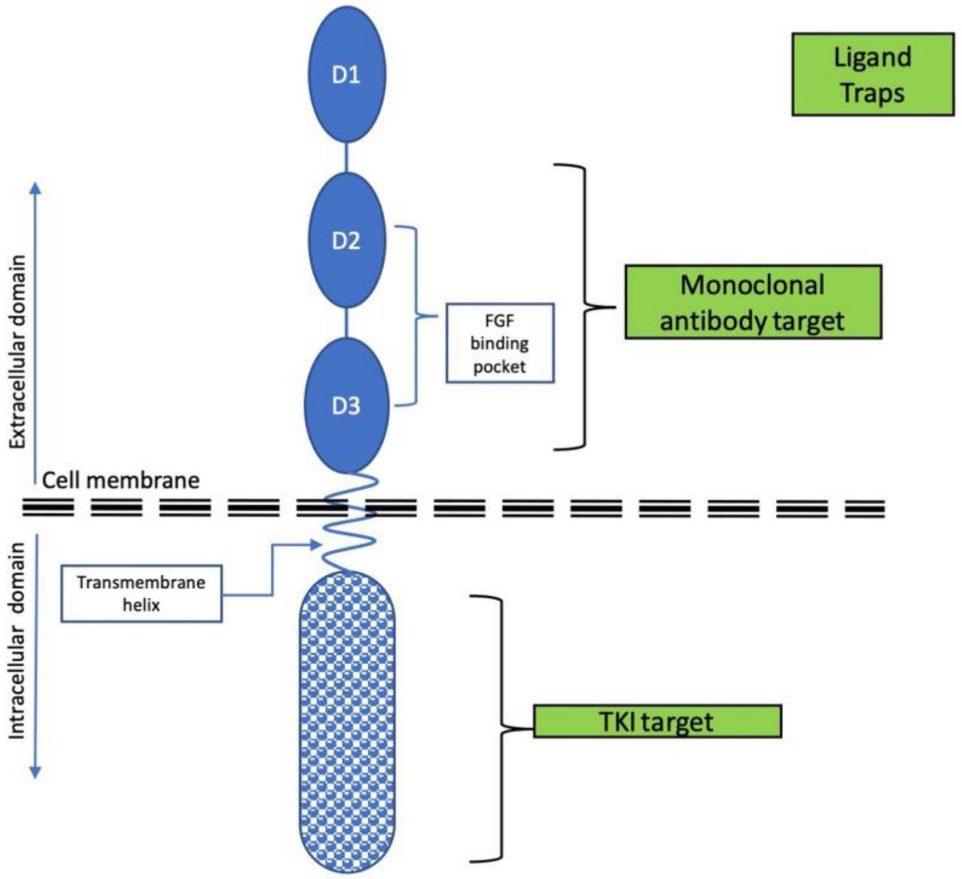

Figure 2 The FGFR structure and targets for FGFR inhibition. FGFRs are composed of a large extra-cellular ligand binding domain, a single transmembrane helix and an intracellular kinase domain. The extracellular domain consists of three immunoglobulin like sub-units (D1-D3), with D2 and D3 forming the FGF binding pocket. TKIs act via competitive ATP inhibition at the ATP binding site on the intracellular kinase domain. Monoclonal antibodies target the extra-cellular domain, competitively inhibiting FGFs and preventing ligand binding. In addition, monoclonal antibodies promote antibody dependent cell mediated toxicity. Ligand traps present decoy receptors which trap FGF ligands and prevent formation of the FGF-FGFR complex.

that displayed *FGFR2* amplification with poor concordance between amplification/polysomy and FGFR2 mRNA expression using FISH testing, representing the need for an alternative biomarker test.[57]

A multi-cohort, phase II trial investigated AZD4547 monotherapy in FGFR dysregulated tumours. *FGFR1/2* amplification was assessed using FISH and of the 288 patients screened, 12/138 (9%) gastroesophageal cancer patients had an *FGFR2* amplification, with 7/138 (5%) having high-amplification, defined as a ratio of *FGFR2* gene to chromosome-10 centromere signals > 5. The objective response rate (ORR) was 33% (3/9) in *FGFR2* amplified GC and the mean duration of response was 5.7 months in the responders.[58] All three responding patients had high-level *FGFR2* amplification as detected by digital droplet PCR (ddPCR) assessment of ctDNA, suggesting a potential role for liquid biopsy as a patient selection tool.[59] High-level *FGFR2* amplification was also associated with sensitivity to FGFR inhibition; the responders exhibited tumours with clonal homogenously amplified tumours (>99% of tumour cells *FGFR2* amplified) while those who did not respond exhibited subclonal heterogeneity or low-level amplification. In the same study using cell lines and patient derived xenograft models, high-level *FGFR2* amplification initiated a distinct oncogene addiction phenotype, characterized by FGFR2-mediated transactivation of alternative receptor kinases, bringing PI3K/mTOR signalling under FGFR control.[59] Screening for high-level *FGFR2* amplifications in ctDNA is an area of development and it may identify potential responders. Whilst for an individual patient the relative incidence of these molecular aberrations is low, on a global scale for a global population, this represents a meaningful benefit.

Recently results were presented from a small phase Ib study (n=21) using a compound alofanib (RPT835), a small molecule allosteric inhibitor of FGFR2-IIIc and IIIb isoforms with IC50 < 10 nM in patients with metastatic gastric adenocarcinoma who had progressed on one or more line of systemic therapy. Noting they did not assess for FGFR

mutations or amplifications, preliminary signs of clinical activity was observed with an ORR of 9.5% (2/21) and disease control rate of 71%. No dose limiting toxicities were reported and the recommended phase II dose was established.[60]

Derazantinib has shown anti-tumour activity in GC murine models[61] and has been shown to inhibit CSF1R and downregulate immunosuppressive macrophage activity which may improve susceptibility to therapeutic immune checkpoint blockade with PD-L1 antibodies.[62,63] Derazantinib is currently being investigated in a phase Ib/II trial. It consists of three sub-studies which will evaluate derazantinib as monotherapy and in combination with paclitaxel and ramucirumab and/or atezolizumab in previously treated patients with advanced GC or GEJ adenocarcinoma harbouring *FGFR2* gene aberrations confirmed using next-generation sequencing (NGS) of ctDNA. (NCT04604132, FIDES-03).

Futibatinib (TAS-120) is an irreversible selective FGFR inhibitor that demonstrated potent anti-tumour activity in vitro and in vivo models. In the first in human study which analysed 36 patients with FGFR gene abnormalities, six patients were gastroesophageal (gastric; n=3, oesophageal; n=3). A clinical response was shown in one of each tumour type with both harbouring *FGFR2* amplification. In a larger Phase I study consisting of 170 patients treated with futibatinib, nine patients (5%) had GC and two had partial responses with an ORR of 22%.[64] Futibatinib is being investigated in advanced GC and GEJ cancers with *FGFR2* gene amplifications (target n=35) in a Phase II, multi-cohort clinical trial where the primary endpoint is ORR (NCT04189445).

Infigratinib (BGJ398) is another TKI being investigated in a phase II, single-arm basket trial in patients with locally advanced or metastatic GC or GEJ cancer with *FGFR2* amplification detected by FISH, or other advanced solid tumours with other FGFR alterations who have failed second line treatments (NCT05019794).

Monoclonal Antibodies

Aprutumab ixadotin (BAY 1187982) was the first ADC to target FGFR2 comprising a fully human anti-FGFR1 monoclonal antibody (BAY 1179470) linked to an auristatin-like cytotoxic payload. Preclinical data demonstrated tumour growth inhibition or regression of cell lines in gastric and breast cancer, leading to the first-in-human phase I trial.[65] Of the twenty patients enrolled, two were GC patients and no responses were reported. The safety profile differed to the preclinical study, and consequently the trial terminated early due to dose-limiting toxicities such as proteinuria, nephropathy, thrombocytopenia and corneal epithelial microcysts.[66]

The FGFR2b selective antibody bemarituzumab (FPA144) has demonstrated promising clinical efficacy in GC patients harbouring *FGFR2* amplification or FGFR2b overexpression. Bemarituzumab monotherapy initially showed tolerability and efficacy in patients with late-line advanced gastroesophageal adenocarcinoma (GEA) who had FGFR2b overexpression in a phase I escalation and expansion study (n=79). Patients were stratified into four cohorts (n=28) based on the level of expression using IHC. Anti-tumour activity was observed in high FGFR2b overexpressing GEA, defined as ≥ 10% of tumour cells with 3+ membranous staining, (n=5) with an ORR of 17.9% and a DCR of 64.3%.[67] The ORR compares favourably to immunotherapy (11–15%).[9,68]

This provided the rationale for a combination strategy of bemarituzumab with chemotherapy.[69,70] The phase II FIGHT trial, a global, randomised, double-blinded, placebo-controlled trial evaluated mFOLFOX6 with or without bemarituzumab in patients with untreated, *HER2* negative, advanced FGFR2b positive gastric or GEJ cancer. Eligible patients had tumours with FGFR2b overexpression detected using IHC (2+/3+) or *FGFR2* gene amplification by ctDNA.[71] It was initially set out to be a registrational phase III trial enrolling 550 patients, however it was changed to a phase II proof-of-concept study after 155 patients were randomized. Patients with GC (n=910) were pre-screened and 275 (30.2%) were FGFR2b positive. Of the 155 randomized, 149 (96%) were FGFR2b positive by IHC, 26 (17%) were *FGFR2* gene amplified by ctDNA and 20 (13%) by both methods. The primary endpoint was met demonstrating a PFS benefit of 2.1 months (9.5 months in the bemarituzumab arm versus 7.4 months in the control arm, HR 0.68, p=0.07). With a median follow up of 12.5 months, the bemarituzumab arm had a median overall survival (mOS) of 19.2 months versus 13.5 months in the placebo arm (HR 0.6, 95% CI: 0.38, 0.94).[72] Among those with measurable disease, the ORR was higher in the bemarituzumab arm, showing an improvement from 40% to 53%.[71] The rate of grade ≥3 adverse events (AEs) were 83% versus 74% in the bemarituzumab and placebo arms with serious AEs in 32% and 36% respectively. Stomatitis and corneal AEs were the most common AEs for bemarituzumab. In contrast to FGFR-TKIs, there were no reported AEs of retinal detachment or hyperphosphatemia.[71] An exploratory analysis showed in a subset of patients (n=96) with IHC 2+/3+ staining in ≥10% tumour cells, a profound improvement in mOS was observed

(25.4 months in bemarituzumab arm versus 11.1 months for placebo, HR 0.41). Although a more meaningful benefit was observed in those with FGFR2b overexpression and ctDNA gene amplification (IHC+/ctDNA+; PFS HR 0.15 and OS HR 0.10), patients benefited from bemarituzumab irrespective of ctDNA gene amplification (IHC+/ctDNA-; PFS HR 0.63 and OS HR 0.66), supporting further evaluation of bemarituzumab without the gene amplification requirement.[72]

The FIGHT study has identified a new biomarker for gastroesophageal cancer for molecular targeted therapy. The positive phase II results support the larger, ongoing randomized phase III trial where the target recruitment is 516 and the primary endpoint is OS (FORTITUDE-101, NCT05052801).[48,71,72] As already highlighted, FGFR2b positive GC is associated with worse survival[36] and the combination strategy of bemarituzumab with cytotoxic chemotherapy may improve outcomes in this important subgroup.

Future Developments

From an immunogenic perspective, the role of immunotherapy in FGFR2 gastroesophageal cancer is an area of interest. The GS genomic subtype shares similarities with diffuse-type GC.[73] Bemarituzumab is glycoengineered for enhanced ADCC which in vivo models resulted in tumour burden reduction, recruitment of natural killer (NK) cells to the tumour and an influx of PD-L1 expressing cells within the tumour microenvironment. For FGFR2b positive GC, the enhanced ADCC activity from bemarituzumab may reprogram the tumour microenvironment, making these tumours immune "hot" subsequently leading to enhanced anti-tumour activity when combined with PD-1 blockade.[74] This preclinical data supports the rationale of FORTITUDE-102, a phase Ib/III trial in set up which will compare bemarituzumab plus chemotherapy and nivolumab versus chemotherapy and nivolumab for FGFR2b overexpressed untreated advanced gastric and GEJ cancer (NCT05111626).

The distinct role of FGFR2 in ESCC is still under early investigation. Various preclinical studies have identified potential targetable pathways, however more robust developments are required to understand its clinical significance. A Japanese study demonstrated that FGFR2-AKT signalling was a driver of keratinocyte differentiation suggesting that activation of FGFR2-AKT signalling could be a future therapeutic option for targeting cancer-like stem cells in ESCC.[75,76] FGFR2 and its upstream regulator miR-671-5p was explored in human ESCC tissue and their matched normal oesophageal tissue (n=35), and an association was observed between higher levels of FGFR2 and lower levels of miR-671-5p. High levels of FGFR2 led to ESCC progression due to activation of the ERK and AKT pathway, while high levels of miR-671-5p specifically reduced the expression of FGFR2. In turn, this led to suppressed progression in vitro and in vivo models, suggesting another prospective treatment approach.[77]

Commensurate with the growth of novel FGFR drugs, directed therapy against FGFR2 in GC has emerged with several small-molecule TKIs and monoclonal antibodies under clinical investigation for treatment of advanced or unresectable GC harbouring *FGFR2* amplification or FGFR2b overexpression (Table 2). FGFR2b overexpression has surfaced as a potential biomarker for molecular targeted therapy in GC but more robust data is needed to constitute its prognostic value, thus results from the first phase III are eagerly awaited.

Challenges in FGFR Positive Gastroesophageal Cancer

Akin to *HER2* amplification or overexpression in gastroesophageal cancer,[78] tumour heterogeneity is a challenge and has potential to affect the accuracy of *FGFR2* amplification or FGFR2 overexpression detection in tumour tissue and have implications for therapeutic targeting.[79] This was highlighted in a study of 188 resected GC patients employing FISH, *FGFR2* mRNA ISH and FGFR2-IIIb splice variant IHC staining. Heterogeneity of FGFR2b protein and FGFR2 mRNA overexpression was observed in 55.5% and 85.7% cases, respectively.[36] *FGFR2* amplification and expression by IHC can be discordant in ~25% of primary and metastatic lesions.[13,36] As tissue heterogeneity poses challenges for molecular diagnostic testing, ctDNA is under investigation as a convenient modality with detection rates comparable or higher than tissue-based methods. In the GOZILA study which enrolled 365 patients with advanced GC, *FGFR2* amplification was more frequently detected by Guardant360 ctDNA sequencing (28, 7.7%) compared to tissue-based methods alone (2.6–4.4%). Furthermore, in a paired tissue and plasma cohort (n=44), six additional cases of *FGFR2* amplification were detected by ctDNA which were not detectable by tissue biopsy.[80] This provides a rationale for potentially selecting patients by either tissue or blood, or both. Assessing amplification clonality in plasma ctDNA is also important as it may predict durable treatment responses to FGFR inhibition. In addition, use of automated in situ heterogeneity mapping by FISH has a potential application in screening patients for rare amplifications.[58,59]

Table 2 Selected Drugs Targeting FGFR2 Currently Under Investigation in Clinical Trials

Drug	Cancer Type	Phase	Population; Gene Target	Treatment Arms	Primary Outcome	Trial ID
Tyrosine kinase inhibitors						
AZD4547	Urothelial carcinoma	I	≥2nd line, advanced; *FGFR2/3* gene alterations	AZD4547 monotherapy	DLT	NCT05086666
Infigratinib	CCA	III	1st line, advanced; *FGFR2* fusion or rearrangement	Infigratinib vs chemotherapy	OS	NCT03773302 (PROOF)
	Gastric or GEJ cancer, solid tumours	II	≥3rd line, advanced; *FGFR2* amplification or *FGFR1-3* fusions/rearrangements/mutation	Infigratinib monotherapy	ORR	NCT05019794
Pemigatinib	CCA	III	1st line, advanced; *FGFR2* rearrangement	Pemigatinib vs chemotherapy	PFS	NCT03656536 (FIGHT-302)
	Colorectal cancer	II	Chemorefractory, advanced; *FGFR* alterations	Pemigatinib monotherapy	ORR	NCT04096417
Derazantinib	Intrahepatic CCA	II	2nd line, advanced; *FGFR2* mutation or amplifications	DZB monotherapy	ORR	NCT03230318 (FIDES-01)
	Gastric or GEJ cancer	II	2nd line, advanced *HER2*- negative; *FGFR2* translocation or amplifications	DZB monotherapy and in combination with ramucirumab + paclitaxel + atezolizumab	ORR	NCT04604132 (FIDES-03)
	Urothelial carcinoma	II	1st and 2nd line, advanced; *FGFR* aberrations	DZB monotherapy, DZB ± atezolizumab	ORR	NCT04045613 (FIDES-02)
Futbatinib	Intrahepatic CCA	III	1st line, advanced; *FGFR2* rearrangements	Futibatinib vs chemotherapy	PFS	NCT04093362 (FOENIX-CCA3)
	Gastric or GEJ cancer, solid tumours, MLN	II	2nd line, advanced; *FGFR2* amplification, *FGFR* rearrangements, *FGFR1* rearrangements	Futibatinib monotherapy	ORR	NCT04189445
	Breast cancer	II	Chemorefractory, advanced; *FGFR1* high-amplification or *FGFR2* amplification	Futibatinib monotherapy and in combination with fulvestrant	ORR	NCT04024436 (FOENIX-MBC2)
Erdafitinib	Gastric, oesophageal, NSCLC, urothelial, CCA	II	Chemorefractory, advanced; *FGFR* alterations	Erdafitinib monotherapy	ORR	NCT02699606
	Urothelial carcinoma	II	2nd line, advanced; *FGFR* alterations	Erdafitinib monotherapy	ORR	NCT04083976
Monoclonal antibodies						
Bemarituzumab	Gastric or GEJ cancer	III	1st line, advanced; *FGFR2* amplification by ctDNA or *FGFR2b* overexpression by IHC	Bemarituzumab plus chemotherapy vs chemotherapy	OS	NCT05052801

https://doi.org/10.2147/OTT.S282718 DovePress

Overcoming acquired resistance is a known challenge with most targeted treatments. FGFR kinase mutations are the most common mechanisms of FGFR-TKI acquired resistance which is illustrated mainly in *FGFR2* altered cholangiocarcinoma studies.[81] In vitro studies have identified gatekeeper mutations which induce resistance to FGFR inhibition,[82] by interfering with TKI access to the hydrophobic ATP binding site.[83] Considering the emergence of gatekeeper mutations in FGFRs, focus should continue the development of irreversible covalent FGFR inhibitors, such as futibatinib, to overcome such resistance.[84] Epithelial-mesenchymal transition (EMT), a complex molecular phenomenon associated with metastasis, poor prognosis, and drug resistance to conventional and targeted therapies, emerged as a potential mechanism of acquired resistance in a study using *FGFR2* amplified resistant GC cell lines. Activation of EMT was associated with loss of FGFR2 expression and reduced expression/activation of transmembrane receptors such as MET, HER2, HER3 and EGFR.[85,86] This potential clinically significant finding warrants further evaluation and there may be opportunity for this through exploratory analyses of the active clinical trials. For FGFR2 GC, the main challenge is inherent resistance. In advanced GC, preclinical studies identified novel fusions such as JHDM1D-BRAF and FGFR2-ACSL5 which confer resistance in gastric cell lines.[87,88] Other mutations have the potential to induce resistance through upregulation of signalling pathways that bypass FGFR inhibition. For example, in a preclinical study using gastric cell models of diffuse-type GC, primary drug resistance to AZD4547 was observed through switching to a protein kinase C (PKC)-mediated inhibition of GSK3β to gain a survival advantage.[89] Increased activation of the MAPK-ERK pathway has also shown a role in FGFR resistance.[31,90–92] It has been suggested that a combinational approach with dual FGFR and MEK inhibition may be a therapeutic strategy to overcome resistance.[31]

Conclusion

The aberrant FGFR pathway has led to an abundance of novel targets, with drug development evolving to refine multi-target kinase inhibitors to more selective TKIs and monoclonal antibodies, to minimise toxicity profiles. In FGFR2b gastroesophageal cancer, the phase III FORTITUDE-101 (previously FIGHT) trial has potential to result in the approval of bemarituzumab in combination with chemotherapy for FGFR2b positive GC. Bemarituzumab also brings hope for the under investigated diffuse-type GC where it may modify the immune tumour microenvironment and in future provide a strategy for a combinational approach with immunotherapy. Whilst gastroesophageal cancer is a heterogenous disease, further research, and validation of ctDNA methods is needed to establish a standardized patient selection tool. Although there are currently no FGFR2 approved therapies available in gastroesophageal cancer, there are multiple active trials which if positive, have the potential to change the treatment paradigm for an important subgroup of patients.

Acknowledgments

The authors are supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London.

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Disclosure

Dr Anderley Gordon discloses no conflicts of interest in this work.

Dr Edwina Johnston discloses no conflicts of interest in this work.

Dr David K Lau discloses he is the recipient of the Australasian Gastro-Intestinal Trials Group/Merck Clinical Research Fellowship.

Dr Naureen Starlings disclosures include the following:

Research Funding: AstraZeneca, BMS, Pfizer, NIHR EME, RMCC, RM/ICR BRC

Travel & Accommodation: AstraZeneca, BMS, Eli Lilly, Merck, Roche, MSD Oncology (02/2019 GI ASCO flights and accommodation)

Honoraria: Eli Lilly, Merck Serono, MSD Oncology, Pierre Fabre, Servier, GSK, Amgen

Advisory Board: Pfizer, AstraZeneca, Servier, MSD (Merck)

The authors report no other conflicts of interest in this work.

References

1. Sung H, Ferlay J, Siegel RL., et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, Phase 3 trial. *Lancet Oncol*. 2018;19(11):1437–1448. doi:10.1016/S1470-2045(18)30739-3
3. 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(9742):687–697. doi:10.1016/S0140-6736(10)61121-X
4. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2014;383(9911):31–39. doi:10.1016/S0140-6736(13)61719-5
5. Doki Y, Ajani JA, Kato K, et al. Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. *N Engl J Med*. 2022;386(5):449–462. doi:10.1056/NEJMoa2111380
6. Boku N, Ryu MH, Kato K, et al. Safety and efficacy of nivolumab in combination with S-1/capecitabine plus oxaliplatin in patients with previously untreated, unresectable, advanced, or recurrent gastric/gastroesophageal junction cancer: interim results of a randomized, phase II trial (ATTRACTION-4). *Annals Oncol*. 2019;30(2):250–258. doi:10.1093/annonc/mdy540
7. Kato K, Shah MA, Enzinger P, et al. KEYNOTE-590: phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer. *Future Oncol*. 2019;15(10):1057–1066. doi:10.2217/fon-2018-0609
8. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*. 2021;398(10294):27–40. doi:10.1016/S0140-6736(21)00797-2
9. Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. *JAMA Oncol*. 2018;4(5):e180013–e180013. doi:10.1001/jamaoncol.2018.0013
10. Chen LT, Satoh T, Ryu MH, et al. A phase 3 study of nivolumab in previously treated advanced gastric or gastroesophageal junction cancer (ATTRACTION-2): 2-year update data. *Gastric Cancer*. 2020;23(3):510–519. doi:10.1007/s10120-019-01034-7
11. Kim J, Bowlby R, Mungall AJ, et al. Integrated genomic characterization of oesophageal carcinoma. *Nature*. 2017;541(7636):169–175. doi:10.1038/nature20805
12. Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. *Nat Rev Cancer*. 2010;10(2):116–129. doi:10.1038/nrc2780
13. Deng N, Goh LK, Wang H, et al. A comprehensive survey of genomic alterations in gastric cancer reveals systematic patterns of molecular exclusivity and co-occurrence among distinct therapeutic targets. *Gut*. 2012;61(5):673. doi:10.1136/gutjnl-2011-301839
14. Betts G, Valentine H, Pritchard S, et al. FGFR2, HER2 and cMet in gastric adenocarcinoma: detection, prognostic significance and assessment of downstream pathway activation. *Virchows Arch*. 2014;464(2):145–156. doi:10.1007/s00428-013-1517-y
15. Jung EJ, Jung EJ, Min SY, Kim MA, Kim WH. Fibroblast growth factor receptor 2 gene amplification status and its clinicopathologic significance in gastric carcinoma. *Hum Pathol*. 2012;43(10):1559–1566. doi:10.1016/j.humpath.2011.12.002
16. Liu YJ, Shen D, Yin X, et al. HER2, MET and FGFR2 oncogenic driver alterations define distinct molecular segments for targeted therapies in gastric carcinoma. *Br J Cancer*. 2014;110(5):1169–1178. doi:10.1038/bjc.2014.61
17. Kunii K, Davis L, Gorenstein J, et al. FGFR2-amplified gastric cancer cell lines require FGFR2 and Erbb3 signaling for growth and survival. *Cancer Res*. 2008;68(7):2340–2348. doi:10.1158/0008-5472.CAN-07-5229
18. Tokunaga R, Imamura Y, Nakamura K, et al. Fibroblast growth factor receptor 2 expression, but not its genetic amplification, is associated with tumor growth and worse survival in esophagogastric junction adenocarcinoma. *Oncotarget*. 2016;7(15):19748–19761. doi:10.18632/oncotarget.7782
19. Schrumpf T, Behrens HM, Haag J, Krüger S, Röcken C. FGFR2 overexpression and compromised survival in diffuse-type gastric cancer in a large central European cohort. *PLoS One*. 2022;17(2):e0264011. doi:10.1371/journal.pone.0264011
20. 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(2):227–238. doi:10.1007/s10120-014-0360-4
21. Farrell B, Breeze AL. Structure, activation and dysregulation of fibroblast growth factor receptor kinases: perspectives for clinical targeting. *Biochem Soc Trans*. 2018;46(6):1753–1770. doi:10.1042/BST20180004
22. Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. *Cell*. 2010;141(7):1117–1134. doi:10.1016/j.cell.2010.06.011
23. Yu P, Wilhelm K, Dubrac A, et al. FGF-dependent metabolic control of vascular development. *Nature*. 2017;545(7653):224–228. doi:10.1038/nature22322
24. Klempner SJ, Madison R, Pujara V, et al. FGFR2-altered gastroesophageal adenocarcinomas are an uncommon clinicopathologic entity with a distinct genomic landscape. *Oncologist*. 2019;24(11):1462–1468. doi:10.1634/theoncologist.2019-0121
25. Su X, Zhan P, Gavine PR, et al. FGFR2 amplification has prognostic significance in gastric cancer: results from a large international multicentre study. *Br J Cancer*. 2014;110(4):967–975. doi:10.1038/bjc.2013.802
26. Matsumoto K, Arao T, Hamaguchi T, et al. FGFR2 gene amplification and clinicopathological features in gastric cancer. *Br J Cancer*. 2012;106(4):727–732. doi:10.1038/bjc.2011.603
27. Hur JY, Chao J, Kim K, et al. High-level FGFR2 amplification is associated with poor prognosis and Lower response to chemotherapy in gastric cancers. *Pathol Res Pract*. 2020;216(4):152878. doi:10.1016/j.prp.2020.152878
28. Das K, Gunasegaran B, Tan IB, Deng N, Lim KH, Tan P. Mutually exclusive FGFR2, HER2, and KRAS gene amplifications in gastric cancer revealed by multicolour FISH. *Cancer Lett*. 2014;353(2):167–175. doi:10.1016/j.canlet.2014.07.021
29. Murase H, Inokuchi M, Takagi Y, Kato K, Kojima K, Sugihara K. Prognostic significance of the co-overexpression of fibroblast growth factor receptors 1, 2 and 4 in gastric cancer. *Mol Clin Oncol*. 2014;2(4):509–517. doi:10.3892/mco.2014.293
30. Kim HS, Kim JH, Jang HJ, Han B, Zang DY. Pathological and prognostic impacts of FGFR2 overexpression in gastric cancer: a meta-analysis. *J Cancer*. 2019;10(1):20–27. doi:10.7150/jca.28204

31. Lau DK, Luk IY, Jenkins LJ, et al. Rapid resistance of FGFR-driven gastric cancers to regorafenib and targeted FGFR inhibitors can be overcome by parallel inhibition of MEK. *Mol Cancer Ther*. 2021;20(4):704–715. doi:10.1158/1535-7163.mct-20-0836
32. Yashiro M, Kuroda K, Masuda G, et al. Clinical difference between fibroblast growth factor receptor 2 subclass, type IIIb and type IIIc, in gastric cancer. *Sci Rep*. 2021;11(1):4698. doi:10.1038/s41598-021-84107-x
33. Shaoul R, Eliahu L, Sher I, et al. Elevated expression of FGF7 protein is common in human gastric diseases. *Biochem Biophys Res Commun*. 2006;350(4):825–833. doi:10.1016/j.bbrc.2006.08.198
34. Nakazawa K, Yashiro M, Hirakawa K. Keratinocyte growth factor produced by gastric fibroblasts specifically stimulates proliferation of cancer cells from scirrhous gastric carcinoma. *Cancer Res*. 2003;63(24):8848–8852.
35. 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(5):1501–1512. doi:10.3892/ijo.2017.3927
36. Han N, Kim MA, Lee HS, Kim WH. Evaluation of fibroblast growth factor receptor 2 expression, heterogeneity and clinical significance in gastric cancer. *Pathobiology*. 2015;82(6):269–279. doi:10.1159/000441149
37. Ornitz DM, Itoh N. The fibroblast growth factor signaling pathway. *Wiley Interdiscip Rev Dev Biol*. 2015;4(3):215–266. doi:10.1002/wdev.176
38. Chaar M, Kamta J, Ait-Oudhia S. Mechanisms, monitoring, and management of tyrosine kinase inhibitors-associated cardiovascular toxicities. *Onco Targets Ther*. 2018;11:6227–6237. doi:10.2147/OTT.S170138
39. Facchinetti F, Hollebecque A, Bahleda R, et al. Facts and new hopes on selective FGFR inhibitors in solid tumors. *Clin Cancer Res*. 2020;26 (4):764–774. doi:10.1158/1078-0432.CCR-19-2035
40. Liu FT, Li NG, Zhang YM, et al. Recent advance in the development of novel, selective and potent FGFR inhibitors. *Eur J Med Chem*. 2020;186:111884. doi:10.1016/j.ejmech.2019.111884
41. Loriot Y, Necchi A, Park SH, et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2019;381(4):338–348. doi:10.1056/NEJMoa1817323
42. Vogel A, Sahai V, Hollebecque A, et al. LBA40 - FIGHT-202: a phase II study of pemigatinib in patients (pts) with previously treated locally advanced or metastatic cholangiocarcinoma (CCA). *Annals Oncol*. 2019;30:v876. doi:10.1093/annonc/mdz394.031
43. 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 (3):276–282. doi:10.1200/JCO.2017.75.5009
44. Mazzaferro V, El-Rayes BF, Droz Dit Busset M, et al. Derazantinib (ARQ 087) in advanced or inoperable FGFR2 gene fusion-positive intrahepatic cholangiocarcinoma. *Br J Cancer*. 2019;120(2):165–171. doi:10.1038/s41416-018-0334-0
45. Fumarola C, Bozza N, Castelli R, et al. Expanding the arsenal of FGFR inhibitors: a novel chloroacetamide derivative as a new irreversible agent with anti-proliferative activity against FGFR1-amplified lung cancer cell lines. *Front Oncol*. 2019;9:179. doi:10.3389/fonc.2019.00179
46. Kalyukina M, Yosaatmadja Y, Middleditch MJ, Patterson AV, Smaill JB, Squire CJ. Tas-120 cancer target binding: defining reactivity and revealing the first fibroblast growth factor receptor 1 (FGFR1) irreversible structure. *ChemMedChem*. 2019;14(4):494–500. doi:10.1002/cmdc.201800719
47. Goyal L, Meric-Bernstam F, Hollebecque A, et al. FOENIX-CCA2: a phase II, open-label, multicenter study of futibatinib in patients (pts) with intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 gene fusions or other rearrangements. *J Clin Oncol*. 2020;38(15_suppl):108. doi:10.1200/JCO.2020.38.15_suppl.108
48. Catenacci DVT, Tesfaye A, Tejani M, et al. Bemarituzumab with modified FOLFOX6 for advanced FGFR2-positive gastroesophageal cancer: FIGHT Phase III study design. *Future Oncol*. 2019;15(18):2073–2082. doi:10.2217/fon-2019-0141
49. Gemo AT, Deshpande AM, Palencia S, et al. Abstract 5446: FPA144: a therapeutic antibody for treating patients with gastric cancers bearing FGFR2 gene amplification. *Cancer Res*. 2014;74(19_Supplement):5446. doi:10.1158/1538-7445.AM2014-5446
50. Xiang H, Chan AG, Ahene A, et al. Preclinical characterization of bemarituzumab, an anti-FGFR2b antibody for the treatment of cancer. *MAbs*. 2021;13(1):1981202. doi:10.1080/19420862.2021.1981202
51. Krook MA, Reeser JW, Ernst G, et al. Fibroblast growth factor receptors in cancer: genetic alterations, diagnostics, therapeutic targets and mechanisms of resistance. *Br J Cancer*. 2021;124(5):880–892. doi:10.1038/s41416-020-01157-0
52. Harding TC, Li L, Servando P, et al. Blockade of nonhormonal fibroblast growth factors by FP-1039 inhibits growth of multiple types of cancer. *Sci Transl Med*. 2013;5(178):178ra39–178ra39. doi:10.1126/scitranslmed.3005414
53. Huynh H, Chow PKH, Tai WM, et al. Dovitinib demonstrates antitumor and antimetastatic activities in xenograft models of hepatocellular carcinoma. *J Hepatol*. 2012;56(3):595–601. doi:10.1016/j.jhep.2011.09.017
54. Gaur S, Chen L, Ann V, et al. Dovitinib synergizes with oxaliplatin in suppressing cell proliferation and inducing apoptosis in colorectal cancer cells regardless of RAS-RAF mutation status. *Mol Cancer*. 2014;13(1):21. doi:10.1186/1476-4598-13-21
55. Crawford K, Bontrager E, Schwarz MA, et al. Targeted FGFR/VEGFR/PDGFR inhibition with dovitinib enhances the effects of nab-paclitaxel in preclinical gastric cancer models. *Cancer Biol Ther*. 2021;22(10–12):619–629. doi:10.1080/15384047.2021.2011642
56. 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(9):2572–2583. doi:10.1158/1078-0432.CCR-12-3898
57. van Cutsem E, Bang Y-J, 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. *Annals Oncol*. 2017;28(6):1316–1324. doi:10.1093/annonc/mdx107
58. Smyth EC, Turner NC, Pearson A, et al. Phase II study of AZD4547 in FGFR amplified tumours: gastroesophageal cancer (GC) cohort pharmacodynamic and biomarker results. *J Clin Oncol*. 2016;34(4_suppl):154. doi:10.1200/jco.2016.34.4_suppl.154
59. 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(8):838–851. doi:10.1158/2159-8290.CD-15-1246
60. Tjulandin S, Statsenko G, Artamonova E, et al. A first-in-human Phase 1b study of a novel allosteric extracellular FGFR2 inhibitor alofanib in patients with refractory metastatic gastric cancer. *J Clin Oncol*. 2022;40(4_suppl):304. doi:10.1200/JCO.2022.40.4_suppl.304
61. McSheehy P, Bachmann F, Forster-Gross N, et al. The FGFR-inhibitor derazantinib (DZB) is active in PDX-models of GI-cancer with specific aberrations in FGFR. *J Clin Oncol*. 2020;38(4_suppl):421. doi:10.1200/JCO.2020.38.4_suppl.421
62. Ries CH, Cannarile MA, Hoves S, et al. Targeting tumor-associated macrophages with anti-CSF-1R antibody reveals a strategy for cancer therapy. *Cancer Cell*. 2014;25(6):846–859. doi:10.1016/j.ccr.2014.05.016

63. Fleming V, Hu X, Weber R, et al. Targeting myeloid-derived suppressor cells to bypass tumor-induced immunosuppression. *Front Immunol*. 2018;9:398. doi:10.3389/fimmu.2018.00398
64. Meric-Bernstam F, Bahleda R, Hierro C, et al. Futibatinib, an irreversible FGFR1–4 inhibitor, in patients with advanced solid tumors harboring FGF/FGFR aberrations: a phase i dose-expansion study. *Cancer Discov*. 2022;12(2):402–415. doi:10.1158/2159-8290.CD-21-0697
65. Sommer A, Kopitz C, Schatz CA, et al. Preclinical efficacy of the auristatin-based antibody–drug conjugate BAY 1187982 for the treatment of fgfr2-positive solid tumors. *Cancer Res*. 2016;76(21):6331–6339. doi:10.1158/0008-5472.CAN-16-0180
66. Kim SB, Meric-Bernstam F, Kalyan A, et al. First-in-human phase i study of aprutumab ixadotin, a fibroblast growth factor receptor 2 antibody–drug conjugate (BAY 1187982) in patients with advanced cancer. *Target Oncol*. 2019;14(5):591–601. doi:10.1007/s11523-019-00670-4
67. Catenacci DVT, Rasco D, Lee J, et al. Phase I escalation and expansion study of bemarituzumab (FPA144) in patients with advanced solid tumors and FGFR2b-selected gastroesophageal adenocarcinoma. *J Clin Oncol*. 2020;38(21):2418–2426. doi:10.1200/JCO.19.01834
68. Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;390(10111):2461–2471. doi:10.1016/S0140-6736(17)31827-5
69. Tejani MA, Cheung E, Eisenberg PD, et al. Phase I results from the phase 1/3 FIGHT study evaluating bemarituzumab and mFOLFOX6 in advanced gastric/GEJ cancer (GC). *J Clin Oncol*. 2019;37(4_suppl):91. doi:10.1200/JCO.2019.37.4_suppl.91
70. Xiang H, Liu L, Gao Y, et al. Population pharmacokinetic analysis of phase 1 bemarituzumab data to support phase 2 gastroesophageal adenocarcinoma FIGHT trial. *Cancer Chemother Pharmacol*. 2020;86(5):595–606. doi:10.1007/s00280-020-04139-4
71. Wainberg ZA, Enzinger PC, Kang YK, et al. Randomized double-blind placebo-controlled phase 2 study of bemarituzumab combined with modified FOLFOX6 (mFOLFOX6) in first-line (1L) treatment of advanced gastric/gastroesophageal junction adenocarcinoma (FIGHT). *J Clin Oncol*. 2021;39(3_suppl):160. doi:10.1200/JCO.2021.39.3_suppl.160
72. Catenacci DVT, Kang YK, Saeed A, et al. FIGHT: a randomized, double-blind, placebo-controlled, phase II study of bemarituzumab (bema) combined with modified FOLFOX6 in 1L FGFR2b+ advanced gastric/gastroesophageal junction adenocarcinoma (GC). *J Clin Oncol*. 2021;39 (15_suppl):4010. doi:10.1200/JCO.2021.39.15_suppl.4010
73. Ling Y, Watanabe Y, Nagahashi M, et al. Genetic profiling for diffuse type and genomically stable subtypes in gastric cancer. *Comput Struct Biotechnol J*. 2020;18:3301–3308. doi:10.1016/j.csbj.2020.10.021
74. Powers J, Palencia S, Foy S, et al. Abstract 1407: FPA144, a therapeutic monoclonal antibody targeting the FGFR2b receptor, promotes antibody dependent cell-mediated cytotoxicity and stimulates sensitivity to PD-1 in the 4T1 syngeneic tumor model. *Cancer Res*. 2016;76 (14_Supplement):1407. doi:10.1158/1538-7445.AM2016-1407
75. Maehara O, Suda G, Natsuizaka M, et al. FGFR2 maintains cancer cell differentiation via AKT signaling in esophageal squamous cell carcinoma. *Cancer Biol Ther*. 2021;22(5–6):372–380. doi:10.1080/15384047.2021.1939638
76. Maehara O, Suda G, Natsuizaka M, et al. Fibroblast growth factor-2–mediated FGFR/Erk signaling supports maintenance of cancer stem-like cells in esophageal squamous cell carcinoma. *Carcinogenesis*. 2017;38(11):1073–1083. doi:10.1093/carcin/bgx095
77. Li X, Nie C, Tian B, et al. miR-671-5p Blocks The Progression Of Human Esophageal Squamous Cell Carcinoma By Suppressing FGFR2. *Int J Biol Sci*. 2019;15(9):1892–1904. doi:10.7150/ijbs.32429
78. Grillo F, Fassan M, Sarocchi F, Fiocca R, Mastracci L. HER2 heterogeneity in gastric/gastroesophageal cancers: from benchside to practice. *World J Gastroenterol*. 2016;22(26):5879–5887. doi:10.3748/wjg.v22.i26.5879
79. Pectasides E, Stachler MD, Derks S, et al. Genomic heterogeneity as a barrier to precision medicine in gastroesophageal adenocarcinoma. *Cancer Discov*. 2018;8(1):37–48. doi:10.1158/2159-8290.cd-17-0395
80. Jogo T, Nakamura Y, Shitara K, et al. Circulating Tumor DNA analysis detects FGFR2 amplification and concurrent genomic alterations associated with FGFR inhibitor efficacy in advanced gastric cancer. *Clin Cancer Res*. 2021;27(20):5619–5627. doi:10.1158/1078-0432.ccr-21-1414
81. Goyal L, Saha SK, Liu LY, et al. Polyclonal secondary FGFR2 mutations drive acquired resistance to FGFR inhibition in patients with FGFR2 fusion–positive cholangiocarcinoma. *Cancer Discov*. 2017;7(3):252–263. doi:10.1158/2159-8290.CD-16-1000
82. Babina IS, Turner NC. Advances and challenges in targeting FGFR signalling in cancer. *Nat Rev Cancer*. 2017;17(5):318–332. doi:10.1038/nrc.2017.8
83. Liu Y, Shah K, Yang F, Witucki L, Shokat KM. A molecular gate which controls unnatural ATP analogue recognition by the tyrosine kinase v-Src. *Bioorg Med Chem*. 1998;6(8):1219–1226. doi:10.1016/S0968-0896(98)00099-6
84. Goyal L, Shi L, Liu LY, et al. Tas-120 Overcomes resistance to ATP-competitive FGFR inhibitors in patients with FGFR2 fusion-positive intrahepatic cholangiocarcinoma. *Cancer Discov*. 2019;9(8):1064–1079. doi:10.1158/2159-8290.CD-19-0182
85. Lee S, Young N, Jeong YA, Kim JL, Oh SC, Lee DH. Upregulation of EphB3 in gastric cancer with acquired resistance to a FGFR inhibitor. *Int J Biochem Cell Biol*. 2018;102:128–137. doi:10.1016/j.biocel.2018.07.008
86. Grygielewicz P, Dymek B, Bujak A, et al. Epithelial–mesenchymal transition confers resistance to selective FGFR inhibitors in SNU-16 gastric cancer cells. *Gastric Cancer*. 2016;19(1):53–62. doi:10.1007/s10120-014-0444-1
87. 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(10):2217–2225. doi:10.1158/1535-7163.MCT-17-1022
88. Kim SY, Ahn T, Bang H, et al. Acquired resistance to LY2874455 in FGFR2-amplified gastric cancer through an emergence of novel FGFR2-ACSL5 fusion. *Oncotarget*. 2017;8(9):15014–15022. doi:10.18632/oncotarget.14788
89. 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 GSK3β. *Mol Cancer Ther*. 2018;17(1):232–242. doi:10.1158/1535-7163.MCT-17-0367
90. Kas SM, de Ruiter JR, Schipper K, et al. Transcriptomics and transposon mutagenesis identify multiple mechanisms of resistance to the FGFR inhibitor AZD4547. *Cancer Res*. 2018;78(19):5668–5679. doi:10.1158/0008-5472.CAN-18-0757
91. Bockorny B, Rusan M, Chen W, et al. RAS–MAPK reactivation facilitates acquired resistance in FGFR1-amplified lung cancer and underlies a rationale for upfront FGFR–MEK blockade. *Mol Cancer Ther*. 2018;17(7):1526–1539. doi:10.1158/1535-7163.MCT-17-0464
92. Zhou Y, Wu C, Lu G, Hu Z, Chen Q, Du X. FGF/FGFR signaling pathway involved resistance in various cancer types. *J Cancer*. 2020;11 (8):2000–2007. doi:10.7150/jca.40531